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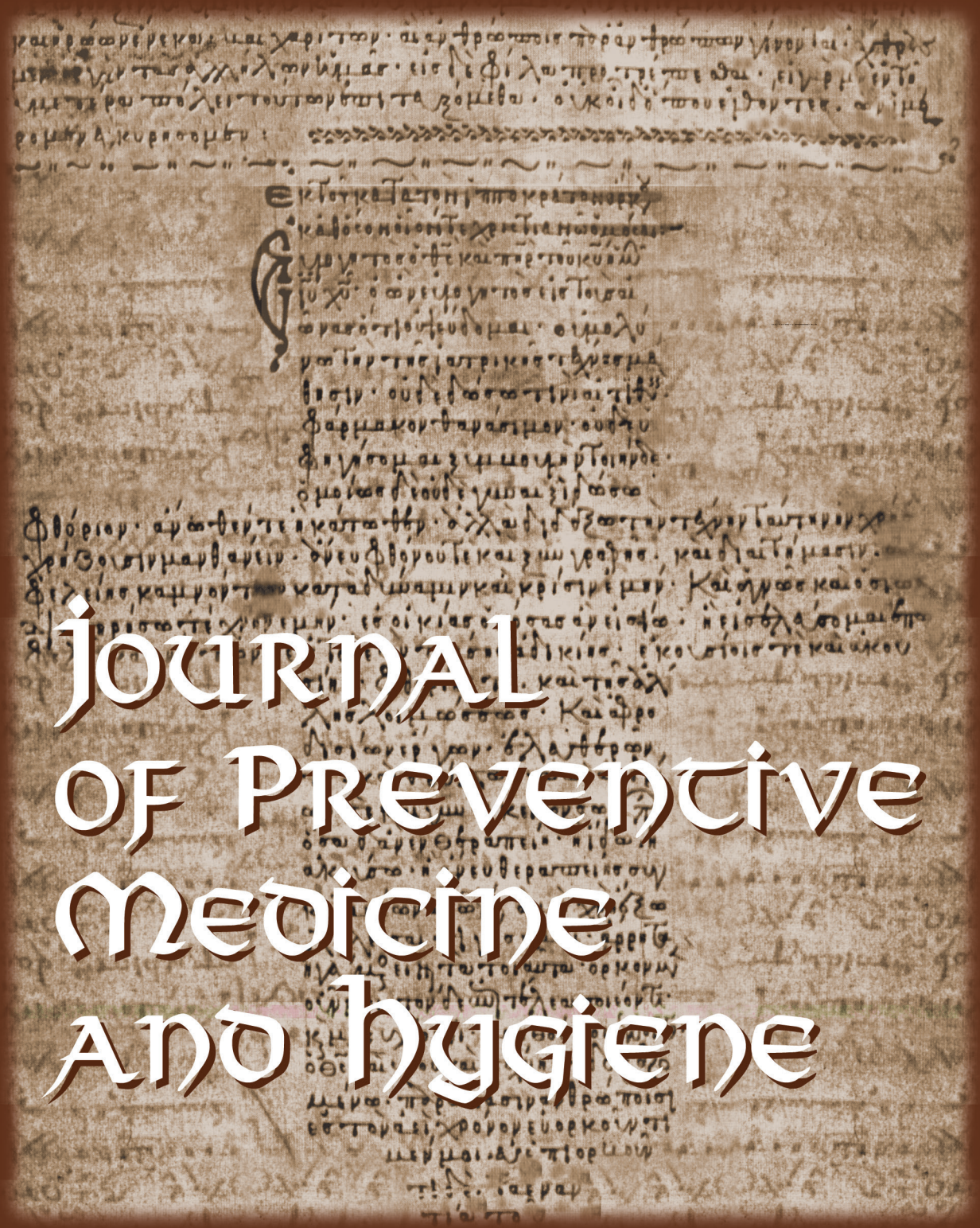

The original document of Hippocrates' oath

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Contents

Research paper

The association between various indicators of hospital capacity, age category, and the number of screening tests performed with case fatality rate and recovery rate during the COVID-19 disease pandemic

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Keywords

COVID-19 • Case fatality rate (CFR) • Recovery rate (RR) • Hospital resource allocation

Summary

Background. *The COVID-19-related deaths are growing rapidly around the world, especially in Europe and the United States.*
Purpose. *In this study we attempt to measure the association of these variables with case fatality rate (CFR) and recovery rate (RR) using up-to-date data from around the world.*
Methods. *Data were collected from eight global databases. According to the raw data of countries, the CFR and RR and their relationship with different predictors was compared for countries with 1,000 or more cases of COVID-19 confirmed cases.*
Results. *There were no significant correlation between the CFR and number of hospital beds per 1,000 people, proportion of population aged 65 and older ages, and the number of computed tomography per one million inhabitants. Furthermore, based on the continents-based subgroup univariate regression analysis, the population (R^2 = 0.37, P = 0.047), GPD (R^2 = 0.80, P < 0.001), number of ICU Beds per 100,000 people (R^2 = 0.93, P = 0.04), and number of CT per one million inhabitants (R^2 = 0.78, P = 0.04) were significantly correlated with CFR in America. Moreover, the income-based subgroups analysis showed that the gross domestic product (R^2 = 0.30, P = 0.001), number of ICU Beds per 100,000 people (R^2 = 0.23, P = 0.008), and the number of ventilator (R^2 = 0.46, P = 0.01) had significant correlation with CFR in high-income countries.*
Conclusions. *The level of country's preparedness, testing capacity, and health care system capacities also are among the important predictors of both COVID-19 associated mortality and recovery. Thus, providing up-to-date information on the main predictors of COVID-19 associated mortality and recovery will hopefully improve various countries hospital resource allocation, testing capacities, and level of preparedness.*

Introduction

Since the first suspected case of coronavirus-2019 disease (SARS-CoV-2/COVID-19) on December 1, 2019, in Wuhan, Hubei Province, China, a total of 4,012,857 confirmed cases and 276,216 deaths in 212 countries and territories have been reported by May 9, 2020 [1]. The COVID-19-related deaths are growing rapidly around the world, especially in Europe and the United States. Case Fatality Rate (CFR) is a measure of the ability of a pathogen or virus to infect or harm a host in infectious disease and is described as the mortality rate in a given population. Globally, the overall CFR for COVID-19 disease estimated by researchers was 3.6-4.3% [2]. There is a disparity in tactics against COVID-19 disease, which different countries used in various protocols and procedures [3]. The US government does not recommend more than 10 people gathered, but San Francisco has ordered everyone to stay home. Italy, France, and Spain, while police or the army are patrolling in some areas, have almost completely shut down their populations, but at the same time, public places were open in the UK. Like many other countries, Germany has closed its schools, but schools are open to children in Sweden.

The capacity of hospitals has long been exhausted, and medical staffs are forced to make annoying choices about who to treat and who will be saved [4]. In today's world, information guides the health care system, and the realization of this depends on the existence of accurate data and reliable information provided from various sources. Hospital indicators are one of the most important tools for measuring the efficiency and productivity of a health care service, which is collected and analyzed correctly; they play an important role in decision making and quality control of services [5]. The intensive care unit (ICU) is one of the essential and vital pillars of hospitals, which provides care to patients with severe and life-threatening conditions. Patients with severe acute respiratory infections due to COVID-19 disease may need supplemental oxygen and mechanical respiratory support. Thus, the higher the number of beds and care equipment in the intensive care unit, the lower the mortality rate in patients with COVID-19 [6, 7]. Computed tomography (CT) scans of the chest in patients

with COVID-19 are usually considered as a tool that can be very helpful in diagnosing the disease in its early stages [8]. Moreover, people of any age can be severely infected with the COVID-19, although it is more common in middle-aged and older adults, especially people older than 60 years [9]; thus, experts believe that age distribution can also play a key role in increased mortality rates.

Considering the importance of CFR and recovery rate (RR), as well as the relationship between these two variables with the number of beds in hospitals and intensive care units, the number of ventilators, the number of CT-scan apparatuses, gross domestic product (GDP), the percentage of people over the age of 60, and the number of screening tests performed during a COVID-19 disease pandemic, in this study, we attempt to measure the association of these variables with CFR and RR using up-to-date data from around the world.

Materials and methods

Data collection

Data were collected from global databases such as World meter [10], WHO [11], the Centers for Disease Control and Prevention (CDC) [12], and the Weekly Report on Complications and Deaths (prepared by the Centers for Disease Control and Prevention), based on the user guide, data sources for disease registration [13]. Due to the rapid increase in data, the analysis in this study was conducted on April 10, 2020. According to the raw data of countries, the CFR and RR and their relationship with the number of beds in hospitals and intensive care units, the number of ventilators in hospitals, the number of CT scans, the gross domestic product (GDP), the number of screening tests performed during an epidemic was compared for countries with 1000 or more cases of COVID-19 confirmed cases [2].

The number of beds in hospitals and intensive care units, the number of ventilators in hospitals, the number of CT scans, the gross domestic product (GDP), the number of screening tests performed during an epidemic were collected from American Hospital Association (AHA) fact sheet (*https://www.aha.org/statistics/fast-facts-us-hospitals*), Critical Care Statistics (*https://www.sccm.org/Communications/Critical-Care-Statistics*), Wikipedia (*https://en.wikipedia.org/wiki/List_of_countries_by_hospital_beds*), research data and infographics from Statista (*https://www.statista.com/chart/21105/number-of-critical-care-beds-per-100000-inhabitants/*) and WHO reports.

Calculate the case fatality rate (CFR) and recovery rate (RR)

The case fatality rate and recovery rate were calculated from the following formulas:

$$CFR = (\text{Total number of deaths due to COVID-19} / \text{Total number of cases of disease}) * 100$$

$$RR = (\text{Total number of cases recovered from COVID-19} / \text{Total number of cases of the disease}) * 100$$

Methods

Based on currently observed parameters we provide insights into the association between various indicators of healthcare systems and COVID-19 results (death or recovery) in global level. So, firstly the univariate regression analysis was performed based on these expletory variables. Furthermore, to assess the simultaneous impact of different risk indicators on the CFR, multiple regression model was fitted using all significant factors in prior step.

Statistical analysis

Linear regression analysis was performed to assess the association between recovery rate and case fatality rate as dependent variables and GPD, population, number of ICU beds, proportion of population aged 65 and older ages, number of ventilators, number of total COVID-19 tests, number of total COVID-19 tests per 1 M population and number of hospital beds as explanatory variables. Regard this process, firstly the univariate model was fitted with all the explanatory variables. Furthermore, based on the univariate findings, to assess the simultaneous impact of different explanatory variables on the recovery rate and case fatality rate, multiple linear regression model was fitted using all significant factors in prior step. However, due to the existence of a correlation between the independent variables (multicollinearity) the Ridge regression model was implemented. Since, the multicollinearity lead to definitely serious problems such as makes it hard to interpret the coefficients in multiple regression, and it reduces the power of the model to identify independent variables that are statistically significant. Furthermore, subgroup analysis was conducted based on country's origin (continent) and class of the country's economy (based on The World Bank classifies). The graphs were also plotted using the scatter plot. Data were analyzed using SPSS 22 and Stata 12. A p-value of less than 0.05 was considered to be significant.

Results

Table I showed all the data about the GDP, number of hospital beds per 1,000 people, number of ICU beds per 100,000 people, number of ventilators, % population of ≥ 65 years age, number of computed tomography apparatus per one million people, with CFR and RR of COVID-19 infection among countries with more than 1,000 infected cases.

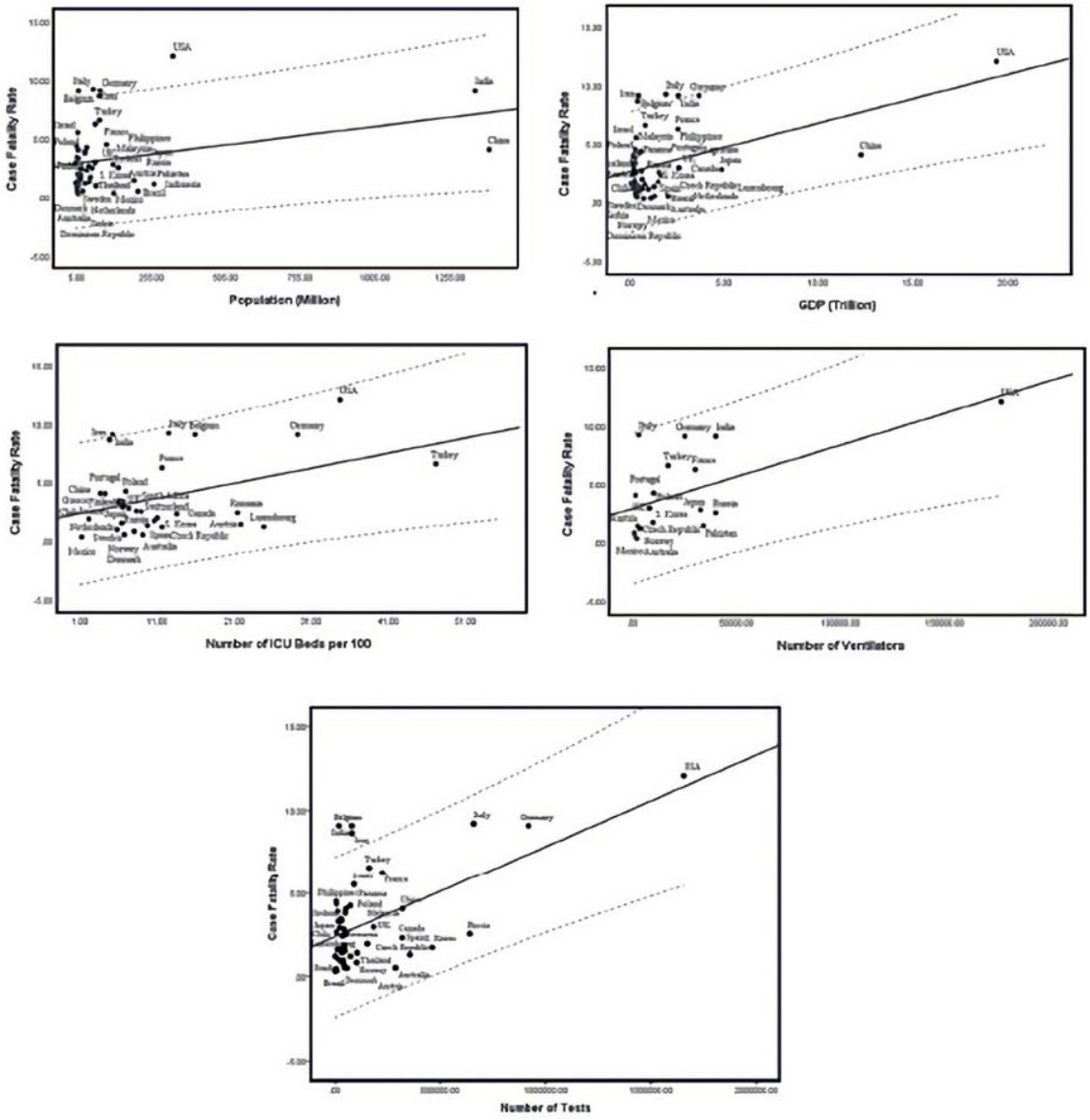
There were no significant correlations between the CFR and the number of hospital beds per 1,000 people, the proportion of population aged 65 and older, and the number of CT per one million inhabitants (Fig. 1). However, CFR was positively correlated to the country's GPD, population, number of ICU beds per 100 individuals, number of ventilators, and total COVID-19 tests performed (Fig. 1).

Furthermore, to assess the simultaneous impact of different risk indicators on the CFR, the ridge regression model was fitted using all significant variables in theunivariate regression model (Fig. 1). Based on ridge regression

Tab. I. Comparison of population, GDP, number of hospital beds per 1,000 people, number of ICU beds per 100,000 people, number of ventilators, % population of ≥ 65 years age, number of computed tomography apparatus per one million people, with case fatality and recovery rates of COVID-19 infection among countries with more than 1,000 infected cases.

Country [reference]	Population (million)	GDP (trillion)	Number of hospital beds per 1,000 people	Number of ICU beds per 100,000 people	Number of ventilators	Total cases	Total deaths	Total recovered	Case fatality rate	Recovery rate	% population ages 65 and older	Number of CT per 1 million inhabitants	Number of tests
USA [14]	327.2	19.39	2.77	34.7	177,000	245,373	6,095	10,403	12.07	4.24	16%	44.390	1,654,409
Italy [15]	60.48	1.935	3.18	12.5	3,000	115,242	13,915	18,278	9.23	15.86	22.4%	34.710	657,224
Spain[15]	46.66	1.311	2.97	9.7	NR	112,065	10,348	26,743	1.31	23.86	19.1%	18.590	355,000
China [16]	1,386	12.24	4.34	3.6	NR	84,794	1,107	22,440	4.07	26.46	11.9%	NR	320,000
Germany [15]	82.79	3.677	8.00	29.2	25,000	81,620	3,322	76,571	9.11	93.81	21.1%	35.130	918,460
France [15]	66.99	2.583	5.98	11.6	30,000	59,105	5,387	12,428	6.26	21.03	20.3%	17.690	224,254
Iran [17]	81.16	0.4395	1.5	4.8	NR	50,468	3,160	16,711	8.66	33.11	6.1%	NR	80,000
UK [15]	66.44	2.622	2.54	6.6	8,175	33,718	2,921	135	2.96	0.40	18.3%	NR	183,190
Switzerland [15]	8.57	0.6789	4.53	11.0	NR	19,106	565	4,846	1.96	25.36	18.3%	39.280	153,440
Turkey [15]	80.81	0.8511	2.81	47.1	17,000	18,135	356	415	6.59	2.29	8.8%	14.770	161,380
Belgium [15]	11.4	0.4927	5.76	15.9	NR	15,348	1,011	2,495	9.11	16.26	18.7%	NR	18,360
Netherlands [15]	17.18	0.8262	3.32	6.4	NR	14,697	1,339	250	1.53	1.70	18.9%	13.480	46,810
Austria [15]	8.822	0.4166	7.37	21.8	2,500	11,283	173	1,979	1.41	17.54	18.8%	28.640	104,134
S. Korea [16]	51.4	1.531	12.27	10.6	9,795	11,238	158	2,022	1.73	17.99	15.1%	38.180	461,233
Canada [18]	37.59	1.653	2.52	13.5	NR	10,062	174	6,021	2.31	59.84	17.2%	15.510	317,972
Portugal [15]	10.29	0.2176	3.39	4.2	1,400	9,034	209	68	4.05	0.75	20.7%	NR	52,086
Brazil	209.3	2.056	2.3	NR	NR	8,066	327	127	0.51	1.57	8.5%	NR	58,824
Israel	8.712	0.3509	3.02	NR	NR	7,030	36	338	5.53	4.81	NR	9.690	90,394
Australia	24.6	1.323	3.84	9.1	1,314	5,568	308	103	0.52	1.85	15.8%	67.200	286,786
Sweden	10.12	0.538	2.22	5.8	NR	5,350	28	585	0.96	10.93	19.6%	17.280	36,900
Norway	5.368	0.3988	3.6	8	800	5,218	50	32	0.82	0.61	17.2%	NR	101,986
Czech Republic [15]	10.65	0.2157	6.63	11.6	3,529	4,149	34	281	1.19	6.77	19.6%	15.670	74,170
Russia [19]	144.5	1.578	8.05	8.3	40,000	3,869	46	71	2.55	1.84	14.6%	13.640	639,606
Ireland	4.83	0.3337	2.96	6.5	NR	3,849	98	5	3.35	0.13	NR	20.500	30,213
Denmark	5.603	0.3249	2.61	6.7	NR	3,672	123	1,089	0.53	29.66	19%	39.780	45,270
Malaysia	31.62	0.3145	1.9	NR	NR	3,404	18	335	3.79	9.84	6.4%	NR	49,570
Chile	18.05	0.2771	2.2	2.11	NR	3,163	120	65	1.87	2.06	11.8%	24.270	44,130
Ecuador	16.62	0.1031	1.50	NR	NR	3,149	59	56	1.60	1.78	NR	NR	10,317
Philippines	104.9	0.3136	1.0	NR	NR	3,116	50	767	4.51	24.61	5.1%	NR	5,530
Poland [15]	37.98	0.5245	6.62	6.9	10,100	3,018	136	52	4.24	1.72	17.5%	16.880	72,901
Romania	19.53	0.2118	6.3	21.4	NR	2,738	116	267	2.41	9.75	18.2%	NR	36,092
Japan [16]	126.8	4.872	13.05	7.3	32,586	2,617	63	472	2.80	18.04	26%	111.490	42,882
Luxembourg	0.613	0.625	4.66	24.8	NR	2,567	72	192	1.21	7.48	14.4%	16.450	NR
Pakistan	197	0.305	0.6	NR	34,000	2,487	30	80	1.43	3.22	4.3%	NR	32,930
India	1,339	2.597	0.53	5.2	40,000	2,450	35	126	9.11	5.14	6.1%	NR	79,950
Thailand	69.04	0.4552	2.1	NR	NR	1,986	181	134	0.96	6.75	11.5%	NR	23,669
Indonesia	264	1.016	1.2	NR	NR	1,978	19	581	1.11	29.37	5.6%	NR	7,896
Saudi Arabia	32.94	0.6838	2.7	NR	NR	1,885	21	328	1.18	17.40	NR	NR	NR
Finland	5.513	0.2519	3.28	6.1	NR	1,615	19	300	3.43	18.58	20.3%	24.510	29,000
Greece	10.74	0.2003	4.24	6.0	NR	1,544	53	61	3.31	3.95	19%	34.220	15,961
South Africa [20]	56.72	0.3494	2.8	8.9	NR	1,510	50	633	2.51	41.92	6.0%	NR	50,361
Mexico	129.2	1.15	1.38	1.2	2,050	1,475	37	9	0.34	0.61	7.2%	5.83	9,481
Peru	32.17	0.2114	1.6	NR	NR	1,462	5	95	3.89	6.50	8.4%	NR	12,669
Panama	4.099	0.6184	2.3	NR	NR	1,414	55	537	4.35	37.98	NR	NR	7,333
Dominican Republic	10.77	0.7593	1.6	NR	NR	1,380	60	16	0.30	1.16	3%	NR	NR
Iceland	0.3642	0.2391	2.96	6.5	NR	1,319	4	284	2.92	21.53	14.2%	20.500	23,640
Argentina	44.27	0.6374	5.0	NR	NR	1,265	37	256	2.65	20.24	11.4%	NR	7,385
Colombia	49.07	0.3092	1.7	NR	NR	1,171	31	42	1.64	3.59	11.4%	1.300	23,760
Serbia	7.022	0.4143	5.7	NR	NR	1,161	19	55	0.45	4.74	20.2%	NR	5,008
Singapore	5.612	0.3239	2.4	NR	NR	1,114	5	266	0.78	23.88	NR	NR	39,000
World	**7,530**	**80.68**	----	-----	-----	**1,019,354**	**53,322**	**214,358**	**2.48**	**21.03**	-----	-----	

Fig. 1. Case fatality rate against the population (R^2 = 0.09, P = 0.035), the country's gross domestic product (GDP) (in trillion) (R^2 = 0.22, P = 0.001), the number of intensive care unit (ICU) beds per 100 individuals (R^2 = 0.17, P = 0.016), and the number of ventilators (R^2 = 0.38, P = 0.007), and the number of screening tests performed (R^2 = 0.31, P < 0.001). Lines represent linear regression analysis together with 95% confidence intervals around the line.



Tab. II. The result of multiple ridge regression of the association of variables of interest with CFR.

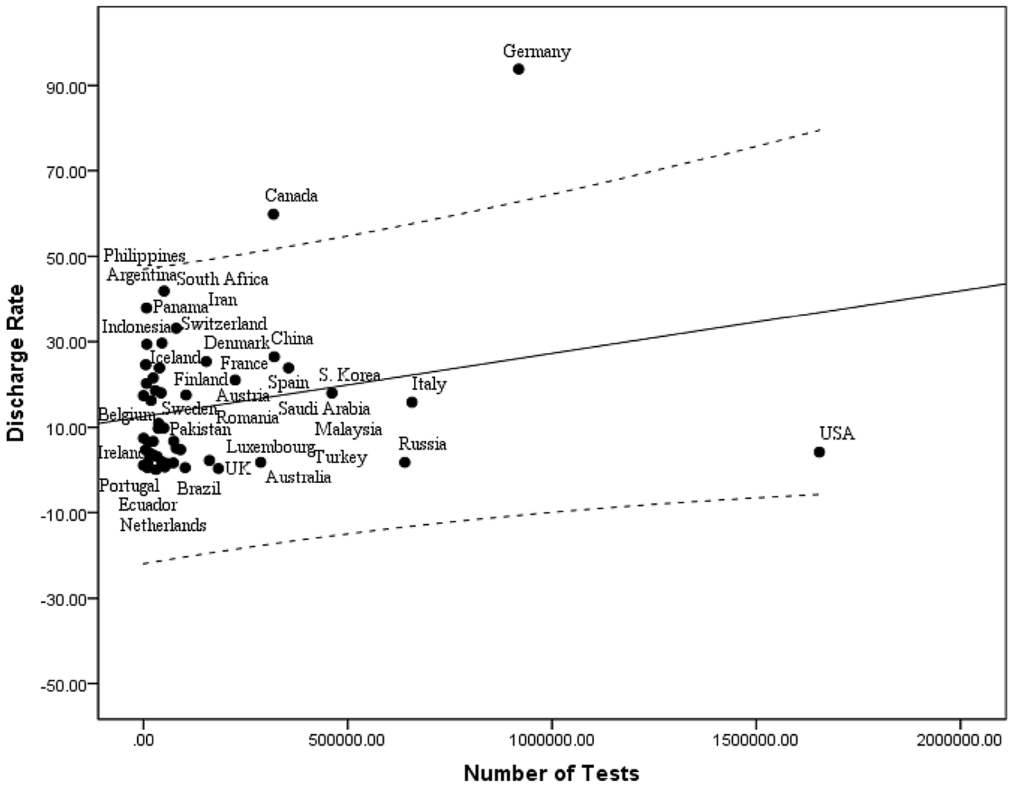
Variables	Standardized beta	SE	P-value	R^2
GPD	0.36	0.002	0.08	0.66
Population	0.38	0.46	0.51	
Number of ICU beds per 100 individuals	0.47	0.079	0.10	
Number of ventilators	0.15	< 0.0001	0.83	
Number of total COVID-19 tests	-0.24	< 0.0001	0.63	

results, these variables simultaneously were not significant, albeit the R^2 was impressive in multiple regression (Tab. II). Furthermore, based on the continents-based subgroup univariate regression analysis, the population (R^2 = 0.37, P = 0.047), GPD (R^2 = 0.80, P < 0.001), number of ICU Beds per 100,000 people (R^2 = 0.93, P = 0.04), and number of CT per one million inhabitants (R^2 = 0.78, P = 0.04) were significantly correlated with CFR in America, which means these variables could be main predictors of CFR in America. In Asia and Europe, there was no significant correlation between the CFR and most of the variables; however, the number of CT per one million inhabitants (R^2 = 0.37) was an important predictor when compared to other variables in Asia, and the GPD (R^2 = 0.30) was the main predictors of CFR in Europe (Tab. III). Moreover, the income-based subgroups analysis showed that the

Tab. III. The result of subgroup analysis of the association of variables of interest with CFR.

Continents	Variables	Standardized beta	R^2	P-value
America (n = 11)	**Population (million)**	**0.61**	**0.37**	**0.047**
	GDP (trillion)	**0.89**	**0.80**	**< 0.001**
	Number of hospital beds per 1,000 people	0.26	0.07	0.44
	Number of ICU beds per 100,000 people	**0.96**	**0.93**	**0.04**
	Number of ventilators	----	----	----
	% population ages 65 and older	0.58	0.34	0.10
	Number of CT Per 1 million inhabitants	**0.89**	**0.78**	**0.046**
	Number of COVID-19 tests	0.40	0.16	0.23
	Number of COVID-19 tests per 1 M population	0.11	0.01	0.74
Asia (n = 14)	Population (million)	0.39	0.15	0.17
	GDP (trillion)	0.07	0.005	0.81
	Number of hospital beds per 1,000 people	-0.24	0.056	0.42
	Number of ICU beds per 100,000 people	0.11	0.012	0.72
	Number of ventilators	0.32	0.11	0.59
	% population ages 65 and older	-0.39	0.15	0.22
	Number of CT Per 1 million inhabitants	-0.61	0.37	0.39
	Number of COVID-19 tests	0.21	0.044	0.47
	Number of COVID-19 tests per 1 M population	0.09	0.008	0.77
Europe (n=23)	Population (million)	0.38	0.14	0.77
	GDP (trillion)	0.55	0.30	0.27
	Number of hospital beds per 1,000 people	0.24	0.057	0.27
	Number of ICU beds per 100,000 people	0.31	0.094	0.16
	Number of ventilators	0.27	0.073	0.45
	% population ages 65 and older	0.40	0.16	0.06
	Number of CT Per 1 million inhabitants	0.29	0.088	0.25
	Number of COVID-19 tests	0.21	0.045	0.33
	Number of COVID-19 tests per 1 M population	-0.05	0.003	0.81
Africa (n = 1)	-----			
Australia (n = 1)	-----			
High income (n = 31)	Population (million)	0.19	0.036	0.31
	GDP (trillion)	**0.55**	**0.30**	**0.001**
	Number of hospital beds per 1,000 people	0.05	0.003	0.77
	Number of ICU beds per 100,000 people	**0.48**	**0.23**	**0.008**
	Number of ventilators	**0.68**	**0.46**	**0.01**
	% population ages 65 and older	0.034	0.001	0.87
	Number of CT Per 1 million inhabitants	0.04	0.002	0.86
	Number of COVID-19 tests	0.23	0.053	0.21
	Number of COVID-19 tests per 1 M population	0.01	< 0.001	0.95
Lower middle income (n = 15)	Population (million)	0.86	0.74	0.14
	GDP (trillion)	0.79	0.63	0.21
	Number of hospital beds per 1,000 people	-0.54	0.29	0.46
	Number of ICU beds per 100,000 people	0.87	0.75	0.13
	Number of ventilators	----	----	----
	% population ages 65 and older	0.67	0.45	0.33
	Number of CT Per 1 million inhabitants	----	----	----
	Number of COVID-19 tests	0.12	0.015	0.88
	Number of COVID-19 tests per 1 M population	-0.43	0.18	0.57
Upper middle income (n = 4)	Population (million)	-0.03	0.001	0.92
	GDP (trillion)	-0.22	0.047	0.44
	Number of hospital beds per 1,000 people	-0.098	0.01	0.73
	Number of ICU beds per 100,000 people	0.35	0.12	0.39
	Number of ventilators	0.23	0.054	0.85
	% population ages 65 and older	-0.24	0.055	0.42
	Number of CT Per 1 million inhabitants	0.72	0.52	0.28
	Number of COVID-19 tests	0.12	0.014	0.67
	Number of COVID-19 tests per 1 M population	-0.05	0.002	0.87

Fig. 2. Recovery rate (RR) against the number of tests. Lines represent linear regression analysis together with 95% confidence intervals around the line (R^2 = 0.06, P = 0.086).



Tab. IV. The result of subgroup analysis of the association of variables of interest with RR.

Continents	Variables	Standardized beta	R^2	P-value
America (n = 11)	Population (million)	-0.28	0.079	0.40
	GDP (trillion)	-0.11	0.012	0.75
	Number of hospital beds per 1,000 people	0.33	0.11	0.31
	Number of ICU beds per 100,000 people	0.08	0.006	0.93
	Number of ventilators	----	----	----
	% population ages 65 and older	0.63	0.38	0.07
	Number of CT Per 1 million inhabitants	-0.06	0.004	0.92
	Number of COVID-19 tests	-0.09	0.009	0.79
	Number of COVID-19 tests per 1 M population	0.15	0.02	0.66
Asia (n = 14)	Population (million)	0.031	0.001	0.91
	GDP (trillion)	0.26	0.069	0.37
	Number of hospital beds per 1,000 people	0.10	0.01	0.73
	Number of ICU beds per 100,000 people	-0.39	0.15	0.19
	Number of ventilators	-0.31	0.098	0.61
	% population ages 65 and older	0.06	0.004	0.86
	Number of CT Per 1 million inhabitants	0.76	0.58	0.24
	Number of COVID-19 tests	-0.04	0.001	0.90
	Number of COVID-19 tests per 1 M population	-0.43	0.19	0.12
Europe (n = 23)	Population (million)	0.24	0.055	0.28
	GDP (trillion)	**0.58**	**0.34**	**0.004**
	Number of hospital beds per 1,000 people	0.29	0.08	0.18
	Number of ICU beds per 100,000 people	**0.58**	**0.33**	**0.005**
	Number of ventilators	0.33	0.11	0.35
	% population ages 65 and older	0.29	0.08	0.19
	Number of CT Per 1 million inhabitants	**0.51**	**0.26**	**0.04**
	Number of COVID-19 tests	0.26	0.07	0.23
	Number of COVID-19 tests per 1 M population	-0.20	0.04	0.36

▶

▶

Tab. IV. The result of subgroup analysis of the association of variables of interest with RR.

Continents	Variables	Standardized beta	R^2	P-value
Africa (n = 1)	-----	-----	-----	-----
Australia (n = 1)	-----	-----	-----	-----
High income (n = 31)	Population (million)	0.097	0.009	0.61
	GDP (trillion)	0.06	0.004	0.75
	Number of hospital beds per 1,000 people	0.16	0.027	0.38
	Number of ICU beds per 100,000 people	**0.37**	**0.14**	**0.05**
	Number of ventilators	-.006	0.001	0.98
	% population ages 65 and older	0.12	0.015	0.54
	Number of CT Per 1 million inhabitants	0.036	0.001	0.87
	Number of COVID-19 tests	-0.015	0.001	0.94
	Number of COVID-19 tests per 1 M population	-0.19	0.034	0.32
Lower middle income (n = 15)	Population (million)	-0.51	0.26	0.49
	GDP (trillion)	-0.33	0.11	0.67
	Number of hospital beds per 1,000 people	**0.98**	**0.97**	**0.02**
	Number of ICU beds per 100,000 people	-0.25	0.06	0.76
	Number of ventilators	-----	-----	-----
	% population ages 65 and older	0.20	0.043	0.79
	Number of CT Per 1 million inhabitants	-----	-----	-----
	Number of COVID-19 tests	0.21	0.046	0.79
	Number of COVID-19 tests per 1 M population	-0.11	0.013	0.89
Upper middle income (n = 4)	Population (million)	-0.13	0.02	0.65
	GDP (trillion)	-0.32	0.10	0.24
	Number of hospital beds per 1,000 people	-0.035	0.001	0.90
	Number of ICU beds per 100,000 people	-0.26	0.07	0.53
	Number of ventilators	0.62	0.38	0.58
	% population ages 65 and older	-0.24	0.059	0.40
	Number of CT Per 1 million inhabitants	-0.29	0.084	0.71
	Number of COVID-19 tests	**0.71**	**0.50**	**0.003**
	Number of COVID-19 tests per 1 M population	-0.19	0.035	0.51

GPD (R^2 = 0.30, P = 0.001), number of ICU Beds per 100,000 people (R^2 = 0.23, P = 0.008), and the number of ventilators (R^2 = 0.46, P = 0.01) had a significant correlation with CFR in high-income countries. The population in low-middle income countries (R^2 = 0.74) and the number of CT per one million inhabitants (R^2 = 0.52) in upper-middle-income countries are as main predictors of CFR (Tab. III).

However, overall analysis for RR showed that there was no significant correlation between the recovery rate and GPD, population, number of ICU beds, percentage of population of aged 65 and older ages, number of ventilators, number of total COVID-19 tests, number of hospital beds, and number of CT (Fig. 2). Only RR was weakly positively related to the number of COVID-19 performed tests (R^2 = 0.06, P = 0.086) (Fig. 2). Since none of the explanatory variables was significantly correlated to recovery rate, the multiple linear regression model was not fitted. It means that these expletory variables could not be as good as predictors to the recovery rate.

Furthermore, subgroup analysis of RR based on origin continents revealed that GPD (R^2 = 0.34, P = 0.004), number of ICU Beds per 100,000 people (R^2 = 0.33, P = 0.005), and number of CT per one million inhabitants (R^2 = 0.26, P = 0.04) are the significant and main predictors of RR in Europe. In America and Asia, there is no significant correlation between the RR and expletory variables. However, the percentage of population of aged 65 and older ages (R^2 = 0.38) is the important predictor compared to other variables in America, and the number of CT per one million inhabitants is the main predictor of recovery rate in Asia (R^2 = 0.58) (Tab. IV). In addition, the result based on income subgroups showed that the number of ICU Beds per 100,000 people (R^2 = 0.14, P = 0.05) is the significant predictor of RR in high-income countries. The number of COVID-19 tests (R^2 = 0.50, P = 0.003) and the number of hospital beds per 1000 people (R^2 = 0.97, P = 0.02) are positively correlated to RR in upper-middle and lower-middle-income, respectively (Tab. IV).

Discussion

This study was aimed to measure the association of indicators of hospital capacity, age category, and the number of screening tests performed with CFR and RR using up-to-date data from around the world, showed that CFR was positively correlated to the country's GPD, population, number of ICU beds per 100 individuals, number of ventilators and number of total COVID-19 tests performed; however, RR had a weak and positive correlation to the number of COVID-19 performed tests.

In mid-February 2020, in a joint report, CDC and WHO announced that although 80% of all patients with COVID-19 had the mild form of the disease, 13.8% of all confirmed cases had serious symptoms 4.7% were in acute conditions as well [21]. This point prompted healthcare and political authorities in all countries to step up their efforts, asking whether the capacity of the hospitals, especially ICUs, was sufficient for patients with acute and severe conditions. Therefore, if the acceleration of the transmission of the disease continues in its current form, the intensive care unit in hospitals in many countries will collapse due to the high number of such patients. The United States and Germany topped the list with 34.7 and 29.2 beds per 100,000 people, while Philippines and India have 1.0 and 0.56 beds per 100,000 people at the bottom of the list [14-16]. One possible reason is that, despite bearing a good hospital and ICU capacity, the number of beds does not cover the large number of confirmed cases. The COVID-19 disease outbreak has put unprecedented pressure on hospitals, as the number of people infected in the country increases exponentially in a very short time. Thus, doctors have been forced to prioritize patients who were more likely to survive, and the rest are left to their own devices. In line with previous reports, one of the variables that positively correlated with CFR was GDP, which means CFR is associated with countries' income, so high-income countries usually have lower mortality than low-income countries [22, 23]. The possible reasons are life expectancy, health expenditure per capita, and the frequency of underlying diseases [24-26].

Especially in American countries, CFR was significantly correlated with GDP, population density, number of ICU beds, and number of CT scans. In this context, a study reported an increase in the COVID-19 test rate is associated with a decrease in the death rate [27]. Thus, to control or possibly decrease the COVID-19 associated mortality, there could be a need to increase the demand for hospital and ICU beds [28]. Our analyses also showed that COVID-19 related mortality is significantly associated with older population fraction, especially in European countries. In line with our findings, a recent study showed that COVID-19 mortality is mainly observed among older people in European countries, such as Italy [29].

Conclusions

In countries of which the average age of infected individuals is lower (Iran, Brazil, Malaysia, Pakistan, India, and Indonesia), and many of the patients are relatively young and healthy, COVID-19 related mortality is accordingly low. The level of country's preparedness and health care system capacities also are among the important predictors of both COVID-19 associated mortality and recovery. Another factor that may lead to the lower CFR and higher RR is testing far more people, which means detecting more infected people at very early stages could increase the confirmed cases, but not the mortalities. Thus, providing up-to-date information on the main predictors of COVID-19 associated mortality and recovery will hopefully improve various countries hospital resource allocation, testing capacities, and level of preparedness.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: MAK.
Methodology: ASM.
Software: ASM.
Validation: MAK.
Formal analysis: ASM.
Investigation: MAK.
Resources: FR.
Data Curation: FR.
Writing - Original Draft: FR, MAK, ASM.
Writing - Review & Editing: FR, MAK.
Visualization: ASM.
Supervision: MAK.
Project administration: FR.

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Research paper

Knowledge, attitudes and practices towards COVID-19 among nursing students of the University of Palermo: results from an online survey

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Keywords

Knowledge • Attitude • Practice • COVID-19 • University students

Summary

Introduction. *The aim of the study was to evaluate the knowledge, attitude and practices towards SARS-CoV-2 among nursing students of University of Palermo during the rapid rise period of the COVID-19 pandemic.*
Materials and methods. *This is cross-sectional study. A survey was provided to all nursing students and consisted of two parts: demographics and Knowledge, Attitude and Practices (KAP) survey. A multivariate linear regression model was used and adjusted Odds Ratios (aOR) are presented.*
Results. *575 students were interviewed, and their mean age was 22.29 ± 4.2. The overall score indicates good knowledge (p=0.046) and good practices among the four courses of study (p=0.038). Multivariate linear regression showed that Attitude score (β = -0.29; p = 0.024) and Knowledge score (β = 0.10; p = 0.026) adjusted for age, gender, year of study, perceived economic status, perceived health status were significantly associated with Practice score.*
Conclusion. *Our results suggest that proper health education is useful for encouraging optimistic attitudes and maintaining safe practices among future category of nurses.*

Introduction

Coronaviruses (CoVs) are a large family of viruses that circulate worldwide having an extensive range of natural hosts. This family includes common human CoVs, that usually cause mild to moderate upper respiratory tract illnesses, and other human coronaviruses (SARS-CoV, MERS-CoV), that can cause serious infections of the lower respiratory tract, especially in infants, the elderly and immunocompromised individuals [1]. SARS-CoV-2 is a new strain of coronavirus that was never identified in humans before being reported in Wuhan, China in December 2019. On 31th December 2019, a cluster of 27 patients with pneumonia of unknown etiology was reported to local Chinese healthcare authorities in Wuhan City. The Chinese authorities reported that the cause of the outbreak was a novel Coronavirus named "2019-nCoV" [2], which was subsequently named SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus 2). The name was chosen based on genetic similarity to the virus responsible for the SARS epidemic in 2002-2003. So, SARS-CoV-2 is responsible for a disease defined COVID-19 (COronaVIrus Disease-19) [3].
People infected with COVID-19 may have few or no symptoms, although some become seriously ill and die. Symptoms may include fever, general fatigue, myalgia, nasal congestion, dry cough and dyspnea. Those with more severe disease may have remains of lymphopenia and imaging of the chest compatible with pneumonia, as well as severe acute respiratory syndrome, a kidney failure, and even begin to death [4]. In the following weeks, there was an exponential increase in new cases and deaths from COVID-19; then the epidemic spread all over the world, therefore on 11 March 2020 the World Health Organization (WHO) declared the epidemic a pandemic [5]. This new virus has the potential to transmit from person to person, especially in healthcare settings. The exact incubation time is uncertain; estimates vary from 1 to 14 days. Initial estimates of the mortality rate from China (2.3% in the largest series of cases) indicate that it appears to be less severe compared to SARS (10%) or MERS (35%); mortality increases with age [6]. SARS-CoV-2 infection is a highly contagious disease, the current base reproductive rate (R0) of COVID-19 (2-2.5) is still controversial. It is probably slightly higher than SARS R0 (1.7-1.9) and higher than MERS (< 1) [7] with variable case fatality rate that increase for subjects aged 60 or older and in those with comorbidities [8] the Italian national health system has prepared itself for admission of additional critically ill patients as a matter of emergency. Therefore, COVID-19 has proposed a new challenge for healthcare workers (HCWs) and as a

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response to the pandemic, Italian Ministry of Health had appointed several designated hospitals for patients with SARS-CoV-2 infection. These emergency situations certainly require the formation of multidisciplinary teams in hospitals to enable to provide the maximum level of care to critically ill while ensuring the protection of HCWs. However, the occurrence of asymptomatic and subclinical SARS-CoV-2 in community or in healthcare settings could be a huge threat to public health. In view of this, HCWs are at great risk of acquiring this infection or become a source of transmission for patients and their colleagues [9]. In this contest, the access to personal protective equipment (PPE) for HCWs is crucial so that containment measures can reduce the rate of infection [10]. The presence of this fatal virus among HCWs brings into light the urgent need of developing a thorough awareness program by initiating infection control measures to cut down the prevalence rate of this rapid disease. As a result, efforts must focus on the prevention of the disease as well as limiting the complications of existing cases. Therefore, HCWs knowledge, attitude and practice play a major role in the prevention and restrain in complications of SARS-CoV-2 infection, in accordance with KAP theory [11, 12]. The knowledge, attitude and practices (KAP) model is one of the most used models in the medical field; the KAP model suggests that any practices (behaviours) are determined by the person's attitude and knowledge towards the behaviours.

The aim of the study was to evaluate the knowledge, attitude and practices towards SARS-CoV-2 among the nursing students of University of Palermo during the rapid rise period of the COVID-19 pandemic. Hence, understanding nursing students' knowledge attitude and practice regards to SARS-CoV-2 will aid in the development of appropriate and tailored strategies and intervention tools to address poor practices, improve knowledge and change attitudes.

Materials and methods

This cross-sectional survey was conducted on March 2020 the week immediately after the lockdown of Italy. A survey was provided to all nursing students of University of Palermo of the three years of course, accompanied by informed consent. Nursing students who understood the aims of the study and agreed to participate in the study were instructed to complete the questionnaire via clicking a special link. Because it was not feasible to do a community-based national sampling survey during the lockdown, we decided to collect the data online during the lessons. The on-line questionnaire was created using Google forms® and all data was deposited in an electronic database protected by password, known only to the data manager. Ethical approval was given by the local Ethical Committee of the University Hospital Paolo Giaccone of Palermo, No. 03/2020 (13. Studio Sars-CoV-2 - KAP Survey Student) of March 16, 2020. The questionnaire consisted of two parts: demographics and Knowledge, Attitude and Practices (KAP) survey. In the first section of the questionnaire, personal information was requested, relating to the course of study undertaken, the perception of the economic and health status and voluptuous habits. According to guidelines for clinical and community management of COVID-19 by the Ministry of Health of Italy [13], a KAP Survey was designed and modified from previously published research articles [14, 15]. It consists of mainly three sections: Knowledge of nursing students towards COVID-19 in which the options "Yes" or "No" against each set of 13 questions were evaluated; Attitude of nursing students towards COVID-19 in which five options: "Strongly agree (SA)", "Agree (A)", "Undecided (U)", "Disagree (D)", "Strongly disagree (SD)" against each set of 7 questions were used; and Practice of nursing students towards COVID-19 in which the options "Yes", "No" or "Sometimes" against each set of 8 questions were evaluated. Three scores can be obtained from the KAP Survey respectively. The survey instrument assessed the knowledge of nursing students by asking questions about the nature, aetiology, symptoms, risk group, consequences, source of transmission, prevention and treatment of SARS-CoV-2. Knowledge score was assessed by giving 1 to correct answer and 0 to wrong answer. The scale measured knowledge of maximum 13 to minimum 0. Score < 9 were taken as poor while ≥ 9 as good. Assessment of attitude was carried out through item questions in which the responses were recorded on 5-point likert scale: a score of 1 was given to "SA", 2 to "A", 3 to "U", 4 to "D" and 5 to "SD". A mean score of ≤ 2 was considered as positive attitude while score of 3-5 was taken as negative attitude. Questions of practices have an overall practice score that ranged from 0 to 8. From the "yes" option was given a score of 1, from the other options ("no" or "Sometimes") it was given a null score. Finally practice scores were dichotomized to good practice (1 point) with score ≥ 6 or poor practice (0 point) with score < 6. For all qualitative variables absolute and relative frequencies have been calculated; categorical variables were analysed by Pearson's Chi-square test (χ^2). A multivariate linear regression was performed, considering it as a dependent variable "Practice score", in order to evaluate the role of the variables in the first section of the questionnaire. The statistical significance level chosen for all analyses was 0.05. The results were analysed using the STATA statistical software version 14 [16]. Results are expressed as adjusted Odds Ratio (aOR) with 95% Confidence Intervals (95% CI).

Results

A total of 575 nursing students were included (response rate of 99.3%). Table I shows the demographic characteristics of the participants and shows the Knowledge, Attitude and Practice scores. The study showed that the mostly participants were female (68.7%) and the mean age was 22.29 ± 4.23. In relation to the year of study, 34.3% of participants

reported attending the first year of study, 32.2% in the second year, 24.9% in the third year and 8.70% were off course. Moreover 20.5% reported a low economic status whilst 90.9% enjoy a medium-high health status. For more details see Table I. Figure 1 describes the current status about SARS-CoV-2 knowledge among nursing students. A total of 554 (94.6%) respondents showed good knowledge while 31 (5.4%) of nursing students had poor knowledge of SARS-CoV-2. The study showed that poor knowledge was more apparent in response to questions regarding the aetiology, risk group, incubation time, correct timing for washing hands with soap, diagnosis and treatment of SARS-CoV-2 in which the rate of incorrect responses were 28.9, 30.6, 56.3, 94.8, 42.1 and 19.3% respectively.

Tab. I. Description of the sample (n = 585).

		N (%)
Gender	Male	180 (31.30)
	Female	395 (68.70)
Year of study	First	197 (34.26)
	Second	185 (32.17)
	Third	143 (24.87)
	Off-course	50 (8.70)
Perceived economic status	Medium-high	457 (79.48)
	Low	118 (20.52)
Perceived health status	Medium-high	523 (90.96)
	Low	52 (9.04)
Knowledge score	Good knowledge	554 (94.60)
	Poor knowledge	31 (5.40)
Attitude score	Positive attitude	521 (90.60)
	Negative attitude	54 (9.40)
Practice score	Good practice	511 (88.87)
	Poor practice	64 (11.13)
Mean age	22.29 ± 4.23	

Mean knowledge score of nursing students was 10.2 ± 1.14. Figure 2 show the current status about SARS-CoV-2 attitude among nursing students. Of 575 respondents, 521 (90.6%) showed positive attitude while 54 (9.4%) participants displayed negative attitude about SARS-CoV-2. Mean attitude score of nursing students was 1.5 ± 0.39. The most negative attitude was shown when asked whether their own participation in infection control program could reduce the prevalence of SARS-CoV-2. Conversely, majority of participants responded positively when queried about the use of protective measures and the importance of share information about SARS-CoV-2. Figure 3 describes the practices of the studied samples regarding infection control measures. The overall mean practice score was 6.9 ± 1.20. The most of the studied sample (88.9%) reported good practice and 11.1% reported poor practice. Items and relative answers are summarized in Figure 3. Table II shows bivariate associations between knowledge, attitude, practice score and years of university course attended. The overall score indicates good knowledge among first year (95.4%), second year (95.6%), third year (95.1%) off-course (86.0%) and showed statistically significant (p = 0.046). In a similar way, the overall score indicates good practices among first year (93.9%), second year (87.6%), third year (85.3%) off-course (84.0%) and showed statistically significant (p = 0.038). No statistically significant results were showed for the overall score of attitudes. Multivariate linear regression showed that Attitude score (β = -0.29; p = 0.024) and Knowledge score (β = 0.10; p = 0.026) adjusted for age, gender, year of study, perceived economic status, perceived health status was significantly associated with Practice score (Tab. III).

Fig. 1. Knowledge of the studied sample about SARS-CoV-2 infection.

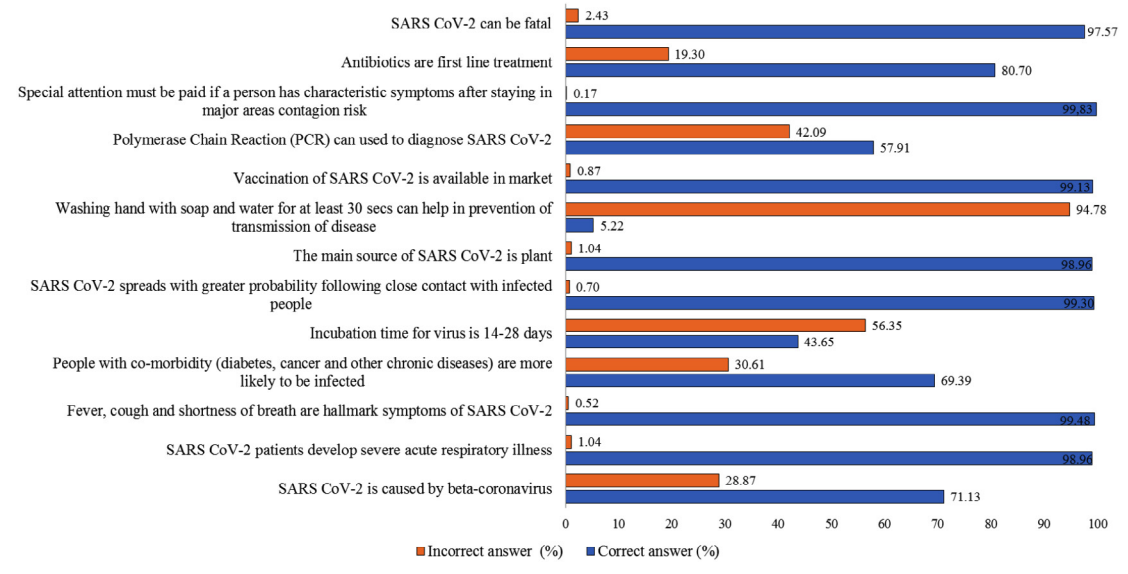
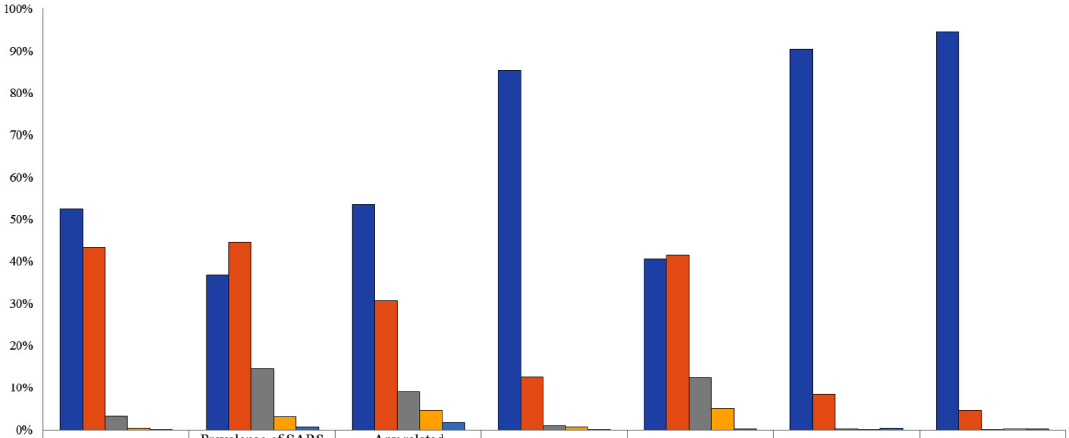
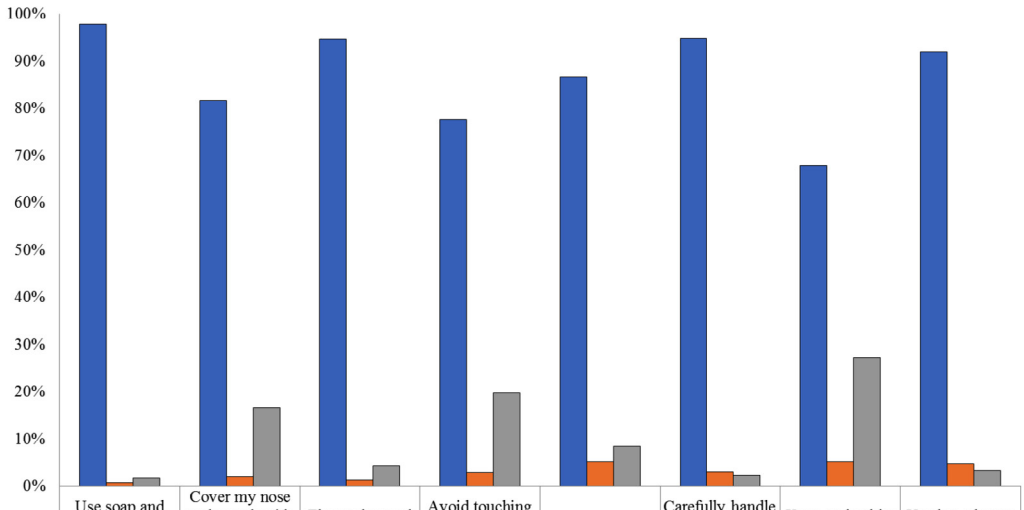


Fig. 2. Attitude of the studied sample towards SARS-CoV-2 infection (SA = strongly agree, A = agree, U = undecided, D = disagree, SD = strongly disagree).



	Transmission of SARS CoV-2 infection can be prevented by using universal precautions given by CDC, WHO	Prevalence of SARS CoV-2 can be reduced by active participation of HCWs in hospital infection control program	Any related information about SARS CoV-2 should be disseminated among peers and other HCWs	SARS CoV-2 patients should be kept in isolation	Intensive and emergency treatment should be given to diagnosed patients	HCWs must acknowledge themselves with all the information about SARS CoV-2	Gowns, gloves, mask and googles must be used when dealing with SARS CoV-2 patients
SA	52,52%	36,87%	53,57%	85,39%	40,52%	90,43%	94,43%
A	43,48%	44,70%	30,78%	12,70%	41,39%	8,52%	4,70%
U	3,30%	14,61%	9,04%	1,04%	12,52%	0,35%	0,17%
D	0,52%	3,12%	4,70%	0,70%	5,22%	0,18%	0,35%
SD	0,18%	0,70%	1,91%	0,17%	0,35%	0,52%	0,35%

Fig. 3. Practices of the studied samples regarding infection control measures.



	Use soap and water to wash my hands continuously	Cover my nose and mouth with a tissue during sneezing or coughing	Throw the used tissue in the trash	Avoid touching my eyes, nose or mouth as far as I can	Use face mask in crowds	Carefully handle suspected patient's belongings	Keep on healthy eating and health styles	Used to educate clients about the disease
Yes	97,73%	81,57%	94,61%	77,57%	86,61%	94,78%	67,83%	92,00%
No	0,70%	1,91%	1,22%	2,78%	5,04%	2,96%	5,04%	4,70%
Sometimes	1,57%	16,52%	4,17%	19,65%	8,35%	2,26%	27,13%	3,30%

Tab. II. Mean score of knowledge, attitude and Practices of nursing students about SARS-CoV-2.

	Knowledge N (%)			Attitude N (%)			Practices N (%)		
	Good	Poor	P-value	Positive	Negative	P-value	Good	Poor	P-value
First year	188 (95.43)	9 (4.57)	0.046	175 (88.83)	22 (11.17)	0.220	185 (93.91)	12 (6.09)	0.038
Second year	177 (95.68)	8 (4.32)		168 (90.81)	17 (9.19)		162 (87.57)	23 (12.43)	
Third year	136 (95.10)	7 (4.90)		135 (94.41)	8 (5.59)		122 (85.31)	21 (14.69)	
Off-course	43 (86.00)	7 (14.00)		43 (86.00)	7 (14.00)		42 (84.00)	8 (16.00)	

Used Pearson chi-square test.

Tab. III. Multivariate linear regression. Each independent variable is adjusted for the other independent variable and for age, gender, year of study, perceived economic status, perceived health status. Based on 575 observations.

	Dependent variable: practice score		
Independent variables	β	95% CI	P-value
Attitude score	-0.29	-0.54/-0.04	0.024
Knowledge score	0.10	0.01/0.18	0.026

$R^2 = 0.04$.

Discussion

To date, April 6th, 2021, according to data published daily by the WHO [17], Italy is the second Country in European Community in terms of confirmed cases of COVID-19 with the sad primacy of deaths, and only 10% of the population received at least the first dose of the vaccine. The contrast action at SARS-CoV-2 has involved healthcare professionals, and in our KAP Survey we analyse the knowledge, attitude and practices of the students of the nursing degree course in relation to SARS-CoV-2. Among the students of the nursing degree course of the University of Palermo there is a good general knowledge of SARS-CoV-2, in accordance with what emerges in literature as regards medical students [18], considered the absence of data for similar studies on nursing students. As specified in Table II, 94.6% of the students obtained a score ≥ 9, although as can be estimated from the percentages of exact answers especially to questions K5-K8-K10, the increase in the degree of detail of the question corresponds the decrease in the percentage of correct answers. More specifically, the respondents present a greater knowledge of the symptoms of SARS-CoV-2 infection, of the transmission modalities, and on the availability of a vaccine, as evidenced by the exact answers to questions K2-K3-K6-K7-K9-K11-K13 (Fig. 1) and intermediate knowledge in relation to the characteristics of the virus and the treatment of the disease, as evidenced by the answers to questions K1-K4-K5-K10-K12 (Fig. 1). Special mention for question K8 ("Washing hand with soap and water for at least 30 secs can help in prevention of transmission of disease"), which has just 5.22% of correct answers from students, probably confused from the temporal data reported in question K8 (30 secs), in line with the times suggested on the portal dedicated to SARS-CoV-2 of the Italian Ministry of Health [19, 20]. We can say that there is a degree of knowledge inversely proportional to the difficulty of the question. The "attitude" parameter, in absolute value, improves from the first to third year of the course of study as reported in Table II, more specifically, among the interviewees there was greater indecision ("U") and disagreement ("D") for questions A2-A3-A5 as shown in Figure 2, all questions that directly concern the communication between HCWs and between hospitals and HCWs [21]. A good method to avoid information overload for health professionals who are on the front line, considering that we are experiencing a historical moment in which the influx of new information is extremely rapid and from multiple sources (hospital administration, scientific societies, departments of prevention, social media, guidelines on the use of PPE, etc.) could be the creation of short summary documents with the most up-to-date information, allowing healthcare workers to read up quickly, avoiding the stress of having to draw from multiple sources [22], summaries should be created using data from official sources. The Practices parameter worsens from the first to the third year of the degree course, but overall the interviewees have habits, in most cases, substantially correct, exception made for P2-P4-P7 (Fig. 3), for which the response "Sometimes" highlights how the habit of "Cover nose and mouth with a tissue during sneezing or coughing", "Avoid touching my eyes, nose or mouth as far as I can "," Keep on healthy eating and health styles "have not yet been perfectly metabolized by a portion of the students. We underline that in our study Knowledge - Attitude - Practices (KAP) on SARS-CoV-2 the increase in knowledge scores ("K" Score) was significantly associated with a lower probability of negative attitudes ("A" Score low) and finally an improvement of the practice (increase of the "P" Score). The results of our KAP Survey on the students of the Nursing degree course of the University of Palermo, although positive, highlight the importance and the need to improve some aspects of the knowledge of SARS-CoV-2, which, consequently, can also lead to improvements in their attitudes and practices [23]. To ensure ultimate success against SARS-CoV-2, the adherence of subjects to social distancing and prevention measures is fundamental but is largely influenced by their knowledge, attitudes and practices (KAP) against the virus and disease, according to the KAP theory [11, 12].

Study limitations

The results of this study should be used with caution for generalization as it describes the situation of nursing students in an area of Sicily (University of Palermo), Southern Italy, this may not allow the results to be generalized to other locations and cities. Additionally, self-reporting practices may not be effective; therefore further studies are warranted. In addition, the KAP measurement may be inaccurate due to different classification systems. The other limitation is that participants could give socially acceptable responses. For goodness of fit of the predictor model on practice, the $R^2 = 0.04$ is rather low to describe determinant factors; other factors need to be explored in future research.

Conclusions

Our results suggest that nursing students of the University of Palermo have a good knowledge of SARS-Cov-2, associated with positive attitudes and appropriate practices towards COVID-19 during the epidemic; however, some of them show gaps about aetiology, risk

factors, diagnosis, transmission and treatment of the virus. Part of the sample shows the most negative attitude when asked whether their participation in the infection control program is necessary to prevent the prevalence of SARS-CoV-2. Nonetheless, they reported adequate practices towards infection. This requires interventions for a proper health education. However, there must be effective and timely communication from the Ministry of Health on the pandemic and good practices through online seminars and in hospitals. The benefits of safe practices such as hand hygiene, maintaining a safe social distance and wearing masks go far beyond containing SARS-CoV-2 disease, in fact it could be an opportunity to implement these practices and make them permanent. Health education programs are useful for encouraging optimistic attitudes and maintaining safe practices, and undoubtedly the highest and noble purpose is prevention. Health education is an essential component of the defence and promotion of health, where surveillance and infection control measures are basic for global public health and certainly this is a topic that fully affects the future category of nurses or other HCWs.

Ethical approval

This study was approved by the Ethical Committee of the University Hospital "P. Giaccone" of Palermo, Minutes No. 03/2020 (13) of March 16, 2020.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

AF, SP and OES conceived, designed, coordinated and supervised the research project. SP and OES performed the data quality control, optimized the informatics database, OES performed the statistical analyses and evaluated the results. SP, OES, FA, GP, AA, ML, AT, GD and AF wrote the manuscript. All Authors revised the manuscript and gave their contribution to improve the paper. All authors read and approved the final manuscript.

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Research paper

Psychosocial Impact of COVID-19 among Young Bangladeshi Adults (18-34 years): An Online-Based Cross-Sectional Study

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Keywords

Coronavirus • COVID-19 • Knowledge • Perception • Behavior

Summary

Objectives. *COVID-19 pandemic is at the fourth stage of boundless local transmission in Bangladesh. The objective of this study was to assess the psychosocial impact of COVID-19 on adult Bangladeshi population.*
Design. *Online-based cross-sectional study.*
Settings. *Data were collected from different parts of the Bangladesh.*
Participants. *Information was collected from 213 young adults who were aged 18-34 years old using convenient sampling technique.*
Results. *More than 90% of participants were responded to possess a good awareness of COVID-19. However, the behavioral characteristics of young individuals in Bangladesh were not impressive. In this cohort, 24.4% of participants showed moderate change and 5.2%-little changes in their behavior due to COVID-19. Approximately 58.2% of participants had some symptoms of mental distress while 59.7% of participants were somewhat worried about COVID-19.*
Conclusion. *In order to control the spread of Covid-19, existing unconsciousness in young adult could turn this situation into a disaster throughout the nation which therefore must be understood by the government and policymakers to incorporate successful measures.*

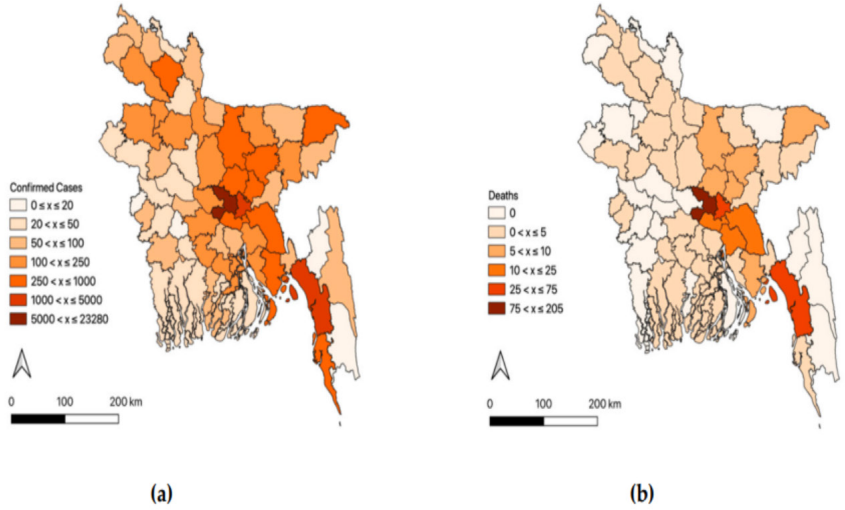
Introduction

World Health Organization (WHO) had declared the outbreak of COVID-19 as a major public health concern after largely expanding across the China and worldwide on 30 January 2020 [1]. On 8 March 2020, Bangladesh found the first coronavirus cases in Dhaka, the capital of Bangladesh [2]. After that, the number of people with positive COVID-19 cases began to spread in this city. Then people get scared and a nationwide lockdown of all educational centers as well as private and government offices had taken place to avoid human transmission from 26 March till 30 May 2020.However, shortly after the lockdown declaration, more than 11 million people started leaving their work place from Dhaka to go into their home districts which further accelerates the risk of COVID-19 in other districts throughout Bangladesh. Observing population density, environmental factors, cultural norms, social structure, and healthcare capacity, it is undoubtedly challenging to install lockdown in Bangladesh [3]. During this novel coronavirus pandemic, humanitarian crises have arisen already into the country, and in most incidents, it will be the combined effects of a variety of shortages that will very likely to culminate in the worst outcomes it's about USA, not relevant with this paper [4, 5]. The recent scenario of the pandemic in Bangladesh is given in Figure 1 [6].

Within four months of its outbreak, that is, by June 15, 2020, 11,474,717 people had been infected worldwide, of whom 6,491,306 had recovered and 535,097 had died. Two hundred and thirteen countries and territories have already been affected, while Bangladesh ranked 17th with 102,292 COVID-19 cases based on June 18, 2020 report and thus become one of the most infected countries in the world [7].

In Bangladesh almost 98% of people know about the pandemic, COVID-19 but the knowledge about its transmission and prevention and perception towards COVID-19 is not sufficient and is also correlated with people's age and profession [8]. In our neighbor country India, it is stated that 43% of people described COVID-19 as a highly contagious disease while only 18.2% regarded fever as a common symptoms of COVID-19. The attitude and anxiety regarding coronavirus among people are much observed [9]. Because of the widespread availability, large genetic variation, and regular recombination, in association with the increased time humans spend in the appearance of animals, coronaviruses may often mutate to infect human hosts. Coronavirus is usually transmitted by airborne droplets into the nasal mucosa and through close touch between individuals, unwashed hands,

Fig. 1. District wise Map of the present situation of COVID-19 pandemic in Bangladesh (May 25, 2020) [6].



(a) (b)

and infrequently as a result of touching infected surfaces in closed environments [10]. Coronaviruses typically cause enteric and central nervous system (CNS), acute and chronic respiratory diseases in many species of animals including humans. There has also been considerable evidence that human coronaviruses are linked with more severe human diseases, such as multiple sclerosis [11], enteric disease, or hepatitis [12] in infants. In 2004, Ding et al. reported that, the disease may have a death rate of around 10%, but it reached nearly 50% in older people, which is a very high incidence compared to other viral diseases [13]. Governments of all countries in the world are working already to put in place countermeasures to stem potential devastating effects. The present study aimed to assess awareness about coronavirus, behavioral changes, and psychological distress caused by coronavirus in Bangladeshi young adults (18-34 years).

Methods

Survey instrument and dissemination

An online-based cross-sectional survey was performed during the first week of May 2020 and responses were collected from Bangladeshi young adults from different parts of the country. The duration of this study was from May, 2020 to June, 2020. The survey covered the participant's demographic characteristics, awareness about coronavirus, behavioral changes, and psychological distress caused by coronavirus.

Inclusion and exclusion criteria

The study included respondents aged between 18 to 34 years old. Prior to the start of the interview, each individual provided written informed consent through online. There was no on-going vaccination program in Bangladesh during the study period. This research focused mostly on young adults, both male and female. Respondents who had previous history of mental instability or were in rehabilitation due to drug or any other addiction at any time in their life, or respondents, who refused consent or were unable to interact properly during data collection were excluded from the study.

Sampling technique and sample size

Around 13% of Bangladeshi used the internet in a population of 162 million, where approximately 25% were young adults. A 23-item overview instrument was adopted utilizing WHO course materials on developing respiratory viruses, including COVID-19 [14]. The developed draft study instrument was made available via a link and was transferred to 10 specialists from various geographic regions to comprehensively evaluate the content domains of the questionnaire. As our sampling frame was 18-34 years old young adults who are familiar with the internet and regularly use online social media, at first, we had collected our data through convenient sampling technique for determining sample size, considering around 267 respondents from a pool of 800 to 1,000 young adults as the population size for this study [15]. A pilot online study was then also undertaken to standardize the questionnaire. A variety of data quality methods was implemented in the survey to ensure the validity of responses and to filter out those who did not fulfill the inclusion requirements. The poll was piloted by the research group as a quality control method (n = 10) before appearing online on social networking sites.

Individuals were excluded from the data if:

- the participant (n = 14) browsed the online questionnaire but did not finish any of the measures;
- the participant (n = 26) did not give complete informed consent;
- the participant did not contain the inclusion requirements (i.e., 18-34 years old, n = 14);
- the minimum completion speed was increased at 10 minutes, which was half of the sample's median completion time;

Tab. I. Scoring categories.

Scores	Category
50% or less	Poor awareness/Poor behavioral characteristics
50-75%	Moderate awareness/Moderate behavioral characteristics
75% or above	Good awareness/Good behavioral characteristics

- although the data were reviewed for consistency of responses, no responses were eliminated based on this criterion;
- there were 213 participants as a result of this;

Variable and scores

For data collection, a structured questionnaire was developed in Bangla from the original version. A pilot survey was conducted online (via Google Forms) to standardize the questionnaire. The pilot survey confirmed the content validity of our questionnaire by both the 10 experts (doctors and psychologist-dealing with patients affecting with COVID-19) and 10 lay persons (literate, aged more than 18 years, not dealing with any COVID-19 patients) [16] and following this pilot research, we modified the questionnaire based on the respondents' responses to each question and their understanding of the questions we asked during the pilot research to ensure that our tool (questionnaire) is reliable to see the psychosocial impact of study participants. Cronbach's alpha (α) test was used to determine the questionnaire's reliability, which was 0.78.

We used Google Forms as a tool for online survey to distribute the survey questionnaire, and participants were given 15 minutes to read, comprehend, and answer all the questions.

Awareness was assessed by questions focusing on COVID-19 transmission, signs, and symptoms, and risk prevention while behavioral characteristics towards COVID-19 were assessed using 9 items. Each response on awareness and behavioral characteristics towards coronavirus (COVID-19) was collected with scores ranging from 0-1 (Tab. I). According to Likert scale, correct responses were scored "1" and incorrect responses were scored "0". The scoring was categorized based on author's discretion where, sum of scores below 50th percentile was considered as having poor awareness and behavioral changes and above 75th percentile as good awareness and behavior changes among participants. If the sum of scores ranges from 50 to 75%, moderate level of awareness and behavior changes due to sudden arrival of COVID-19.

Statistical analysis

The data obtained were coded and analyzed using IBM SPSS version 26.0 (IBM SPSS Statistics Inc, Chicago, IL, USA). The data were analyzed for percentages, mean for continuous variables, standard deviation and, frequency measured for the categorical variables. Chi-square test was employed to assess the degree of correlation between dependent (good, moderate, poor knowledge, respondent's characteristics (sex, living area) and independent variables (awareness changes, behavioral changes). A chi-square test was performed to determine the strength of correlation of the independent variables with the outcome variable. The level of significance for all statistical tests was set at 0.05.

Ethical consideration

This work was carried out in compliance with the ethical guidelines of the Declaration of Helsinki. Prior to the survey, the respondents' permission was taken, and they remained anonymous. Until continuing to fill out the questionnaire, all the participants were told about the specific objective of this study. Participants were only able to complete the survey once and could terminate the survey whenever they wished. Anonymity and confidentiality of the data were ensured. Formal ethical permission of this study was obtained from the respective authority (i.e., Noakhali Science & Technology University, Sonapur, Noakhali, Bangladesh).

Results

Overview

Table II shows the socio-demographic characteristics of the participants. From a total of 213 young adults, comprising 72% (n = 154) male and 28% (n = 59) female. All participants were between18-34 years of age. The majority of the participants were living in urban settings (n = 130, 61%) and the rest of others were from the rural area (n = 83, 39%). Approximately 74% (n = 158) of

Tab. II. Socio-demographic characteristics of young age populations (n = 213).

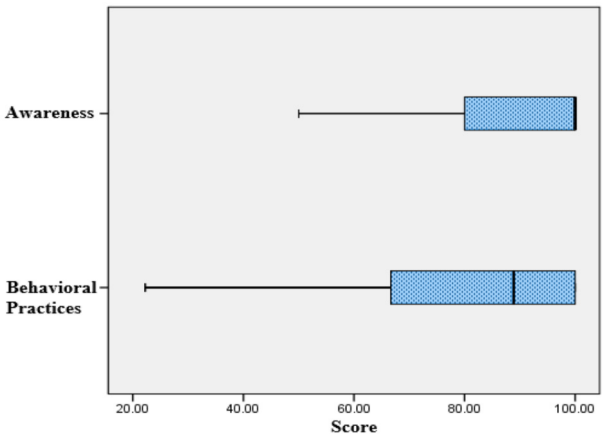
Characteristics	Frequency (%)
Gender	
Female	59 (28%)
Male	154 (72%)
Living area	
Urban	130 (61%)
Rural	83 (39%)
Age group (years)	
18-24 years	20 (10%)
25-29 years	158 (74%)
30-34 years	35 (16%)
Education level	
High school diploma or equivalent	35 (16%)
Undergraduate	142 (67%)
Graduate	36 (17%)
Religion	
Muslim	201 (94%)
Hindu	10 (5%)
Christian	2 (1%)
Marital status	
Single	158 (74%)
Married	55 (26%)

Tab. III. Distribution of frequencies on awareness about Coronavirus and behavioral characteristics changes caused by Coronavirus in Bangladeshi young adults (n = 213).

Scoring category	Awareness, n (%)	Behavior change, n (%)
[a] Good	195 (91.5%)	150 (70.4%)
[a] Moderate	17 (8.0%)	52 (24.4%)
[a] Poor	1 (0.5%)	11 (5.2%)

N = number of participants. A P-value < 0.05 was considered statistically significant. Scores sharing a common superscript indicates significant differences between awareness and behavior changes.

Fig. 2. Box plots showing distribution of scores by awareness, behavioral practices towards COVID-19.



the participants in this study were single. Among the respondents, 142 respondents (67%) have undergraduate degree, and most of the participants 94% (n = 201) were Muslims in terms of religion.

The data (Tab. III) showed that 91.5% of young adults had good, 8.0% had moderate, while only 0.5% of young adults had poor awareness about COVID-19. Merely 70.4% of young adults had good, 24.4% had moderate, and only 5.2% showed poor behavioral characteristics on COVID-19. Statistically significant differences were observed (P < 0.05) between awareness and behavior characteristics scores among the participants.

Box plots (Fig. 2) of the awareness scores (90.61 ± 13.25) showed that youngest adults had a good awareness of COVID-19 while the behavioral characteristics scores (81.32 ± 17.90) had lower than the awareness scores.

Source of information

When we asked about the reliable sources of information towards COVID-19, the primary sources listed as social media and official websites of the Bangladesh government. Approximately 30.0 percent (n = 63) of participants reported using social media (Facebook, WhatsApp, Twitter, YouTube, Snapchat, Instagram) and news media (TV, newspapers, magazines, and radio) to access information about COVID-19. In addition, approximately 70.4% (n = 150) of the participants often discussed with their family and friends about COVID-19-related topics.

Tab. IV. Young adult participants' knowledge of COVID-19 (n = 213).

Statement	Yes, n (%)	No, n (%)
[a] COVID-19 is transmitted through air, contact, fecal-oral routes	199 (93%)	14 (7%)
[a] Headache, fever, cough, sore throat, and flu are symptoms of aCOVID-19	194 (91%)	19 (9%)
COVID-19 leads to pneumonia, respiratory failure, and death	198 (93%)	15 (7%)
[a] Supportive care is the current treatment for COVID-19	175 (82%)	38 (18%)
[a] Hand hygiene, covering nose and mouth while coughing, and avoiding sick contacts can help in the prevention of COVID-19 transmission	199 (93%)	14 (7%)

N = number of participants. A P-value < 0.05 was considered statistically significant. Scores sharing a common superscript indicates significant differences between two responses: Yes and No.

Awareness about COVID-19

More than 91.5% (n = 195) of young adults showed good awareness of COVID-19. The majority of young adults expressed that COVID-19 is transmitted via fecal-oral routes, contact, air (n = 199, 93%).194 individuals (91%) expressed that fever, cough, headache, sore throat, and flu are symptoms of COVID-19 while 198 individuals (93.0%) also expressed that COVID-19 leads to respiratory failure, pneumonia, and death. Additionally, 82% (n = 175) did feel that supportive care is now being used for treating COVID-19, and 93% (n = 199) agreed on covering the nose and mouth while coughing& sneezing, frequent practice of hand hygiene, and avoiding sick contacts can help prevent COVID-19 transmission (Tab. IV).

Behavioral characteristics of COVID-19

Items related to behavioral characteristics among young adults were assessed using a chi-square test to examine their correlation with sex (Tab. V) and living areas (Tab. VI). Nearly 34.6% (n = 45) of participants from urban settings and 31.2% (n = 48) of the males had gone outside their home for job purposes; the differences among groups were statistically significant (P < 0.05). In addition, 73 participants (56.2%) from urban settings had gone to supermarkets, grocery stores, or pharmacies. 36.2% (n = 47) of participants from urban settings and 32.5% (n = 50) males were found spending leisure times with outsiders and these findings were statistically significant (P < 0.05).

Even 17.7% (n = 23) of participants from urban settings were significantly found to attend public

Tab. V. Correlation between respondents' characteristics and behavioral changes of coronavirus disease 2019 (COVID-19) (based on gender).

Question and response	Female, n (%)	Male, n (%)
[a] Gone outside home for job purposes		
Yes	4 (7%)	48 (31%)
No	55 (93%)	106 (69%)
[a] Gone to supermarkets, grocery stores, or pharmacies		
Yes	11 (19%)	73 (47%)
No	48 (81%)	81 (53%)
Gone to restaurants, cafes or shopping centers		
Yes	0 (0.0%)	6 (4%)
No	59 (100%)	148 (96%)
[a] Spent leisure times with outsiders		
Yes	6 (10%)	50 (33%)
No	53 (90%)	104 (68%)
Attend public events		
Yes	4 (7%)	21 (14%)
No	55 (93)	133 (86%)
[a] Used public transportation for travel mode use		
Yes	1 (2%)	15 (10%)
No	58 (98%)	139 (90%)
Avoid social distancing		
Yes	13 (22%)	39 (25%)
No	46 (78%)	115 (75%)
Wash hands with soaps after public gatherings		
Yes	53 (90%)	133 (86%)
No	6 (10%)	21 (14%)
Used face masks in outdoor gatherings		
A little of the time	2 (3%)	6 (4%)
All of the time	36 (61%)	90 (58%)
Most of the time	14 (24%)	33 (21%)
None of the time	4 (7%)	9 (6%)
Some of the time	3 (5%)	16 (11%)

Data were collected from 154 male and 59 female adults aged 18 to 34 years throughout Bangladesh. N = number of participants. A P-value < 0.05 was considered statistically significant. Scores sharing a common superscript indicates significant differences between gender.

events ($p < 0.001$). 9.7% (n = 15) of males used public transportation for *travel* mode *use* (n = 14, 10.8%), and 25.3% (n = 39) males avoid social distancing where this nature is also common in urban participants (n = 46, 35.4%) ($p < 0.05$). A large number of participants from urban settings used face masks in outdoor gatherings (n = 82, 63.1%) although the result was not significant ($p > 0.05$) and 111 individuals (85.4%) have the nature of washing hands with soaps after public gatherings.

Clinical symptoms of COVID-19 among young age participants

In our study, 16.9% of participants suffered from headaches, aches and 13.6% had neck pain, and 8.9% had a stuffy or runny nose. Only 2.8, 5.2, and 5.6% of participants respectively suffered from fever, sore throat, and fatigue.

Psychological distress during COVID-19

In our study, 42.8% (n = 91) of participants had no feelings of distress about COVID 19. However, 58.2% (n = 122) of participants had some symptoms of mental distress regarding COVID-19. On the other side, 41.3% (n = 88) of participants were not worried about COVID-19 while 59.7% of participants (n = 125) were somewhat worried about COVID-19.

Discussions

Globally, COVID-19 is a subject of debate among the public and in the media, particularly among young age groups. With the mounting transmission of coronavirus disease, an important question arises as to how we are implementing positive health messages in times of pandemic to assist in reducing the spread. In searching for the answer, we were investigating the awareness about Coronavirus, behavioral changes, and psychological distress caused by coronavirus in Bangladeshi young adults (18-34 years). Awareness and behavioral characteristics towards COVID-19 vary across various categories of young age participants. Our study reported that young age participants have satisfactory awareness about COVID-19 but the behavioral changes are not satisfactory as it may fuel spread.

Most participants were living in urban areas. An age-based study based on coronavirus patients found that 20% of the infected cases were found between 21-30 years, followed by 23% between 31-40 years, and 19% between 41-50 years of age [17]. Mainly young age population is at risk group because the median age of Bangladeshis is 27.1 years [18].The outbreak of the COVID-19 disease in the country is rising with days as lack of behavioral characteristics is commonly

Tab. VI. Correlation between respondents' characteristics and behavioral changes of coronavirus disease 2019 (COVID-19) (based on living area).

Question and response	Living area	
	Urban, n (%)	Rural, n (%)
[a] Gone outside home for job purposes		
Yes	45 (35%)	7 (8%)
No	85 (65%)	76 (92%)
[a] Gone to supermarkets, grocery stores, or pharmacies		
Yes	73 (56%)	11 (13%)
No	57 (44%)	72 (87%)
[a] Gone to restaurants, cafes or shopping centers		
Yes	6 (5%)	0 (0.0%)
No	124 (95%)	83 (100%)
[a] Spent leisure times with outsiders		
Yes	47 (36%)	9 (11%)
No	83 (64%)	74 (89%)
[a] Attendpublic events		
Yes	23 (18%)	2 (2%)
No	107 (82%)	81 (98%)
[a] Used public transportation for travel mode use		
Yes	14 (11%)	2 (2%)
No	116 (89%)	81 (98%)
[a] Avoided social distancing		
Yes	46 (35%)	6 (7%)
No	84 (65%)	77 (93%)
Wash hands with soaps after public gatherings		
Yes	111 (85%)	75 (90%)
No	19 (15%)	8 (10%)
Used face masks in outdoor gatherings		
A little of the time	5 (4%)	3 (4%)
All of the time	82 (63%)	44 (53%)
Most of the time	27 (21%)	20 (24%)
None of the time	3 (2%)	10 (12%)
Some of the time	13 (10%)	6 (7%)

Data were collected from 130 urban and 84 rural adults aged 18 to 34 years throughout Bangladesh. N = number of participants. A P-value < 0.05 was considered statistically significant. Scores sharing a common superscript indicates significant differences between living area (urban and rural).

practiced by its population which in future will surely bring a disaster if the intergenerational households do not take preventive steps right now. This form of transmission of disease probably contributed to the overall illness burden in Bangladesh.

Preventing the transmission of COVID-19 depends mostly on proper health knowledge, hand hygiene practices, adequate staff training, and in particular, appropriate personal behavior. It is recommended that social and physical distancing interventions prevent transmission of coronavirus [6, 7, 13, 14, 19, 20]. Many preventive measures and actions have been taken by canceling or postponing major events such as sports events, festivals, ceremonies, conferences, and other types of public events. Such measures, of course, have the potential to reduce cases and, if successful, will require fewer people to seek health care, thus reducing the burden on the healthcare system [21]. Many measures to incorporate social and physical distance include working from home, online home-based learning for students at school and university, teleconferencing instead of face-to-face meetings have already been taken [22].

Current findings showed that psychological distresses caused by coronavirus in Bangladeshi young adults (18-34 years) were more common. Furthermore, pandemic-related measures such as isolation, social distancing, quarantine, and economic distress can also trigger psychological mediators such as worry, depression, dissatisfaction, anger, anxiety, frustration, nervousness, and loneliness. These are the characteristic features of typical mental health distress that many individuals endured during and after the crisis [23-26]. Finally, as indicated by researches, the role of a psychiatrist during a pandemic like COVID-19 should include: (i) informing people about common adverse psychological effects, (ii) encouraging health-promoting behaviors among individuals, (iii) incorporating available health-care services [22], (iv) promoting problem-solving, (v) inspiring patients, their families, and health-care [24].

The use of proper statistical analysis techniques has strengthened this article with high response rate. Additionally, using well-designed questionnaire controls inter-rated biases. However, this study is not without limitations. Firstly, the study was online-based which may have introduced respondent bias. Secondly, the study was conducted with low sample size and finally, cross-sectional study may limit the use findings for causal inference.

Conclusions

The findings suggest that most of the Bangladeshi youth populations possess good awareness, but their behavioral characteristics towards COVID-19 were not impressive. In addition, awareness and behavioral characteristics are related to demographic features. Mass awareness programs and proper educational strategies would help boost to adopt preferable behavioral characteristics to control disease spread. Effective preventive steps, guidelines, and healthy practices must be enforced by different government agencies while the assistance of professional *organizations* and academic institutions is also necessary. Additionally, citizens must need to comply with the WHO guidelines. The results of this research would be very useful to public health decision-makers and health professionals. Hoping that with the joint efforts of people and the Bangladesh Government, the country will win the fight against the COVID-19 pandemic unquestionably.

Ethical approval

The ethical approval for this study was taken from Ethics board of Noakhali Science and Technology University.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MAH has designed the study and contributed on the data collection, data analysis, interpretation and the manuscript writing. RJR has contributed on data collection. TR and AIC have contributed on data analysis, interpretation and manuscript writing as well. MAZ has critically review the manuscript and made final version of paper as well.

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Research paper

Psychological state, family functioning and coping strategies among undergraduate students in a Nigerian University during the COVID-19 lockdown

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Keywords

COVID-19 • Anxiety • Depression • Family functioning • Coping

Summary

Introduction. *The curtailment of social gatherings and the lack of online academic engagement during the COVID-19 lockdown could have potentially damaging effects on the psychological state of university students in Nigerian public universities. This study examined the prevalence of anxiety and depression, including associated factors and coping methods, among undergraduate students.*
Methods. *This cross-sectional study, which involved 386 undergraduate students, was assigned approval number UI/EC/20/0242. An online questionnaire consisting mainly of the Hospital Anxiety and Depression Scale and the McMaster Family Assessment Device was circulated among the students. The results were analysed by means of descriptive statistics, chi-square, Analysis of Variance (ANOVA) and linear logistical regression, at* α *0.05.*
Results. *Mean age was 21 ± 2.9 years, with females constituting 60.1% of the sample. The prevalence rates of anxiety and depression were 41.5 and 31.9%, respectively. Students in health-related faculties were significantly less anxious than others. Inability to afford three square meals, negative family functioning, chronic illness and living in a State/Region with a high incidence of COVID-19 were significantly associated with depression. These factors jointly accounted for 14% of depression. Coping methods included the use of social media, watching movies and participating in online skills-development programs.*
Conclusion. *The overall level of anxiety and depression among undergraduate students during the COVID-19 lockdown was higher than the levels previously reported. Inadequate nutrition and poor family functioning contributed significantly to this. Proactive measures ought to be taken to support undergraduate students in order to prevent the negative consequences of poor mental health.*

Introduction

The novel coronavirus disease (COVID-19) pandemic, which was first detected in December 2019, has continued to ravage the entire world. The outbreak started in Wuhan, China [1] and has since spread to almost all the countries in the world [2]. Six months since the first case was reported, the number of confirmed cases had risen to 9,633,157 [2]. A little less than a year later, the number of confirmed cases had risen by over 13-fold (131,487,572) [3]. Mortality from the disease is high, with the estimated death toll reaching 2,857,702 by early April 2021 [3]. Although the number of cases was slow to rise in Africa, the increase was exponential [4], placing an enormous burden on the already weak health system [5].

On March 11, 2020, the World Health Organization (WHO) declared the novel Coronavirus disease a pandemic, owing to its worldwide spread and its impact on lifestyles and social interactions [6]. It was subsequently termed a Public Health Emergency of International Concern by the WHO [7].

The first case of coronavirus in Nigeria was confirmed on February 27, 2020 [8], following which the Nigerian Centre for Disease Control (NCDC) issued several guidelines for curtailing the spread, in line with the internationally-approved standard [9]. Despite these measures, the number of cases continued to rise and was estimated to have reached 163,388 by April 7, 2021 [10]. Already by March 2020, the spread of the virus had prompted the federal and state governments and their various para-statal authorities to shut down activities in the country. By March 23, both land borders and air space had been closed and the weekly meeting of the federal executive council had been suspended, among other measures [11]. On Monday, March 23, 2020, the Nigerian University Commission (NUC) ordered the lockdown of all universities and affiliated schools [12]. This halted academic activities, causing students to go home or discontinue their industrial training - an unplanned break.

In addition, a lockdown was imposed on activities in three major states in the country from March 30, 2020, and a partial lockdown in most other states prohibited all social and religious gatherings [13]. As a result, the residents of Lagos and Ogun States and the Federal Capital Territory, where the lockdown was total, as well as those of other States, where it was partial, had to spend most of their time at home.

Many employers have since enabled their employees to work from home, while many private universities and secondary schools are taking measures to provide online

tuition for their students. Unfortunately, this is not the case among students of public tertiary institutions, who form the bulk of Nigerian youths. Even before academic activities were halted because of the coronavirus pandemic, university staff across the country had already gone on strike from March 9, 2020 [14]. Hence, there was no plan in place to engage public tertiary institution students during the COVID-19 lockdown, nor was it possible to continue industrial training/internship in companies, owing to the lockdown.

A feeling of being stalled in academic progress could lead to the development of anxiety or other psychological disorders, since the period of youth is perceived as a period of opportunities [15]. It is also unclear what role youths' family functioning may be playing in their psychological state. Given the increase in the incidence of mental disorders, particularly anxiety and depression, among young people [16], it has become crucial to examine the psychological state and coping mechanisms of undergraduate students in Nigeria. This assertion is in line with the significant function of nurses in caring for the bio-psychosocial state of individuals, whether sick or well.

Further, in 2019 the WHO reported that mental health problems accounted for 16% of the global health burden among people aged 10-19 years [17]. It also asserted that, if left undiagnosed and untreated, such disorders could lead to a myriad of physical and mental health issues, hence preventing these individuals from living fulfilling lives as adults [17]. Some authors have reported an increased prevalence of anxiety and depression among university/college students in China and Greece during the lockdown [18-21]. However, there is a dearth of information on the prevalence of anxiety and depression and their associated factors among undergraduate students in Nigeria during the COVID-19 lockdown. We therefore studied the psychological effects of the lockdown, its associated factors, family functioning and coping strategies among undergraduate students of the University of Ibadan in Nigeria.

Materials and methods

Study design, setting and population

A descriptive study design was used, and the study was conducted among undergraduate students of the University of Ibadan between April 29th and May 5th, 2020. The University of Ibadan is the first university in Nigeria and was founded on November 17, 1948. It is located in Oyo State, south-western Nigeria. Founded and funded mainly by the federal government, the university consists of sixteen faculties [22]. Study participants were drawn from 12 faculties, which were merged into seven major faculties, namely: Social Sciences; Clinical Sciences & Public Health; Pharmacy & Basic Medical Sciences; Law & Arts; Sciences & Technology; Education; Agriculture & Veterinary medicine. Inclusion criteria were: undergraduate students attending regular courses, i.e. full-time students as opposed to those enrolled in the Open Distance Learning (ODL) mode; students who had access to a web-based method of communication, specifically Whatsapp messaging platform, and were included on the Faculty Whatsapp pages.

Sample size and sampling technique

At a confidence level of 95% and a 4.94 confidence interval (margin of error), a sample of 386 students was calculated by means of an automatic sample-size calculator to be representative of the total undergraduate population of 14,833 [23]. The representatives of students' (sub) unions in the faculties were contacted through the university Students' Union (SU) vice president, who is a student at the researchers' department. The faculty executives then contacted their colleagues via an online messaging platform (Whatsapp). Information about the study (aims, benefits and study population) was provided on students' Faculty and Department Whatsapp pages, from which a convenience sample of students chose to participate in the study.

Instrument

The study instrument consisted of a questionnaire made up of the following parts: Sociodemographic characteristics/history of chronic illness, Hospital Anxiety Depression Scale (HADS), Family Assessment Device (FAD) and coping strategies. Questions on Sociodemographic characteristics included: age, year of study, state of residence, whether there was a lockdown in the state of residence, among others. A higher level of psychological distress is associated with higher regional/state prevalence of COVID-19, as a result of perceived higher risk [24]. Hence, in this study, participants' states of residence were categorised as low-, medium- and high-risk states on the basis of the number of cases reported in each state of the federation by the NCDC at the time of data collection. Moreover, as the closure of many businesses, due to measures to curtail the spread of the coronavirus, may have reduced family income, participants were asked if they could afford three meals a day. Also, with regard to average weekly personal income, five options were provided: less than 1,000; 1,000-5,000; 6,000-10,000; 11,000-15,000; above 15,000 naira; these were reduced to two categories, as most of the students chose the first option. These last two questions, together with questions regarding the number of cars owned by the family and whether the family owned their own house were used to roughly estimate the socioeconomic status of the students. The four questions, however, did not constitute a composite unit, but were assessed individually. To determine the presence of chronic illness(es), students were asked if they had any of the following illnesses: asthma, sickle cell disease, diabetes, hypertension, kidney disease, depression, and were instructed that they could tick more than one option. These chronic conditions are common among university students in Nigeria, to the best of the researcher's knowledge. However, another option, 'others', was provided so that students could tick this

option if their chronic/long-term illness was not listed. Participants were thereafter grouped into two categories according to the presence or absence of chronic illness.

The Hospital Anxiety Depression Scale (HADS) is a questionnaire made up of 14 items consisting of questions that evaluate anxiety and depression. It has been found suitable for use among psychiatric, non-psychiatric and healthy populations [25]. Specificity and sensitivity values of 80% have been reported for both sections of the questionnaire (anxiety and depression) and the subscale scores range from 0-7, which denotes 'normal' or no anxiety/depression; 8-10 denoting 'suspicious' or mild, and 11-21 which points to the presence of anxiety or depression. These categories also show that the higher the score is, the greater the anxiety or depression is. Moreover, the specificity and sensitivity values of the scales have been established to range between 85 and 92.9% among Nigerians [26]. The author of that study, which was carried out in both hospital and community settings, recommended the instrument for use in community surveys in developing countries. Another author classified the scale scores into four [27], but did not provide data on the specificity and sensitivity based on these classifications. We therefore used the three original categories in our study.

Family Assessment Device (FAD): this is based on the McMaster Family Functioning model. The FAD is a scale whereby the structural and organisational characteristics of families are assessed, together with the methods of interactions among family members. It is able to distinguish between "healthy" and "unhealthy" families, thereby guiding the possible provision of social support. It has seven [8] subscales: Problem Solving, Communication, Roles, Affective Responsiveness, Affective Involvement, Behaviour Control and General Functioning. The scale is available free of charge. The reliability α ranges from 0.72 to 0.83 for the subscales, and is 0.92 for general functioning. In a previous study [28], test-retest reliability of 0.86 on the general functioning scale was obtained among Nigerians. In the present study, we used only the general functioning section, consisting of 12 items, as it assesses the overall health or pathology of the family, since the various subscales have been incorporated into it. Moreover, including the entire scale consisting of 60 questions, which would have meant adding further sections to the questionnaire, might have reduced the response rate. Responses are marked on a four-point Likert scale: "strongly agree," "agree," "disagree," and "strongly disagree. Negatively structured questions are reversed, and higher scores indicate problematic functioning. The highest obtainable score is 48, while the lowest obtainable score is 12. The higher the score, the poorer the family functioning [29].

Data collection and analysis

After ethical approval had been obtained from the University of Ibadan/University College Hospital ethical review board, the link to the questionnaire, which was created by means of a Google form, was sent to undergraduate students, together with an introductory message explaining the purpose of the study. The message and the link were sent through the Whatsapp messaging platform, as students were not reachable at school owing to the lockdown. The data collected were cleaned and transferred from the Google form excel spreadsheet to Statistical Package for Social Sciences (SPSS) version 20.0 for analysis. Frequencies, percentages and means were used to report the sociodemographic variables. These variables were tested by means of the chi-square test and ANOVA for their association with anxiety and depression. Those that were significant were entered into a linear regression model to determine to what degree they predicted depression. Depression and anxiety were classified into three scales: 0-7, which denotes 'normal' or absence of anxiety/depression; 8-10 denoting 'suspicious' or mild anxiety/depression, and 11-21, pointing to the presence of moderate-to-severe anxiety or depression. These two measures were also tested by means of ANOVA for their association with family functioning. Post-hoc analysis was carried out by means of Fisher's Least Significant Difference, to determine the pair means that were statistically different. Coping methods used by the students and their willingness to be seen by a healthcare provider if they were experiencing anxiety or depression were presented as bar charts.

Ethical considerations

The study protocol was submitted for ethical approval to the University of Ibadan/ University College Hospital Ibadan (U.I. /UCH) ethical review committee, which assigned it an approval number (UI/EC/20/0242). Moreover, the questionnaire, which was circulated as a Google form, included an introduction explaining the aims and benefits of the study. Students who completed the form gave their consent implicitly.

Results

Sociodemographic characteristics and their association with anxiety and depression

Respondents' sociodemographic characteristics and their association with anxiety and depression, as evaluated by the Chi-square test, are presented in Table I. The mean age of the undergraduates was 20.8 (± 2.9) years, with a little over half (50.2%) in the 20-23 year age-range. Most were female (60.1%), and Christianity was the most prevalent religion. Almost 20% of the participants could not afford three square meals. Eight percent (8%) of the participants suffered from some form of chronic illness, and 35.2% reported that a total lockdown was in force in their state at the time of data collection. Inability to afford three square meals and being under complete lockdown in the State of Residence were associated with depression ($p < 0.001$ and $p < 0.05$, respectively). There was a significant association between students' academic faculty and anxiety.

Tab. I. Analysis of association between respondents' sociodemographic characteristics and psychological state.

Variable	F (N = 386)	%	Anxiety		Depression	
			X^2	P-value	X^2	P-value
Age (in years) 16-9:						
20-23	128	33.2				
24-27	204	52.8	7.43	0.26	4.42	0.60
28 & over	46	11.9				
Mean 21 ± 2.9	8	2.1				
Gender:						
Female	232	60.1	2.14	0.35	0.21	0.93
Male	154	39.9				
Faculty:						
Social Sciences	82	21.2				
Clinical Sciences & Public Health	71	18.4				
Pharmacy & Basic Medical Sciences	65	18.8	2.34	0.03[a]*	1.01	0.42
Law & Arts	59	15.2				
Sciences & Technology	48	12.4				
Education	34	8.8				
Agriculture & Vet. medicine	27	7.0				
Level of study:						
1st year	104	26.9				
2nd year	84	21.8				
3rd year	83	21.5	16.89	0.08	12.97	0.23
4th year	88	22.8				
5th year	23	6.0				
6th year	4	1.0				
Religion:						
Christianity	322	83.4	8.53	0.13	3.62	0.68
Islam	57	14.8				
Others	7	1.8				
Presence of chronic illness:						
Yes	36	8.0	2.57	0.30	8.29	0.02*
No	355	92.0				
Able to afford 3 meals/day:						
Yes	311	80.6	11.63	0.003*	22.44	0.000*
No	75	19.4				
Ownership of cars:						
≥ 3	55	14.3	8.71	0.36	5.70	0.68
0-2	331	85.7				
Personal income:						
< 1,000 naira (< $2.6)/week	230	59.6	9.21	0.30	5.67	0.67
≥ 1,000 naira (≥ $2.6)/week	156	40.4				
Currently working part-time:						
Yes	60	15.5	0.52	0.79	1.71	0.41
No	326	84.5				
Total lockdown in place of residence:						
Yes	186	35.2	2.74	0.26	7.47	0.02*
No	250	64.8				
Place of residence during the lockdown:						
Staying with family or friends	370	95.9	0.79	0.67	0.90	0.64
Staying alone	16	4.1				
State of residence during lockdown:						
High-risk state (> 300 cases)	87	22.5				
Medium-risk state (50-299 cases)	33	8.5	1.86	0.76	5.36	0.25
Low-risk state (< 50 cases)	266	69				
Family members exposed/on front line:						
Yes	78	20.2	0.41	0.84	2.09	0.36
No	308	79.8				

[a] ANOVA test. The rest are chi-square test. * Significant at $p < 0.05$.

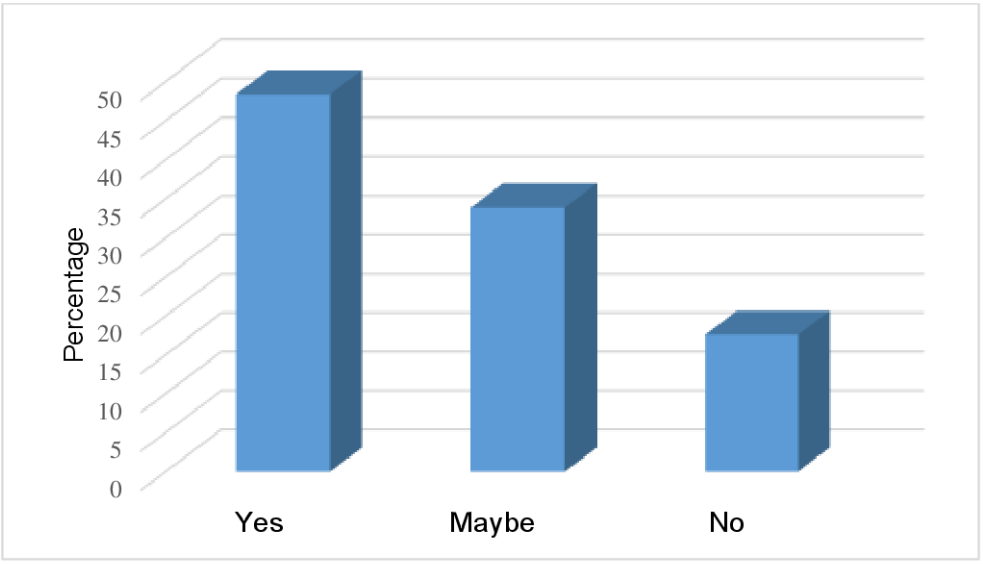
Faculty of study and inability to afford three square meals were significantly associated with anxiety. Having a chronic illness, inability to afford three square meals and presence of lockdown in the state of residence were significantly associated with depression.

Post-hoc analysis (LSD - Least Significant Difference) of mean scores among the different faculties showed that students in the faculties of Clinical Sciences/Dentistry/Public Health displayed a significantly lower level of anxiety (5.2 ± 4.1) than their counterparts in Social Sciences and Economics (6.61 ± 4.50, p = 0.046); Science and Technology (7.4 ± 4.5, p = 0.01); Education

Tab. II. Prevalence of anxiety and depression.

Psychological state	Category	Frequency	Percent
Anxiety	No anxiety, i.e. normal	226	58.5
	Anxiety suspected, i.e. mild	80	20.7
	Anxiety present, i.e. moderate-to-severe	80	20.7
	Total	386	100
Depression	No depression, i.e. normal	263	68.1
	Depression suspected, i.e. mild	81	21
	Depression present, i.e. moderate-to-severe	42	10.9
	Total	386	100

Fig. 1. Reporting students' willingness to speak to a health professional shows that about half of the students (48.4%) were willing to see a healthcare professional if they were feeling anxious or depressed.



(7.7 ± 4.1, p = 0.01) and Agriculture/Veterinary Medicine 7.9 ± 5.4, p = 0.01). However, there was no significant difference between the scores of those in Clinical Sciences/Dentistry/Public Health and Pharmacy/Basic Medical Sciences (5.7 ± 3.4), p = 0.64.

Additionally, students in the Faculty of Education had a higher mean score on depression (7.2 ± 3.9) than those in the faculties of Pharmacy/Basic Medical Sciences (5.7 ± 3.4), p = 0.04.

Prevalence of anxiety and depression and willingness to consult a health professional

Table II shows that 20.7% of the students experienced moderate-to-severe anxiety, with another 20.7% suffering from mild anxiety. Also, the prevalence of moderate-to-severe depression was 10.9%, while 21% had mild depression.

More than 40% of the undergraduates had mild-to-severe forms of anxiety, while a little over 30% had some degree of depression.

A good number of students were open to discussing their mental health state with a health professional.

Coping with the lockdown

As shown in Figure 2, students coped with the lockdown and the cessation of academic activities by using social media (17.9%), watching television or videos (11.1%), or engaging in online skills-building activities (15.3%). Other methods of coping included sports activities, meditation, helping at home, games and music.

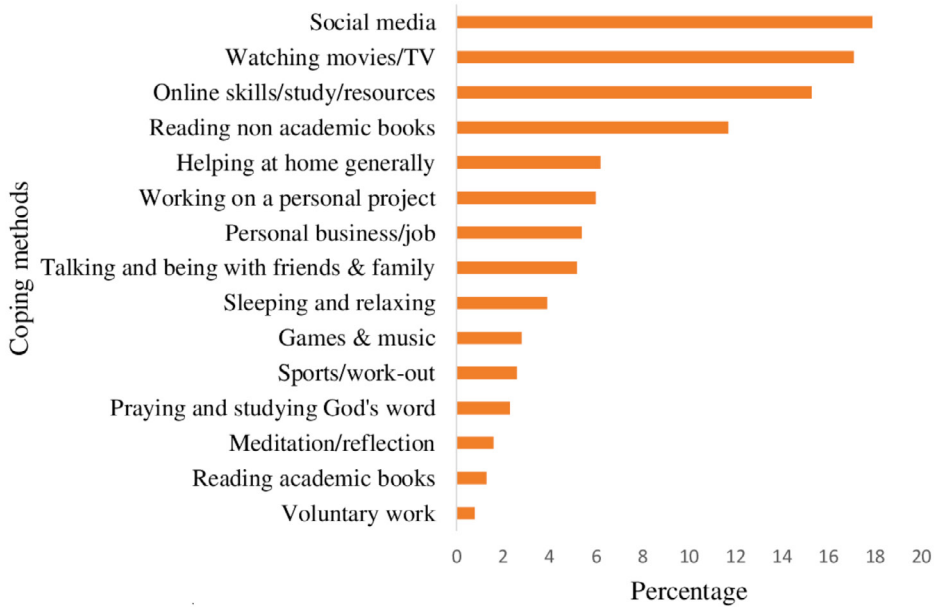
Association between family functioning and psychological states

Table III shows a significant effect of family functioning on the presence, suspected presence or absence of anxiety at $p < 0.01$ [$F(2, 383) = 15.49$, $p = 0.000$], on Analysis of Variance (ANOVA).

The mean difference between undergraduate students who were anxious or had suspected anxiety was significant.

Moreover, post-hoc comparison of the mean scores of the three categories, on Fisher's Least Significant Difference (LSD) (Tab. IV) revealed that the mean score for family functioning among students with no anxiety (23.2 ± 5.1) was significantly different from that of students in whom anxiety was suspected (24.8 ± 6.0); p = 0.03. Similarly,

Fig. 2. Students' favourite activities for coping with the lockdown included virtual entertainment, watching television and skills acquisition.



Tab. III. ANOVA showing association between family functioning and anxiety.

	N	Mean	Standard deviation	F	P-value
No anxiety	226	23.2	5.1	15.49	0.000[a]
Anxiety suspected	80	24.8	6.0		
Anxiety present	80	27.2	6.5		

[a] significant at $p < 0.01$.; two-tailed.

Tab. IV. Post-hoc analysis of family functioning and state of anxiety.

Anxiety Category	Anxiety category	Mean difference	P-value	95% Confidence Interval	
				Lower bound	Upper bound
No anxiety	Anxiety suspected	-1.564	0.03	-2.99	-0.13
	Anxiety present	-4.014	0.000[a]	-5.44	-2.58
Anxiety suspected	No anxiety	1.564	0.03	0.13	2.99
	Anxiety present	-2.450	0.01	-4.19	-0.71
Anxiety present	No anxiety	4.014	0.000[a]	2.58	5.44
	Anxiety suspected	2.450	0.01	0.71	4.19

[a] $p < 0.01$.

Tab. V. ANOVA showing association between depression and family functioning.

Category	N	Mean	Standard deviation	F	P-value
No depression	263	23.4	5.4	14.209	0.000[a]
Depression suspected	81	25.9	5.9		
Depressed	42	27.6	6.1		

[a] significant at $p < 0.01$; two-tailed.

there was a significant difference between those with no anxiety (23.2 ± 5.1) and those in whom anxiety was present (27.2 ± 6.3, $p = 0.000$). Higher scores denote poor family functioning.

The family functioning of students who were not anxious at all was significantly different from that of students who were suspected of having anxiety at $p < 0.05$ and from those with anxiety, at $p < 0.01$. There was also a significant difference in family functioning between students in whom anxiety was suspected and those with actual anxiety.

ANOVA results on depression and family functioning (Tab. V) showed a significant association between the two variables [$F(2, 383) = 14.209$, $p = 0.000$].

There was a significant association between family functioning and depression.

In addition, Fisher's Least Significant Difference (LSD), in Table VI, showed that the mean score for

Tab. VI. Post-hoc analysis of family functioning and depression.

Depression category	Depression category	Mean difference	P-value	95% Confidence Interval	
				Lower Bound	Upper Bound
No depression	Depression suspected	-2.527	0.000[a]	-3.93	-1.13
	Depressed	-4.245	0.000[a]	-6.08	-2.41
Depression suspected	No depression	2.527	0.000[a]	1.13	3.93
	Depressed	-1.719	0.11	-3.82	0.38
Depression	No depression	4.245	0.000[a]	2.41	6.08
	Depression suspected	1.719	0.11	-0.38	3.82

[a] $p < 0.01$.

family functioning among students without depression (23.35 ± 5.44) was significantly lower than that of students who had borderline (suspected) depression (25.88 ± 5.87); p = 0.000 and of those who were depressed (27.6 ± 6.13), p = 0.000.

However, there was no significant difference between the family functioning of those with borderline depression (25.88 ± 5.87) and those who were depressed (27.6 ± 6.13), p = 0.108.

Students who were depressed had significantly better family functioning than students who had suspected and actual depression.

Multiple linear regression on variables that predict depression

A multiple linear regression was performed to determine to what extent some variables predicted the presence of depression, as shown in Table VII. The results indicated that the model explained 14.3% of the variance and that the model was a significant predictor of depression, F (4,381) = 15.92, p < 0.001. The results also showed that three meals/day, [Beta = 0.19, t (381) = 3.97, p < 0.01]; chronic illness [Beta = 0.123, t (381) = 2.5, p = 0.01] and family functioning [Beta = 0.264, t (381)] = 5.52, p < 0.01] significantly predicted the presence of depression. However, current residence in a state under lockdown was not statistically significant.

Participants' predicted depression score was - 2.58 + 1.68 (3 meals/day) + 0.61 (lockdown in state of residence) + 1.59 (chronic illness) + 0.16 (family functioning), where 3 meals/day and lockdown in the state of residence were coded as 2 = Yes, 1 = No; and chronic illness was coded as 2 = Yes, 1 = No. Students who were unable to afford three square meals, who had chronic illness(es) and who had poor family functioning were more depressed.

The model shows that the four factors were able to predict 14% of depression seen in the students.

Discussion

The lockdown prompted by the coronavirus pandemic was an exceptional event in Nigeria. Every sector of the country has been affected, although the Federal and State Governments have finally eased the lockdown. In January 2021, which was a few months before this report was written, the undergraduate students were able to resume their academic activities, after eight months' interruption.

The response rate to this survey was 21.2%. Most of the participants were female (60%), although the male: female ratio in schools is usually around 53:47 [30]; hence, it was expected that a slightly higher or an equal number of male students would participate in the study. However, the higher percentage of females participants could be explained by the greater interest of women in psychology-related issues. Indeed, the dominance of women in psychology is supported by research [31], which has revealed that there are more females in the field of psychology – both in education and the workforce. Similarly, some authors [32] have found that a significantly higher number of females than males enrol in postgraduate programmes in psychology, the proportion being as high as 75% females *vs* 25% males; this trend has been under way for about 10 years.

Students with one or more chronic illness had a significantly higher level of anxiety and depression than those who did not have such illnesses. This finding is in line with data from Wang et al. [33], who reported a higher level of psychological distress among people with a medical history of chronic illness in a population-based study involving 1210 people in China.

Contrary to the findings of some authors [18, 19, 34], in which female participants had a significantly higher level of depression than their male counterparts during the COVID-19 pandemic, there was no significant association

Tab. VII. Multiple linear regression analysis of the relationship between selected variables and depression.

	B	Standard error	β	t	P-value
(Constant)	-2.577	1.189		-2.168	0.03
3 meals/day	1.683	0.424	0.19	3.97	0.000
Lockdown in State	0.614	0.35	0.084	1.752	0.08
Chronic illness	1.589	0.614	0.123	2.59	0.01
Family functioning	0.16	0.029	0.264	5.517	0.000

F (4,381) = 15.92; p < 0.001; R^2 = 0.143 (14.3%); R^2 Adjusted 0.134

between gender and anxiety or depression among the participants in this study. This difference may be due to the difference in demography. Indeed, whereas the present study was carried out among university students aged 16 to 30 years, the above authors [18, 19, 34] carried out their surveys among all age-groups. Conversely, the present findings are in keeping with those of some other studies [16, 35, 36], which were all carried out among university students. Thus, it is possible that other factors, such as age, combine to make females more prone to psychological distress. However, a study [37] conducted among university students in China showed a significantly higher prevalence of depression among female students.

Although such measures of socioeconomic status as the number of cars owned by the family, the level of private income and living in one's own house were not associated with anxiety and depression, students who could not afford three square meals/day had a significantly higher level of anxiety and depression. However, being able to provide three meals is linked to income. Hence, it can be presumed that students who could not afford three square meals were of low socioeconomic background. Cao et al. [18] also reported that poor socioeconomic status was associated with anxiety among the university students who participated in their study, with those living in poorer conditions experiencing considerably more anxiety. At the beginning of the lockdown in Nigeria, the federal government and some state governments promised to provide financial support to ease the economic burden of the lockdown. However, owing to the limited resources available, these palliative measures could only be provided for the 'poorest of the poor'. This socioeconomic group, which constitutes 49.66% of the population, is mostly resident in the rural areas of the country [38]. Therefore, residents of urban areas, which is where most university students live, were not provided with support, hence the inability to afford three square meals a day.

Regarding the prevalence of anxiety, Cao et al. [18] reported that about 25% of Chinese university students experienced mild-to-severe forms of anxiety during the COVID-19 pandemic. In the present study, by contrast, a higher percentage of Nigerian university students (41.5%) experienced mild-to-severe forms of anxiety. The higher rate could be due to the different periods of data collection. Indeed, while Cao et al. [18] collected their data in February 2020, before the pandemic reached its peak in most parts of the world, the data for the present study were collected in May 2020, a period during which cases were increasing exponentially in Nigeria. Before the COVID-19 pandemic, some authors [39] had reported a lower rate of anxiety (14.8%) among undergraduate students in five universities in South-western Nigeria. Again, this is not surprising, since several studies conducted in Italy, the United States, China and Spain [19-21, 35, 40] have averred that the lockdown/self-quarantine associated with COVID-19 has put considerable psychological strain on college students.

Furthermore, mild-to-severe depression was detected in 31.9% of the university students who participated in this study, one-third of whom were adolescents (aged 16-19 years). Although there are no national data on the prevalence of depression among Nigerian youths, there are reports of studies carried out in the same geopolitical zone where the present study was conducted. For instance, the prevalence found in this study was higher than that reported earlier among Nigerian adolescents [41], according to which 21.2% of rural adolescents in south-western Nigeria were found to have varying degrees of depression. It is not surprising that more participants in this study experienced depression, since the COVID-19 lockdown was something that put emotional strain on many people. Likewise, in 2019, a somewhat lower prevalence rate of depression (21.6%) was reported by Ayandele et al. [39] among undergraduate students in five universities located in the same region where the present study took place.

Earlier, in 2013, Peltzer et al. [42] had documented a prevalence of 25.2% of moderate-to-severe forms of depression among undergraduate students in Western Nigeria. However, 10.9% of undergraduate students who participated in this study experienced moderate-to-severe depression. This difference could be due to the fact that, in the study by Peltzer et al. [42], other sensitive information, such as the experience of sexual abuse, physical violence or injury and substance abuse, was elicited from the participants at the same time as data on depression. This information might have brought on some negative feelings leading to a higher score on depression were collected.

Moreover, students who lived alone did not experience a significantly higher level of anxiety than those living with family or friends, a finding which is in line with Mazza et al. [19]. Since most participants were young adults, it could be that those living alone were able to fend for themselves and therefore did not suffer from a significantly higher level of anxiety. Furthermore, the results of post-hoc ANOVA showed that students in non-health-related faculties had a considerably higher level of anxiety than those in health-related fields. This inter-faculty difference is congruent with what was reported in another study among college students in China and Spain [37, 40].

Another contributory factor to depression among undergraduate students was family functioning. Participants with poor family functioning experienced mild-to-severe depression, while those with good family functioning were not depressed. As mentioned earlier, living alone or with family or friends did not significantly influence the experience of depression. Nevertheless, living with family or friends, as almost all the participants did, while at the same time experiencing poor functioning, was a significant causal factor of depression. Cao et al. [18] reported a negative correlation between social support and anxiety, with anxiety decreasing as social support increased. Furthermore, Li et al. [43] reported that good family functioning was associated with a decreased level of psychological distress among students of the health professions.

This was also the position of Jianjun et al. in a study conducted among undergraduate students in China [44]. The top three coping methods used by our undergraduate students were: using social media - Whatsapp, status challenges, Instagram, among others - watching television or movies and participating in online skills-acquisition programmes or extra-curricular study activities. These methods are similar to those mostly used by university students in Jordan, as reported by Al-Tamemmi et al. [36]. Also, students in states where there was a total lockdown experienced a significantly higher level of depression. This difference is logical, since states under lockdown had a higher number of cases of COVID, and the students must have felt more exposed to coronavirus infection, as well as being deprived of social gatherings or religious interaction. This is in agreement with what has been reported by some authors of studies involving higher institution students in China [45, 46]. Another interesting finding is the students' responses regarding their willingness to speak to a health professional if they were experiencing anxiety or depression. Almost half (48.4%) of the students answered "Yes", while about a fifth (17.6%) answered 'No'; the rest were undecided. Two studies, carried out in 2017 and 2018 [47, 48], showed a negative attitude towards mental illness among young people in a secondary school and a University in Nigeria, respectively. Another study reported a more positive (accepting) attitude on the part of Pharmacy students [49].

On the whole, the factors that proved significant on univariate analysis and were included in the linear regression showed that not being able to afford three meals in a day, poor family functioning, having a chronic illness and residing in a state under total lockdown accounted for 14% of the depression seen among participants in the study.

Conclusions

In conclusion, the lockdown due to COVID-19 has placed a lot of psychological stress on university students; indeed, more than a third of those who participated in this study had varying degrees of anxiety and depression. It is recommended that measures such as financial support or the provision of food for needy families, counselling for dysfunctional families, and appropriate education and support for students with chronic illnesses be put in place in order to alleviate the psychological distress of these students. There is also a need to recommence academic activities through online engagement in order to positively channel the energy of university students.

Study limitations

The Hospital Anxiety and Depression scale (HADs) used in data collection does not distinguish between moderate and severe forms of the two psychological states.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

LYO conceptualized and designed the study; reviewed literature, collected and analysed data; and wrote the manuscript

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Research paper

Results of an universal screening for SARS-CoV-2 in women admitted for delivery in a geographical area with low incidence of COVID-19 infection

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Dear Editor,
SARS-CoV-2 is the coronavirus responsible for the associated respiratory infection termed COVID-19.
At present, more than 213 countries all over the world are affected of COVID-19 but numbers are rising daily. By the end of September 2020, there were in the world more than 23 millions confirmed COVID-19 cases and more than 900.000 deaths, with significant numbers occurring in Italy, Spain and USA [1].
SARS-CoV-2 has similar genomic sequences to other coronaviruses [2], such as SARS-CoV-1 (79% analogy) and MERS-CoV (50% analogy) although the viruses show differences in clinical manifestations and mortality rates. During pregnancy SARS and MERS were both associated with more severe respiratory infection. Approximately, 30% of pregnant women infected with SARS died, compared to less than 10% of the general population and 60% of pregnant women required intensive care, compared to 20% of the general population. Although limited data available for MERS, a more severe disease with a higher mortality and more frequent need for intensive care admission are reported [3]. Severe respiratory infections (like pneumonia) in pregnancy are usually associated with adverse outcomes for women and babies, these including an increase in maternal mortality, eclampsia, stillbirth, low birth weight and preterm birth. So, it is important to check the presence of the virus in pregnant women and to understand the possible influences on pregnancy and delivery as well as the possibility of transmission to the newborn. In addition, it must be considered that pregnant women have multiple interactions with the health system; for this reason, their possible role in virus spread should not be neglected.
On the other hand, current evidence suggests that COVID-19 is not associated with a significantly increased risk for pregnant women [3]. Also, no definitive evidence of vertical transmission exists at present [4]. However, these observations are limited and do not allow to draw any definitive conclusion. It is thus important to monitor pregnant women and their outcomes. With this letter we present the preliminary results of our ongoing study, aimed to evaluate SARS-CoV-2 circulation among pregnant women in Foggia (Apulia Region, South Eastern Italy). 974 women were enrolled in the study, between April the 1st and August 20th, referring to Institute of Obstetrics and Gynecology, University of Foggia for delivery, ranging from 18 to 45 years (mean age 25.3 years). All of them, regardless the presence of signs or symptoms of infection, were subjected at the admission to nasopharyngeal swab for SARS-CoV-2 RNA.
For this purpose, Viral RNA was extracted within 2 hours from sample collection using the STARMag 96 X 4 Universal Cartridge kit with the Microlab NIMBUS IVD instrument according to the manufacturer's instructions (Seegene Inc. Seoul, Korea). Amplification and detection of target genes (N, E and RdRP) were performed using the commercially available kit AllplexTM 2019-nCoV Assay (Seegene Inc. Seoul, Korea) with the CFX96TM instrument (Bio-Rad, Hercules, CA). Results interpretation was performed with the Seegene Viewer software [5].
If the result of the nasopharyngeal swab was negative, in the clinical suspicion of SARS-CoV-2 infection a second swab was performed after 24-48 hours.
16 women had symptoms compatible with COVID-19 infection (10 had fever, 1 pneumonia, 3 diarrheas, 2 cough). None of the women were positive for SARS-CoV-2 among the patients enrolled in the study, regardless the presence of symptom.
The results from our study, performed in a region of Italy with a relatively low incidence of COVID-19 infection [5], allow probably a cautious optimism regarding the relevance of COVID-19 infection in pregnancy, at least in our geographical area; however a prudential strict screening of pregnant women, possibly with a wide use of serological test in addition to biomolecular tests, will help in the future to draw more definitive conclusions about the relationships between SARS-CoV-2 and pregnancy.

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Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

JRF, LN and FA supervised the project and the manuscript preparation, FS and FG collected data and clinical information and contributed to manuscript preparation, MDS, GF, ML AND RDN did care about laboratory work and contributed to manuscript writing.

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Research paper

Epidemiological and clinical characteristics of the COVID-19 epidemic and associated factors for mortality in Golestan province, Iran: a retrospective cohort study

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Keywords

COVID-19 • Acute Respiratory Distress Syndrome • Death • Iran

Summary

Background. *We aimed to further clarify the epidemiological and clinical characteristics of 2019-nCoV pneumonia and risk factors associated for mortality.*

Methods. *In this study, we included inpatient with acute respiratory distress syndrome at Golestan Hospitals who had been discharged or had died in 2020. Epidemiological, and clinical data were extracted from electronic medical records and compared between recovered and died cases. We used multiple logistic regression methods to explore the risk factors associated with in-hospital death.*

Results. *Overall 2,835 acute respiratory distress syndrome patients were included in this study, and 874 (30.83%) were positive for 2019-nCoV. Five hundred and sixty-three patients (19.86%) died, 1,687 patients (59.51%) were recovered. Of the total deaths, only 288 (10.15%) were attributed to COVID-19. The most common symptoms at onset of illness were respiratory distress [1,795 (63.32%)], fever [1,601 (56.47%)], dry cough [1,595 (56.26%)], sore throat [445 (15.70%)], and myalgia [342 (12.06%)]. One thousand and twelve (35.7%) had 1 or more coexisting medical conditions. In multiple logistic regression analysis, risk factors associated with the death included older age [OR (Odds Ratio) = 1.03; 95% CI; 1.02-1.04], blood oxygen level (SPO_2 < 93%) (OR = 2.44; 95% CI; 1.79-3.31), comorbidities (OR = 2.15; 95% CI; 1.62-2.84), respiratory distress (OR = 1.74; 95% CI; 1.28-2.37), and headache (OR = 0.44 95% CI; 0.21-0.92).*

Conclusions. *The 2019-nCoV infection caused collections of severe respiratory illness and was associated to a high ratio of hospitalization in ICU and high mortality. Older age and comorbidities were associated with more risk of death among patients with 2019-nCoV.*

Introduction

In December 2019, a number of cases of pneumonia by unknown origin were identified in Wuhan, the capital city of Hubei province, China [1]. Clinical evidence showed that these cases were very similar to viral pneumonia [2-4]. Most patients reported to have worked or lived near the seafood market, as well as had contacts with live wild animals. In the early stages of the pneumonia, severe acute symptoms of respiratory infection occurred, with some patients rapidly developing acute respiratory distress syndrome (ARDS), acute respiratory failure, and other serious complications. On January 7th, a new coronavirus was detected by the Chinese Centers for Disease Control and Prevention, which was subsequently named by the World Health Organization as the new Coronavirus 2019 (nCoV-2019) [5].

Emergency of 2019-nCoV has attracted global attention, and WHO has declared the COVID-19 a public health emergency of international concern (PHEIC) [6, 7]. Since the outbreak of Acute Respiratory Syndrome (SARS) in Guangdong, China, in 2003, WHO has announced five PHEIC cases: H1N1 (2009, polio (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in the Democratic Republic of the Congo (2019) [8]. Announcing a PHEIC is an immediate call at the highest level for the international community to launch a global concerted effort to stop the spread of the disease, which requires serious public health activities, high-level political commitment and a sufficient budget [6]. Common symptoms of this infection include respiratory

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symptoms, fever, cough, and respiratory distress. In more severe cases, the infection can cause pneumonia, severe acute respiratory syndrome, kidney failure, and even death [9].

According to the latest World Health Organization report, since the announcement of the first case of COVID-19, 4,248,389 cases and 294,046 deaths due to the disease have been reported in more than 180 countries. So that more than 80% of deaths in the United States and Europe, as well as 37% and 55.5% of deaths, were reported in the United States and Europe, respectively. In Iran, 112,725 cases and 6,783 deaths have been reported [10] . Due to the fact that the disease has spread to all countries of the world, including Iran, this study was conducted to determine epidemiological, clinical characteristics and risk factors for mortality of inpatients with COVID-19 in Golestan province, Iran.

Methods

This is a retrospective cohort study, conducted on 2,835 patients acute respiratory distress syndrome aged < 1 to 99 years and hospitalized at Golestan University of Medical Sciences Hospitals in Golestan provinces, Iran. The study was approved by the Research Ethics Commission of Golestan University of Medical Sciences (IR.GOUMS.REC.1398.385). The patients with acute respiratory distress syndrome admitted to Hospitals of Golestan university of Medical Sciences in 2020, were enrolled. We obtained the medical records and compiled data for hospitalized patients with laboratory-confirmed COVID-19. A confirmed case of COVID-19 was defined as a positive result on RT-PCR assay of nasal and pharyngeal swab specimens and suspected cases of 2019-nCoV or Acute Respiratory Distress Syndrome was defined the negative test of PCR and hospitalized. We obtained epidemiological, demographic, clinical, laboratory, management and outcome data from patients' medical records. The primary end point was admission to an intensive care unit (ICU), or the use of mechanical ventilation. Secondary end point involved patients' death.

Descriptive analyses of the variables were expressed as median [interquartile range (IQR)], or number (%) or simple ranges, as appropriate. No imputation was made for missing data. Means for continuous variables were compared using independent group t tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Proportions for categorical variables were compared using the χ^2 test, although the Fisher exact test was used when the data were limited. All epidemiological, demographic and clinical exposures were tested for association with end point in univariate analysis and those with $p < 0.20$ were then entered into a logistic regression model to examine their independent effect. All statistical analyses were performed using STATA 12.0 software (Stata Corporation, College Station, TX, USA).

Results

In overall, 2,835 hospitalized patients with suspected 2019-nCoV nasal and pharyngeal swab specimens were prepared and send to the laboratory for PCR. Of these patients, 874 (30.83%) were positive for 2019-nCoV, 1,046 (36.90%) were negative and 915 (32.28%) were not available for PCR result (Tab. I).

The demographic and clinical characteristics of the patients are shown in Table I. The median age was 54 years (IQR: 41-67; range: 0-99 years), and 1,635 (57.67%) were males. The median durations from first symptoms to hospital admission and death were 2 days (IQR: 0-3), and 7 days (IQR: 4-13), respectively. Among them, there were 32 patients with exposure history of COVID-19 (Tab. I). Of these patients, 17.92 % were ventilated, 14.50% had SpO_2 less than 93%, and 11.99% were admitted to the ICU.

Of the 2,835 patients, 1,012 (35.7%) had one or more coexisting medical conditions. Cardiovascular disease [486 (17.14%)], diabetes [423 (14.92%)], chronic lung disease [177 (6.24%)] and hypertension [77 (2.72%)] were the most common coexisting conditions (Tab. I).

The most common symptoms at onset of illness were respiratory distress [1,795 (63.32%)], fever [1,601 (56.47%)], dry cough [1,595 (56.26%)], sore throat [445 (15.70%)], and myalgia [342 (12.06%)]. Less common symptoms were headache, fatigue, abdominal pain, chest pain, diarrhea, nausea and vomiting (Tab. I).

A secondary end-point (death) event occurred in 563 patients (19.86%), that 1,687 patients (59.51%) were recovered, and 585 (20.63%) under treatment. However, of the total deaths, only 288 deaths were confirmed by the Golestan University of Medical Sciences Death Committee for COVID-19 (Tab. I). Thus, the mortality rate was 10% for COVID-19.

Table II demonstrates that when compared with death and recovered cases, the death cases were older ($p < 0.001$) and most of them were males (54.53%; $p = 0.03$). More death cases presented with initial symptoms of respiratory distress compared with those recovered (77.08 *vs* 59.63%; $p < 0.001$) and with lower oxygen saturation ($SpO_2 < 93\%$) (33.68 *vs* 12.27%; $p < 0.001$). Compared with recovered cases, death cases had a higher proportion of comorbidities, including cardiovascular disease (27.78 *vs* 13.22%), diabetes (23.61 *vs* 12.98%; $p < 0.001$), chronic lung disease (11.81 *vs* 4.68%; $p < 0.001$), chronic kidney disease (7.64 *vs* 2.37%; $p < 0.001$) and cancer (3.47 *vs* 0.95%; $p = 0.001$).

Multiple logistic regression models showed that several factors were associated with death in confirmed cases of 2019-nCoV, which included age of patents (OR = 1.03, 95% CI: 1.02-1.04), oxygen saturation ($SpO_2 < 93\%$) (OR = 2.44, 95% CI: 1.79-3.31), comorbidities (OR = 2.15 95% CI: 1.62-2.84), respiratory distress (OR = 1.74, 95% CI: 1.28-2.37) and headache. Although most of the variables mentioned were associated with higher likelihood of death, but headache was negatively associated with death (OR = 0.31; 95% CI, 0.13-0.70) (Tab. III).

Tab. I. Baseline characteristics of patients suspected and infected with 2019-nCoV.

Variables	Total (n = 2,835)	Confirmed cases (n = 874)	Suspected cases (n = 1,046)	Not available of PCR result (n = 915)	P-value
Age, median (IQR), y	54 (41-67)	56 (43-68)	52 (39-65)	55 (42-67)	F = 11.60 < 0.01*
Sex, n (%)					
Female	1200 (42.33)	366 (41.88)	453 (43.31)	381 (41.64)	$\chi^2(1) = 0.39$ 0.71 **
Male	1635 (57.67)	508 (58.12%)	593 (56.69)	534 (58.36)	
Onset of symptom to, median (IQR)					
Hospital admission	2 (0-3)	2 (0-4)	1 (0-4)	2 (1-3)	F = 0.23 0.63*
Death	7 (4-13)	8 (4-13)	8 (3-14.5)	6 (3-8)	F = 0.03 0.86*
Discharge	8 (5-12)	8 (5-12)	8 (5-12)	6 (4-9)	F = 1.15 0.78*
History of exposure with COVID-19, n (%)					
Yes	32 (1.13)	11 (1.26)	21 (2.01)	0 (0.0)	$\chi^2(1) = 1.63$ 0.2**
No	2803 (98.87)	863 (98.74)	1025 (97.99)	915 (100)	
Ventilation, n (%)					
Yes	508 (17.92)	227 (25.97)	179 (17.11)	102 (11.15)	$\chi^2(1) = 0.12$ 0.72**, ***
No	289 (10.19)	105 (12.01)	88 (8.41)	96 (10.49)	
Admitted to ICU, n (%)					
Yes	340 (11.99)	105 (12.01)	127 (12.14)	108 (11.80)	$\chi^2(1) = 0.45$ 0.49**, ***
No	1153 (40.67)	377 (43.14)	412 (39.39)	364 (39.78)	
SPO_2, n (%)					
93% >	411 (14.50)	168 (19.22)	150 (14.34)	93 (10.16)	$\chi^2(1) = 8.21$ 0.001**, ***
93% <	408 (14.39)	119 (13.62)	179 (17.11)	110 (12.02)	
Comorbidities, n (%)	1012 (35.70)	356 (40.73)	335 (32.03)	321 (35.08)	$\chi^2(1) = 15.66$ <0.001**
Cardiovascular disease, n (%)	486 (17.14)	168 (19.22)	160 (15.30)	158 (17.27)	$\chi^2(1) = 5.18$ 0.02**
Diabetes, n (%)	423 (14.92)	155 (17.73)	131 (12.52)	137 (14.97)	$\chi^2(1) = 10.19$ 0.01**
Chronic lung disease, n (%)	177 (6.24)	65 (7.44)	71 (6.79)	41 (4.48)	$\chi^2(1) = 0.30$ 0.58**
Hypertension, n (%)	77 (2.72)	22 (2.52)	25 (2.39)	30 (3.28)	$\chi^2(1) = 0.03$ 0.85**
Chronic kidney disease, n (%)	106 (3.74)	46 (5.26)	39 (3.73)	21 (2.30)	$\chi^2(1) = 2.65$ 0.10**
Chronic liver disease, n (%)	21 (0.74)	6 (0.69)	12 (1.15)	3 (0.33)	$\chi^2(1) = 1.08$ 0.29**
Cancer, n (%)	44 (1.55)	13 (1.49)	20 (1.91)	11 (1.20)	$\chi^2(1) = 0.50$ 0.47**
Immune deficiency disease, n (%)	34 (1.20)	5 (0.57)	15 (1.43)	14 (1.53)	$\chi^2(1) = 3.43$ 0.06**
Signs and symptoms					
Respiratory distress, n (%)	1795 (63.32)	565 (64.65)	692 (66.16)	538 (58.80)	$\chi^2(1) = 0.48$ 0.48**
Fever, n (%)	1601 (56.47)	495 (56.64)	599 (57.27)	507 (55.41)	$\chi^2(1) = 0.07$ 0.78**
Dry cough, n (%)	1595 (56.26)	478 (54.69)	575 (54.97)	542 (59.23)	$\chi^2(1) = 0.01$ 0.90**
Sore throat, n (%)	445 (15.70)	160 (18.31)	176 (16.83)	109 (11.91)	$\chi^2(1) = 0.72$ 0.39**
Myalgia, n (%)	342 (12.06)	89 (10.18)	155 (14.82)	98 (10.71)	$\chi^2(1) = 9.22$ 0.002**
Headache, n (%)	157 (5.54)	43 (4.92)	36 (3.93)	78 (7.46)	$\chi^2(1) = 5.19$ 0.02**
Confusion, n (%)	140 (4.94)	39 (4.46)	62 (5.93)	39 (4.26)	$\chi^2(1) = 2.05$ 0.15**

▶

Tab. I. Baseline characteristics of patients suspected and infected with 2019-nCoV.

Variables	Total (n = 2,835)	Confirmed cases (n = 874)	Suspected cases (n = 1,046)	Not available of PCR result (n = 915)	P-value
Nausea and Vomiting, n (%)	136 (4.80)	45 (5.15)	59 (5.64)	32 (3.50)	$\chi^2(1) = 0.23$ 0.63**
Chest pain, n (%)	112 (3.95)	34 (3.89)	48 (4.59)	30 (3.28)	$\chi^2(1) = 0.56$ 0.45**
Temperature C, median (IQR)	39 (39-39)	39 (38.5-39)	39 (39-39)	39 (39-39)	F = 0.42 0.07*
Secondary end point, n (%)					
Death	563 (19.86)	288 (32.95)	190 (18.16)	85 (9.29)	$\chi^2(1) = 60.13$ < 0.01**
Recovered	1687 (59.51)	414 (47.37)	648 (61.95)	625 (68.31)	
Hospitalization	585 (20.63)	172 (19.68)	208 (19.89)	205 (22.40)	

* This test compared the Positive PCR group *vs* Negative PCR group, One-way analysis of variance (ANOVA); ** Chi-squared test (χ^2); *** Some of the status variables are missing.

Tab. II. Epidemiological and clinical characteristics among death and recovered cases.

Variables	Death (n = 288)	Recovered (n = 1687)	Total (n = 1975)	P-value
Age, median (IQR), y	65 (54-76)	50 (39-62)	53 (41-65)	T = 12.01 <0.01*
Sex, n (%)				
Female	119 (41.32)	681 (40.37)	800 (40.51)	$\chi^2(1) = 0.09$ 0.76**
Male	169 (58.68)	1006 (59.63)	1175 (59.49)	
Onset of symptom to, median (IQR), day				
Hospital admission	1 (0-4)	2 (1-4)	2 (0-4)	T = 0.98 0.32*
Discharge	4 (2-10)	7 (4-11)	7 (4-11)	T = 0.77 0.44*
History of exposure with COVID-19, n (%)				
Yes	5 (1.74)	20 (1.19)	25 (1.27)	$\chi^2(1) = 0.59$ 0.44**
No	283 (98.26)	1667 (98.81)	1950 (98.73)	
Ventilation, n (%)				
Yes	96 (76.19)	235 (57.18)	331 (61.64)	$\chi^2(1) = 14.74$ <0.01**
No	30 (23.81)	176 (42.82)	206 (38.36)	
Admitted to ICU, n (%)				
Yes	36 (22.22)	197 (22.70)	233 (22.62)	$\chi^2(1) = 0.01$ 0.89**
No	126 (77.78)	671 (77.30)	797 (77.38)	
SPO_2, n (%)				
93%>	191 (66.32)	1480 (87.73)	1671 (84.61)	$\chi^2(1) = 86.59$ < 0.01**
93%<	97 (33.68)	207 (12.27)	304 (15.39)	
Comorbidities, n (%)	164 (56.94)	486 (28.81)	650 (32.91)	$\chi^2(1) = 88.19$ <0.01**
Cardiovascular disease, n (%)	80 (27.78)	223 (13.22)	303 (15.34)	$\chi^2(1) = 40.14$ < 0.01**
Diabetes, n (%)	68 (23.61)	219 (12.98)	287 (14.53)	$\chi^2(1) = 22.37$ <0.01**
Chronic lung disease, n (%)	34 (11.81)	79 (4.68)	113 (5.72)	$\chi^2(1) = 23.13$ < 0.01**
Hypertension, n (%)	13 (4.51)	39 (2.31)	52 (2.63)	$\chi^2(1) = 4.65$ 0.03**
Chronic kidney disease, n (%)	22 (7.64)	40 (2.37)	62 (3.14)	$\chi^2(1) = 22.45$ < 0.01**
Chronic liver disease, n (%)	1 (0.35)	14 (0.83)	15 (0.76)	$\chi^2(1) = 0.76$ 0.38**
Cancer, n (%)	10 (3.47)	16(0.95)	26 (1.32)	$\chi^2(1) = 12.06$ < 0.01**

▶

Tab. II. Epidemiological and clinical characteristics among death and recovered cases.

Variables	Death (n = 288)	Recovered (n = 1687)	Total (n = 1975)	P-value
Immune deficiency disease, n (%)	2 (0.69)	14 (0.83)	16 (0.81)	$\chi^2(1) = 0.05$ 0.81**
Signs and symptoms				
Respiratory distress, n (%)	222 (77.08)	1006 (59.63)	1228 (62.18)	$\chi^2(1) = 31.85$ < 0.01**
Fever, n (%)	162 (56.25)	1037 (61.47)	1199 (60.71)	$\chi^2(1) = 2.81$ 0.09**
Dry cough, n (%)	161 (55.90)	1041 (61.71)	1202 (60.86)	$\chi^2(1) = 3.47$ 0.06**
Sore throat, n (%)	49 (17.01)	284 (16.83)	333 (16.86)	$\chi^2(1) = 0.005$ 0.94**
Myalgia, n (%)	25 (8.68)	241 (14.29)	266 (13.47)	$\chi^2(1) = 6.63$ 0.01**
Headache, n (%)	9 (3.13)	120 (7.11)	129 (6.53)	$\chi^2(1) = 6.40$ 0.01**
Confusion, n (%)	11 (3.82)	80 (4.74)	91 (4.61)	$\chi^2(1) = 0.47$ 0.49**
Nausea and vomiting, n (%)	11 (3.82)	94 (5.57)	105 (5.32)	$\chi^2(1) = 1.50$ 0.22**
Chest pain, n (%)	17 (5.90)	57 (3.38)	74 (3.75)	$\chi^2(1) = 4.34$ 0.03**
Temperature C, median (IQR)	39 (39-39)	39 (39-39)	39 (39-39)	T = -0.80 0.42*

* Two-Sample t-Test; ** Chi-squared test (χ^2).

Tab. III. Multiple logistic regression analysis showing factors independently associated with death caused by 2019-nCoV.

Variables	AOR (CI 95%)	P-value
Age	1.03 (1.02-1.04)	< 0.001
SPO_2 < 93%	2.44 (1.79-3.31)	< 0.001
Comorbidities	2.15 (1.62-2.84)	< 0.001
Respiratory distress	1.74 (1.28-2.37)	< 0.001
Myalgia	0.77 (0.48-1.22)	0.27
Headache	0.44 (0.21-0.92)	0.03

AOR: Adjusted Odds Ratio.

Discussion

During this study, the clinical status of patients admitted to hospitals of Golestan province including the common symptoms of COVID-19 patients and their companions, as well as the clinical outcomes and characteristics of patients were evaluated. In addition, this study reviewed the influencing factors of fatality as a retrospective cohort study. As of April 20th, 2020, 2,835 cases of suspect COVID-19 were hospitalized, of which about 31% were reported to be a definite case of COVID-19. About 12% of the patients had to be admitted to the ICU, and about 20% of the patients expired. Among them, only 51% tested positive for COVID-19. Therefore, fatality rate for COVID-19 about 10%. Moreover, about 60% of the patients were discharged from the hospitals with complete recovery.

Coronavirus is among the basic pathogens of respiratory diseases. SARS-Corona and MERS-Corona virus are the two most robust pathogens that have caused an epidemic in recent years. These two pathogens cause severe respiratory symptoms in patients. These viruses caused the involvement of a huge part of human society in the world [11]. However, the new coronavirus has caused a totally different condition all over the world.

The experience of previous viruses had shown that the mortality rate for the SARS virus was more than 10% and for the MERS was more than 35% [12-14]. However, this value is different for the new coronavirus, in a way that the mortality rate has shown to be 1.5% in the present study. Nevertheless, it should be noted that future death records should be reported in inpatients.

The most common clinical symptoms of the patients of the trial include shortness of breath, fever and dry cough. Unlike the present study, the most common one in Wuhan city of China was fever (in 98% of patients) [1]. A reason for this difference in the clinical signs between the patients in Iran and China is the way of providing services based on the type of patient. In Wuhan, all patients with mild symptoms were kept in hospital or tested for the virus; however, between Iranian patients, only those with severe respiratory symptoms were admitted or PCR-tested. This difference in methods led to the fact that most of the patients included in the present study had severe symptoms of coronavirus including severe shortness of breath. However, in general, the basic presented symptoms in patients were similar to the previous coronavirus diseases, including SARS and MERS [15, 16].

During our study, it was shown that the total reported cases of coronavirus in males were higher than in females. The same rate of infection incidence was also seen in MERS and SARS. The lower susceptibility of

females to the disease may be partly due to the female hormones that give them immunity [17]. In addition, about half of the patients of coronavirus in the present study had at least one underlying disease, which was mainly cardiovascular and diabetes disease. This finding was similar to that of MERS [18]. Basically, our findings indicate that the disease regularly invades males of elder ages with underlying diseases and suppression of the immune system.

Moreover, the risk factors of deaths due to the coronavirus were investigated in our study. It was shown that the age, SpO_2 of less than 93%, having underlying diseases and the onsets of symptoms with respiratory distress are among the main risk factors or predictors of fatalities due to coronavirus. The findings of the present study are consistent with the results of the study of Wu et al. [19]. These findings are also consistent with the results of the study of Wu et al. [19] and Zhou et al. [20]. Nonetheless, these findings can be explained by the fact that the PCR test does not have a high sensitivity in detecting coronavirus in COVID-19 patients, so that a number of patients with CT scan results showing evidence of severe pulmonary involvement and had negative PCR results. On the other hand, during the early and middle periods of the epidemic, there were multiple sampling errors for PCR because of the fear of the healthcare staff from being infected by the virus, as well as not having the proper skills. As a result, these errors led to misclassification of patients. Therefore, it should be noted that dead patients with a negative PCR result were necessarily not free of the Coronavirus infection. This is the reason for the similar death risk factors for both groups. Interestingly, the onset of symptoms with a headache in cases where their PCR test was positive showed an inverse relationship with fatality and reduced chance of death up to 70%. However, it should be noted that obtaining a history for the headache is a subjective concept that may not be recorded accurately in the epidemic situation. Therefore, this finding should be cautiously interpreted and used.

There were a number of limitations in our study that may have affected the results. First, there was a number of missing data in some variables that may have reduced the study's power to assess the effect of that variable on death. This shows that there is a need for a more robust database of patients in Iran [21], and unfortunately, there is a severe weakness. Second, in this study, we were not able to use laboratory data. This was because of the fact that the laboratories data were not accurate enough. Third, we did not have access to the CT scan reports, because the patients' database only included the CT images, not the reports, which were used in the clinical setting. We were also not able to re-examine the whole CT images because of the current emergency situation.

Conclusions

However, according to the conducted search, this is the first retrospective cohort report in Golestan province. The 2019-nCoV infection caused collections of severe respiratory illness and was associated high ratio of hospitalization in ICU and high mortality. This study generally identified two important factors for fatality including old age and underlying diseases. On that account, we can try to decrease the fatality by planning on care for these groups. Among the underlying diseases, diabetes, as well as cardiac, lung, and kidney diseases play an important role in the fatality of Coronavirus patients.

Abbreviations

ARDS: Acute Respiratory Distress Syndrome; nCoV-2019: New Coronavirus 2019; PHEIC: Public Health Emergency of International Concern; SARS: Sever Acute Respiratory Syndrome; RT-PCR: Reverse-Transcriptase-Polymerase-Chain-Reaction; ICU: Intensive Care Unit; CT: Computerized Tomography.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Research Ethics Commission of Golestan University of Medical Sciences (IR.GOUMS.REC.1398.385).

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MRH, GR and AR originated the research idea and analyzed the data. HS, AT, MG, AJ and MM designed the study protocol. AT and AT confirmed the samples. AF, SA, and NJ managed the data collection. AR, MRH and GR drafted the manuscript. All authors confirmed that they meet ICMJE criteria for authorship.

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Research paper

Coronavirus 2019-like illness and public adherence to preventive measures, Sudan 2020

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Keywords

COVID-19 • Protective measures • Suspected • Screening

Summary

Introduction. *In December 2019, a novel corona virus disease was identified and was responsible for the new cases of respiratory tract infections in Wuhan, China. This virus was responsible for the pandemic with more than 84 million cases and 1.82 million deaths worldwide. In Sudan till now the reported cases exceed 23,000 with 1.400 deaths. This study aims to determine the prevalence of COVID-19 suspected cases, health seeking behavior and public adherence to protective measures.*
Methods. *Descriptive community based cross-sectional study using nonprobability snowball sampling technique, conducted in Khartoum state 2020. 3499 respondents with diverse socio-demographic backgrounds were finally enrolled in the study. Data was collected through Manitoba Coronavirus 2019 screening form which distributed through online anonymous Google forms. Data was entered and analyzed by Statistical Package of Social Sciences version 23.*
Results. *The study revealed that 26.5% of the respondents were clinically suspected with headache or fatigability being the most common symptom followed by pharyngitis and then dry cough. Asthma and chronic respiratory disease as the commonest comorbidities. Wearing facial masks and regular hand washing were found to be the most used protective measures with only 39.4% implicates social distancing in their daily life. Health seeking behavior was significantly different among suspected respondents the majority tend to use antibiotics than to isolate themselves or undergo testing.*
Conclusion. *COVID-19 suspected cases were prevalent among Sudanese population; screening capacity has to be increased with more strong policies for implications of personal protective measures in the daily life.*

Introduction

The World Health Organization (WHO) on March 11, 2020, has declared the novel coronavirus (COVID-19) outbreak a global pandemic [1].
At a news briefing, WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, noted that over the past 2 weeks, the number of cases outside China increased 13-fold and the number of countries with cases increased threefold. Further increases are expected. He said that the WHO is "deeply concerned both by the alarming levels of spread and severity and by the alarming levels of inaction," and he called on countries to take action now to contain the virus. "We should double down," he said. "We should be more aggressive." Among the WHO's current recommendations, people with mild respiratory symptoms should be encouraged to isolate themselves, and social distancing is emphasized, and these recommendations apply even to countries with no reported cases [2].
Novel COVID-19 "can often present as a common cold-like illness," wrote Roman Wöelfel et al. [3]. They report data from a study concerning nine young- to middle-aged adults in Germany who developed COVID-19 after close contact with a known case. All had generally mild clinical courses; seven had upper respiratory tract disease, and two had limited involvement of the lower respiratory tract. Pharyngeal virus shedding was high during the first week of symptoms, peaking on day 4. Additionally, sputum viral shedding persisted after symptom resolution. The German researchers say the current case definition for COVID-19, which emphasizes lower respiratory tract disease, may need to be adjusted [3]. But they considered only young and "normal" subject whereas the story is different in frail comorbid older patients, in whom COVID-19 may precipitate an interstitial pneumonia, with severe respiratory failure and death [4].
High level of attention should be paid to comorbidities in the treatment of COVID-19. In the literature, COVID-19 is characterized by the symptoms of viral pneumonia such as fever, fatigue, dry cough, and lymphopenia. Many of the older patients who become severely ill have evidence of underlying illness such as cardiovascular disease, liver disease, kidney disease, or malignant tumors. These patients often die of their original comorbidities. They die "with COVID" but were extremely frail and we therefore need to accurately evaluate all original comorbidities.
In addition to the risk of group transmission of an infectious disease, we should pay full attention to the treatment of the original comorbidities of the individual

while treating pneumonia, especially in older patients with serious comorbid conditions and poli-pharmacy. Not only capable of causing pneumonia, COVID-19 may also cause damage to other organs such as the heart, the liver, and the kidneys, as well as to organ systems such as the blood and the immune system. Patients die of multiple organ failure, shock, acute respiratory distress syndrome, heart failure, arrhythmias, and renal failure [3, 5].

As of March 1, 2020, 79,968 patients in China and 7,169 outside of China had tested positive for coronavirus disease 2019 (COVID-19). Among Chinese patients, 2873 deaths had occurred, equivalent to a mortality rate of 3.6% (95% CI 3.5-3.7), while 104 deaths from COVID-19 had been reported outside of China (1.5% [1.2-1.7]). However, these mortality rate estimates are based on the number of deaths relative to the number of confirmed cases of infection, which is not representative of the actual death rate; patients who die on any given day were infected much earlier, and thus the denominator of the mortality rate should be the total number of patients infected at the same time as those who died. Notably, the full denominator remains unknown because asymptomatic cases or patients with very mild symptoms might not be tested and will not be identified [6].

Regarding Sudan, the first case was reported on 13 March 2020, and up to 3 July 2020 there are 9,894 confirmed cases and 616 deaths. The case fatality rate was 6.23%. There is variation in case fatality rate, which in some cities (like Khartoum) was low (3.8%), but in others (like North Darfur) it was very high (31.7%) [7].

So, the novel corona virus pandemic constitutes a major health concern that need to be understood and controlled. COVID-19 pandemic is a catastrophic event affecting all aspects in life, and because of the low social awareness and ignorance toward the basic concepts of protection, symptoms and treatment believes, it is vital to assess all Sudanese population and even the small sector of them about the symptomatology and related aspects of COVID-19.

This study aims to determine the prevalence of COVID-19 suspected cases as well as public adherence to the protective measures and the association between these and the diverse socio-demographic backgrounds.

Methods

This was a descriptive community based cross-sectional study conducted in Khartoum state (November-December 2020), in which resides almost one quarter of the Sudanese population and most c of the cases of COVID-19.

The study population includes those aged 18 years and above of Sudanese nationality with exclusion of those unwilling or refused to participate.

Our aim was to recruit as much as possible sample size with diverse socio-demographic backgrounds. 3,499 respondents were finally included in the study. Data was collected using screening form adopted from Manitoba COVID-19 screening questionnaire [8].

The questionnaire was distributed through an online anonymous Google form. The form contains 21 items that emphasizes the socio-demographic characteristics, comorbidities, symptoms that might suggests COVID-19 or other viral infections,duration of the illness, health seeking behaviors along with adherence to the protective measures.

Scoring system

The scoring system for suspected cases in this study was adopted from Sudanese federal ministry of health scoring system, marks were assigned as following:

- history of contact with suspected or confirmed case = 2;
- shortness of breath = 2;
- dry cough = 2;
- fever > 38 = 1;
- pharyngitis = 1;
- headache or fatigability = 1;
- anosmia or loss of taste sensation or both = 1;
- nausea/vomiting/diarrhea = 1.

The response score of 5 or more is considered as suspected cases, and scores of less than 5 is considered non suspected case.

The study was approved by local ethical committee, Department Community Medicine University of Khartoum. Written consent was taking from the participants prior to data collection.

The data was entered and analyzed using statistical package of social sciences (SPSS-25) version 25, categorical variables were presented as frequencies and percentages, and continuous variables as means and standard deviations, qi square test was used to test the difference between categorical variables and Pearson's correlation coefficient was used to determine the nature of the relationship between continuous variables, P-value < 0.05 was considered to be statistically significant.

Results

A total of 3,399 participants were finally enrolled in the study, 2,313 (68%) of them were females and 1,086 (32%) were males. most of the respondents (80.6%) were found to be within the age group of 18-32 year (Tab. I).

Among those who have chronic diseases, more than half of them 325 (60.8%) are suffering from asthma and respiratory tract diseases, 100 (2.9%) were hypertensive, 85 (2.5%) were diabetics, 14 (0.4%) having cardiovascular diseases, while only 2 (0.1%) suffering from cancer. 1,168 (34.4%) were unemployed and 1,841 (54.2%) of the employed respondents have job requirements of direct contact with people.

In regard to the symptoms suggesting COVID-19 infection, 2075 (61%) have symptoms suggesting the disease, Fatigability or headache were found to be the most prevalent symptoms in 1,739 (51.2%) followed by pharyngitis 1,381 (40.6%) then comes dry cough 781 (23%, Tab. II).

Regarding the presentation with combined symptoms,

Tab. I. Socio-demographic characteristics of the respondents.

	Frequency (%)
Gender	
Male	1,086 (32%)
Female	2,313 (68%)
Age groups	
18-32	2,739 (80.6%)
33-47	443 (13%)
48-62	175 (5.1%)
More than 62 year	42 (1.2%)
Smoking and snuffing	
Yes	423 (12.4%)
No	2,976 (87.6%)
Chronic diseases	
Yes	550 (16.2%)
No	2,849 (83.8%)

Tab. II. Symptoms suggesting COVID-19 infection.

Symptom	Frequency (%)
Pharyngitis	1,381 (40.6%)
Shortness of breath	456 (13.4%)
Anosmia	664 (19.5%)
Nausea and vomiting/diarrhea	244 (7.2%)
Cough	781 (23%)
Fatigability or headache	1,739 (51.2%)
Fever	448 (13.2%)

185 (9%) are having pharyngitis and dry cough, followed by 115 (5.6%) having pharyngitis and anosmia.
More than half of the respondents 2,156 (63.4%) had a history of contact with a confirmed or suspected case. Other symptoms that might suggest viral infections are runny nose 1,478 (43.5%), rash 97 (2.9%) and red eyes 205 (6%).
Of total 2,468 (53.9%) have symptoms for less than one week, (18.8%) still having the symptoms while (15.4%) have the symptoms for 2 weeks. 1,348 (39.7%) have a family member suffering of similar symptoms.
Despite the fact of having symptoms suggesting COVID-19 infection in the middle of the second wave, the majority 827 (38.2%) took antibiotics and 500 (23.1%) underwent COVID-19 testing, only 129 (6%) isolated themselves for 14 days, 312 (14.4%) used traditional medicine (Tab. III).
Of total of 471 underwent COVID-19 diagnostic test with 100 (21.2%) were positive and 371 (78.7%) were negative.
More than two thirds of the participants 2,403 (70.7%) did not attend social or religious activities within the last 2 weeks.
About personal protective measures, 17.3% found to be adherent to only one protective measure. 2,131 (62.7%) wear masks regularly outside home, and 1,779 (52.3%) were using antiseptics and 39.4% maintain social distancing.
About one quarter of the candidates 898 (26.4%) were clinically suspected for having COVID-19 infection with score of 5 or more with a mean of (2.997 ± 2.666). Suspicion score is significantly inversely correlated with the number of protective measures that a participant use ($r = -0.4$, p-value = 0.028).
Female were more frequently suspected than male, and this difference was found to be statistically significant with a p-value = 0.000). Asthma and respiratory tract diseases were significantly the most prevalent chronic diseases in clinically suspected cases (p-value = 0.006). Among those who underwent COVID-19 diagnostic test, positive results significantly present in clinically suspected cases (p-vaue = 0.000).
Of total 898 clinically suspected participants, 542 have a family member suffering the same symptoms (p-value = 0.000). Most of the suspected respondents have a significant combination of both pharyngitis and dry cough (p-value = 0.000).
Having a family member suffering from the similar symptoms was found to have significant association with the use of protective measures with those adherent to protective measures are less likely to have family member having symptoms (p-value = 0.000).
regarding the symptoms and COVID-19 diagnostic tests, those presented with pharyngitis, Anosmia or combination of anosmia and fever are more likely to have positive test results (p-value = 0.000) with those who suffered from the symptoms for less than a week duration are more likely to have positive results (p-value = 0.000).

Tab. III. Health seeking behavior.

	Frequency (%)
Traditional medicine	312 (14.4%)
Antibiotics	827 (38.2%)
COVID-19 diagnostic testing	500 (23.1%)
Isolation for 14 days	129 (6%)
Did noting	397 (18.3%)

Discussion

This was a descriptive community-based study which was conducted in Khartoum state (November-December 2020) to assess prevalence of COVID-19 like symptoms and about three thousand and half populations were involved.
More than half were females and almost more than two thirds were in the middle age group, which can be attributed to the use of social media mostly by this age group.
Most of them were nonsmokers nor snuffers with no co morbidities. The majority of those having comorbidities suffers from asthma and respiratory tract illnesses followed by diabetes mellitus, hypertension, chronic heart disease and cancer which is similar to the study conducted on China [9].
More than half of responds were employed with their job requires direct daily contact with people and is very important when we deal with a disease transmitted

through air droplets or contact. Regarding the symptoms suggesting COVID19 infection, almost more than half suffered from fatigability or headache as the main symptom followed by pharyngitis, then dry cough and a this contradicts study done on united states which came out with dry cough, muscle aches and nasal congestion as main presenting symptom [10]. Another study done in united states revealed that fever is not a main presenting symptom,present on small group of patient as a main compliant [11], and this in correspond to the results of our study.

Which also contradict what was found on a study conducted on UK that represent loss of taste and smell sensation as the main symptom [12], and that done in Germany which reported loss of taste sensation, nausea and diarrhea not a presenting symptom [13]. And a third one done in china that ranked the top symptoms of presentation of COVID-19 the as fever, cough [9]. Not far, in Saudi Arabia, the main top three presenting symptoms as said on self-reports were fever, headache and anosmia [14]. This variation in the presentation of symptoms can be attributed to the different geographical characteristics and genetic variation of the individuals in addition to the viral mutations!

In addition to that, ranking headache and fatigability as the most the presenting symptom in our community can lead to delayed identification of the active cases as those two presentations may be mistaken for other non-respiratory illness like malaria unlike the combined presentation of pharyngitis and dry cough or pharyngitis with anosmia which is more specific to the disease, so the situation in our community is critical!

Most of the suspected cases had positive history of contact with suspected or confirmed with the disease and this explains the positive test results in this group.

Finding other nonspecific viral infection symptoms like runny nose with high positive predictive value for positive COVID-19 screening testing is of great importance as these symptoms are not categorized under the COVID-19 screening questionnaire adopted by the Sudanese federal ministry of health and can be easily missed due to their presence in other viral diseases. Half of responders said that symptoms duration lasts for less than a week and about third of them have family member suffered from similar symptoms this important in regard to the spreading of these symptoms among family members as those individuals don't tend to use personal protective measures in the house.

In spite of being symptomatic at the middle of the second wave of the wave, the health seeking behavior was not appropriate as almost half of population used antibiotics or traditional medicine with only a small fraction isolated themselves for 14 days or underwent COVID-19 diagnostic testing These behaviors to some extend differ from that of a study done on Saudi Arabia where the concern of social distance and use of herbal medications show different results [15].

Of those who underwent COVID-19 testing, two third were found to be negative and small proportion found to be positive, and among those who underwent COVID-19 diagnostic test, positive results significantly present in clinically suspected cases.

This can be attributed to the finding that the majority of symptomatic individuals don't undergo the diagnostic testing and fall under the categorization of active suspected cases in the individuals.

As this study revealed a small proportion of symptomatic cases isolated themselves for 14 the majority did not as daily life requires being out of home for some time for work or obtaining daily needs.

Testing here is another challenging entity because of financial issues first and the fact that people on the remote areas and countryside have no access to it. Personal protective measures such as hand hygiene and face mask use are included in public health guidelines for pandemic preparedness. Hand hygiene effectively reduces the transmission of respiratory infections through indirect contact in the community setting, and it should be practiced by all individuals and the larger population to limit the risk of transmission through fomite [16]. Most coronaviruses, including severe acute respiratory syndrome coronavirus 2, are inactivated by alcohol-based hand sanitizers and disinfectants such as bleach. Environmental disinfection with appropriate sanitizers is also recommended [16]. The efficacy of face masks among healthy individuals is unclear, but masks may protect others, particularly healthcare workers, from actively symptomatic individuals with COVID-19. However, the combination of masks and hand hygiene has been shown to reduce transmission of respiratory viruses and serves to highlight that layering of NPIs (Non-Pharmaceutical Interventions) is more effective at reducing disease transmission than any NPI alone [16].

On the field of protective measures; almost half or more of the participants documented the of wearing face mask,washing hands followed by the use of antiseptics and the social distance being the least one, and this lies in parallel with the study done on Japan in regard to hand hygiene but show contradictions on the area of using face mask and isolation [17] also these results show some similarities to results of study done on Saudi Arabia [18], and contradicts another one in regard of social contact and isolation [19].

This could be explained by the different population level of awareness and daily life requirements and socioeconomic classes.

All personal issues can be achieved but the big entity of social distancing may be a challenge and needs more efforts from community to commit and government policies to set more forced regulations.

Suspicion score was found to be significantly associated with the use of personal protective measures. As those suspected tend to use protective measures less often than those non-suspected and this can be explained by the protection effect of these measures, being less adherent being more susceptible to have the disease.

Female were more frequently suspected than male, and this is important on that most of homes and houses cared by females as mothers, grandmother and so and this may increase the infection rate through contacts. Here also to

put on regard if they are caring children and elderly as they may contact infection easily.
Asthma and respiratory tract diseases were significantly the most prevalent chronic diseases in clinically suspected cases. This result is different largely from what is said on this study, and also different from results of that done on United States which found that diabetes is the most prevalent [20]. Also a study done on Wuhan, china showed different results [21]. This may be of significance because respiratory tract is the main target of the virus and this comorbidity may give synergistic effect to the viral action increasing the rates of respiratory failure and deaths. Those categorized as suspected have positive history of a family member being symptomatic and this can be explained by the less use of indoor protective measure.
Females of the age group (33-52), postgraduates were found to be more adherent to protective measures than others, this can be explained by the fact that education is an important factor in the awareness of the disease and self-protection People with comorbidities, and those having a job that necessitates direct contact with people were also found to be more adherent than others this can be explained by the awareness of these individuals of being more at risk than others to catch up the disease.
It was found that those who attending social activities (parties, religious occasion…) with no consideration to the social distance were found to be less adherent to protective measures also there is association between adherence to protective measures and submitting COVID-19 test. This can be explained by the background knowledge about the disease process.
Regarding the symptoms and COVID-19 diagnostic test, those presented with pharyngitis, Anosmia or combination of anosmia and fever are more likely to have positive test results, with duration of symptoms for less than a week this can be added to the epidemiology of the disease in the community.

Conclusions

In conclusion COVID-19 like illness is quiet common in our community with many suspected cases, personal protective measures use is adequate with social distancing not being implicated as optimal, health seeking behavior if the community toward COVID-19 like illness and action toward undergoing diagnostic testing is suboptimal.

Recommendation

1. Federal ministry of health has to increase the capacity of screening COVID-19 In the community.
2. More restricted actions should be taken by the ministry of health toward the implication of personal protective measures whenever gathering is suspected.
3. Community awareness about the disease must be increased.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

BHMI provide the concept of the study. BHMI, MMMN, WSA contribute in writing the manuscript. BHMI and MMMN analyzed and interpret respondent's data. SMA supervise all the steps. All authors read and approved the final manuscript.

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Review

Case fatality rate of COVID-19: a systematic review and meta-analysis

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Keywords

Case fatality rate • COVID-19 • Meta-analysis • Epidemic • Epidemiology

Summary

Objective. *The ongoing novel coronavirus disease 2019 (COVID-19) is the leading cause of morbidity and mortality due to its contagious nature and absence of vaccine and treatment. Although numerous primary studies reported extremely variable case fatality rate (CFR) of COVID-19, no review study attempted to estimate the CFR of COVID-19. The current systematic review and meta-analysis were aimed to assess the pooled CFR of COVID-19.*

Methods. *Electronic databases: PubMed, Science Direct, Scopus, and Google Scholar were searched to retrieve the eligible primary studies that reported CFR of COVID-19. Keywords: ("COVID-19"OR "COVID-2019" OR "severe acute respiratory syndrome coronavirus 2"OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "SARS-CoV-2" OR "2019nCoV" OR (("Wuhan" AND ("coronavirus" OR "coronavirus")) AND (2019/12[PDAT] OR 2020[PDAT]))) AND ("mortality "OR "mortality" OR ("case" AND "fatality" AND "rate") OR "case fatality rate") were used as free text and MeSH term in searching process. A random-effects model was used to estimate the CFR in this study. I^2 statistics, Cochran's Q test, and T^2 were used to assess the functional heterogeneity between included studies.*

Results. *The overall pooled CFR of COVID 19 was 10.0%(95% CI: 8.0-11.0); P < 0.001; I^2 = 99.7). The pooled CFR of COVID-19 in general population was 1.0% (95% CI: 1.0-3.0); P < 0.001; I^2 = 94.3), while in hospitalized patients was 13.0% (95% CI: 9.0-17.0); P < 0.001, I^2 = 95.6). The pooled CFR in patients admitted in intensive care unit (ICU) was 37.0% (95% CI: 24.0-51.0); P < 0.001, I^2 = 97.8) and in patients older than 50 years was 19.0% (95% CI: 13.0-24.0); P < 0.001; I^2 = 99.8).*

Conclusion. *The present review results highlighted the need for transparency in testing and reporting policies and denominators used in CFR estimation. It is also necessary to report the case's age, sex, and the comorbidity distribution of all patients, which essential in comparing the CFR among different segments of the population.*

Introduction

The ongoing coronavirus 2019 (COVID-19) was initially reported from Wuhan, China, in December 2019. After few weeks, it has been involved in several countries and became a significant global public health problem [1-3]. World Health Organization (WHO) designated COVID-19 as a pandemic disease on March 11, 2020 (WHO, situational Report-52). The most known symptoms of COVID-19 are fever, cough, shortness of breathing, and occasional watery diarrhea [4]. Even though COVID-19 often causes mild symptoms compared to other respiratory infections, it can cause severe illness in certain groups of people, such as the elderly and people with major underlying health problems (cardiovascular disease and diabetes) [5].

There are two key parameters to understand the epidemiological features of an outbreak or epidemic. These are primary reproduction numbers (R_0) and case-fatality rates (CFR) [6, 7]. The R_0 is an epidemiologic metric that has been used to assess the infectiveness of the agents that cause an outbreak. This index explains the average number of new cases generated from an infected person. The higher amount of R_0 indicates the highest transmissibility of the infection agent. An estimated R_0 of the COVID-19 virus is 3.32, which means one infected case can transmit the virus to 3 to 4 susceptible individuals [8]. CFR is another essential index that helps to understand the epidemiological characteristics of an outbreak. The CFR of COVID-19 is defined as the number of deaths in COVID-19 cases divided by the total number of people infected by COVID-19 [9]. Previously reported CFR of COVID-19 is highly variable. The primary cause of this heterogeneity could be varied as a result of surveillance systems sensitivity. Surveillance system sensitivity low due to more than 80% of cases does not show symptoms of the disease or show mild symptoms. Thus, cases missed by the surveillance system are not considered in the denominator and could lead to overestimation of CFR [10, 11]. Several primary studies have been conducted to estimate the CFR of COVID-19 across the world and reported extremely heterogeneous

magnitude. However, no review study has attempted to estimate pooled CRF of COVID-19 from the available literature to understand better the nature of an outbreak and the virulence of the disease. Thus, the current study was aimed to estimate pooled CFR of COVID-19 from primary studies reported from different countries using systematic review and meta-analysis.

Materials and methods

Search strategy

This systematic review and meta-analysis were performed to estimate pooled CRF of COVID-19 from the primary studies published in international electronic databases. Electronic databases: PubMed, Scopus, Science Direct, and Google Scholar were searched to retrieve eligible studies that were conducted to estimate CFR of COVID-19. Keywords: ("COVID-19"OR "COVID-2019" OR "severe acute respiratory syndrome coronavirus 2"OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "SARS-CoV-2" OR "2019nCoV" OR (("Wuhan" AND ("coronavirus" OR "coronavirus")) AND (2019/12[PDAT] OR 2020[PDAT]))) AND ("mortality "OR "mortality" OR ("case" AND "fatality" AND "rate") OR "case fatality rate") were used in free text and MeSH terms.

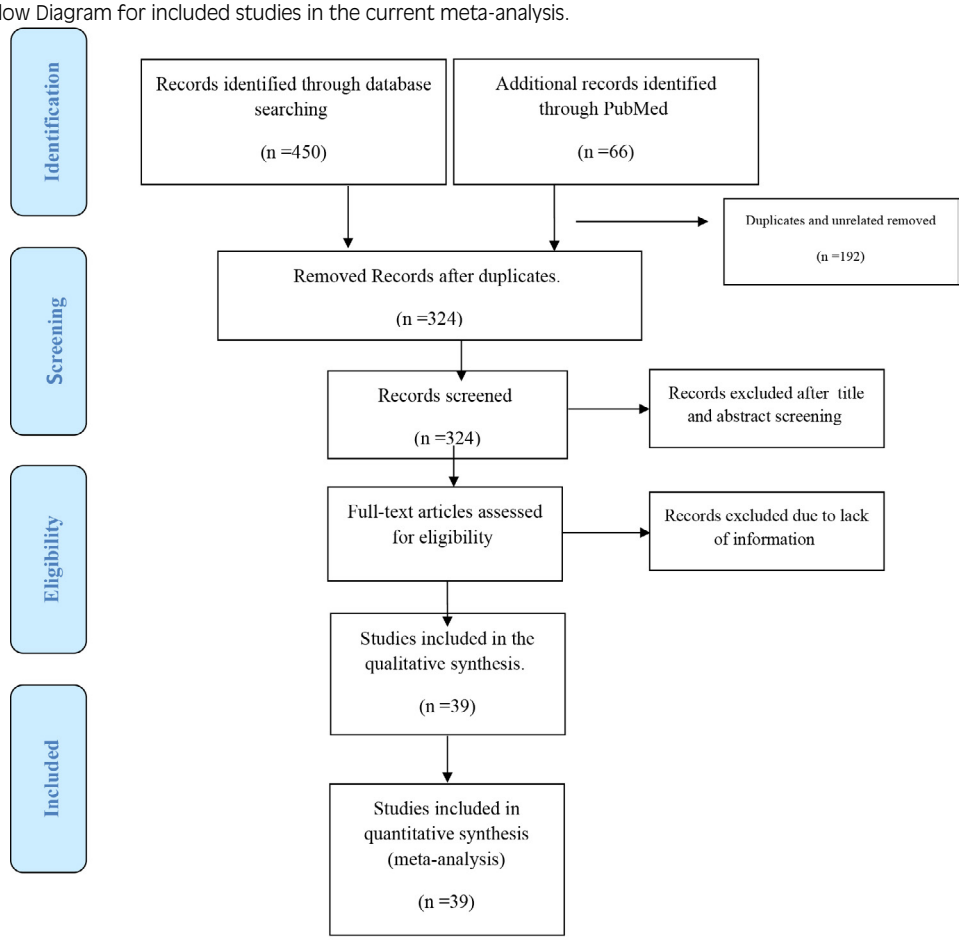
Study selection and data extraction

All studies published in 2020 and reported CFR for COVID-19 were included in this review (Fig. 1). From each included study, extracted information on the first author's name, the country from where the study was reported, year of study, sample size, type of study, age, gender, comorbidity, and CFR with a 95% confidence interval (Tab. I and II).

Statistical analysis

Cochran's Q test's heterogeneity in the CFR of COVID-19 between different studies was assessed with a significance level of $P < 0.1$ and I^2 statistic with values > 75% [12]. A random-effects meta-analysis model was used to estimate pooled CFR because of the presence of high heterogeneity (I^2 = 99.7% and Cochran's Q ($p < 0.001$). The univariate meta-regression model was used to assess the effect of sample size on the heterogeneity of pooled CFR. Publication bias was evaluated by Beggs and Eggers tests. Also, the risk of bias analysis performed using the Newcastle-Ottawa Scale for observational studies [13]. Data were analyzed by STATA v 11 (StataCorp, College Station, TX, USA).

Fig. 1. PRISMA Flow Diagram for included studies in the current meta-analysis.



Tab. I. Included studies in the current meta-analysis.

The first author (publication year)	Country	Sample size	Sex of participant	Mean/ med of age	Study design (randomization, blinding)	Study based	CFR estimation
Wang et al. (2020) [13]	China	138	Both	58	Retrospective single-center case series	Hospitalized	0.043
Grasselli et al. (2020) [14]	Italy	1591	Both	63	Retrospective, case series	ICU, Hospitalized, Total	0.26
Grasselli et al. (2020) [14]	Italy	786	Both	64<=	Retrospective, case series	ICU, Hospitalized	0.36
Grasselli et al. (2020) [14]	Italy	795	Both	<=63	Retrospective, case series	ICU, Hospitalized	0.15
Guo et al. (2020) [15]	China	187	Both	58.5	Retrospective, single-center case series	Hospitalized	0.23
Wei et al. (2020) [16]	China	1975	Both		Cross-sectional	Unknown	0.0284
Yin et al. (2020) [17]	China	449	Both	65.1	Retrospective-cohort	Hospitalized	0.298
Chen et al. (2020) [18]	China	99	Both	55.5	Retrospective, single-center study	Hospitalized	0.11
Xiaobo Yang et al. (2020)[19]	China	52	Both	59.7	Retrospective observational	ICU, Hospitalized	0.615
Zhou et al. (2020) [20]	china	191	Both	56	Retrospective cohort	Hospitalized	0.2827
Barrasa et al. (2020) [21]	Spain	48	Both	63	Cross-sectional	ICU, Hospitalized	0.13
Tang et al. (2020) [22]	China	179		67	Retrospective case-control	Hospitalized	0.288
Lei et al (2020) [23]	China	34	Both	55	Retrospective review patient	Hospitalized, Total	0.206
Lei et al (2020) [23]	China	15	Both	55	Retrospective review patient	ICU admitted	0.467
Lei et al (2020) [23]	China	19	Both	47	Retrospective review patient	Hospitalized	0
Shim et al. (2020) [5]	South-Korea	6284	Both	NR	Cross-sectional	General Population, Total	0.007
Shim et al. (2020) [5]	South-Korea	2345	Male	NR	Cross-sectional	General Population	0.011
Shim et al. (2020) [5]	South-Korea	3939	Female	NR	Cross-sectional	General Population	0.004
Li et al (2020) [24]	China	279	Both	56	Ambispective cohort study	Hospitalized	0.011
Li et al (2020) [24]	China	269	Both	65	Ambispective cohort study	ICU admitted	0.325
Tian et al. (2020) [25]	China	262	Both	47.5	Retrospective	Hospitalized	0.009
Tian et al. (2020) [25]	China	46	Both	61.4	Retrospective	Hospitalized	0.065
Tian et al. (2020) [25]	China	216	Both	44.5	Retrospective	General Population	0
Liu et al. (2020) [26]	China	56	Both	NR	Retrospective study	Hospitalized, Total	NR
Liu et al. (2020) [26]	China	18	Both	68	Retrospective study	Hospitalized	0.0556
Liu et al. (2020) [26]	China	38	Both	47	Retrospective study	Hospitalized	0.0526
Liu et al. (2020) [27]	China	245	Both	43.95	Retrospective cohort	Hospitalized	0.1347
Lei et al (2020) [28]	China	20	Both	43.2	Cross-sectional	Hospitalized	0
Sun et al. (2020) [29]	China	288	Both	44	Cross-sectional	Unknown	0.135

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Tab. I. Included studies in the current meta-analysis.

The first author (publication year)	Country	Sample size	Sex of participant	Mean/ med of age	Study design (randomization, blinding)	Study based	CFR estimation
Mei et al (2020) [30]	World	96580	Both		Cross-sectional	Unknown	0.0363
Cao et al. et al. (2020) [31]	China	199	Both	58	Randomized, controlled, open-label trial	Hospitalized	0.161
Cao et al. (2020) [31]	China	99	Both	58	Randomized, controlled, open-label trial	Hospitalized	0.152
Cao et al. (2020) [31]	China	100	Both	58	Randomized, controlled, open-label trial	Hospitalized	0.17
Bhatraju et al. (2020) [32]	USA	24	Both	64	Retrospective case series	Hospitalized	0.5
Grein et al. (2020) [33]	USA, Canada, Europe, Japan	53	Both	64	Cohort	Hospitalized	0.13
Grein et al. (2020) [33]	USA, Canada, Europe, Japan	34	Both	67	Cohort	Hospitalized	0.18
Grein et al. (2020) [33]	USA, Canada, Europe, Japan	19	Both	53	Cohort	Hospitalized	0.05
Liang et al. (2020) [34]	China	1590	Both	48.9	Retrospective cohort	General Population	0.031
Liang et al. (2020) [34]	China	647	Both	55.1	Retrospective cohort	General Population	0.073
Liang et al. (2020) [34]	China	943	Both	44.6	Retrospective cohort	General Population	0.003
Gao et al. (2020) [35]	China	54	Both	60.4	Cohort	Hospitalized	0.333
Du et al. (2020) [36]	China	109	Both	70.7	Multi-center observational	ICU	0.661
Du et al. (2020) [36]	China	51	Both	68.4	Multi-center observational	ICU	0.706
Du et al. (2020) [36]	China	58	Both	72.7	Multi-center observational	Hospitalized	0.620
Xiao-Wei Xu et al. (2020) [37]	China	62	Both	41	Retrospective study	Hospitalized	0
Cai et al (2020) [38]	Hong-Kong	298	Both	47.5	Retrospective study	General Population, Total	0.01
Cai et al (2020) [38]	Hong-Kong	240	Both	41	Retrospective study	General Population	0
Cai et al (2020) [38]	Hong-Kong	58	Both	62.5	Retrospective study	General Population	0.052
Cao et al. (2020) [39]	China	102	Both	54	Cohort	Hospitalized	0.167
Liu et al. (2020) [40]	China	137	Both	57	Retrospective	Hospitalized	0.118
Young et al. (2020) [41]	Singapore	18	Both	47	Case-series	Hospitalized, Total	0
Young et al. (2020) [41]	Singapore	12	Both	37	Case-series	Hospitalized	0
Young et al. (2020) [41]	Singapore	6	Both	56	Case-series	Hospitalized	0
Wang et al. (2020) [42]	China	69	Both	42	Retrospective review patient	Hospitalized	0.075
Jian Wu et al. (2020) [2]	China	80	Both	46.1	Retrospective	Hospitalized	0

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Tab. I. Included studies in the current meta-analysis.

The first author (publication year)	Country	Sample size	Sex of participant	Mean/ med of age	Study design (randomization, blinding)	Study based	CFR estimation
McMichael et al. (2020) [43]	USA	167	Both	72	Cross-sectional	General Population	0.21
Yanli Liu et al. (2020) [44]	China	383	Both	46	Retrospective cohort	Hospitalized	0.128
Yanli Liu et al. (2020) [44]	China	68	Both	52	Retrospective cohort	Hospitalized	0.309
Yanli Liu et al. (2020) [44]	China	315	Both	43	Retrospective cohort	Hospitalized	0.089
Chen et al. (2020) [45]	China	203	Both	54	Retrospective case series	Hospitalized	0.128
Ning Tang et al. (2020) [46]	China	183	Both	54.1	Cross-sectional	Hospitalized	0.115
Morteza Abdullatif Khafaie et al. 2020 [47]	World	337570	Both		Retrospective-cohort	Unknown	0.0434
Huang et al. (2020) [48]	China	41	Both	49	Prospective	Total	0.15
Huang et al. (2020) [48]	China	13	Both	49	Prospective	ICU	0.38
Huang et al. (2020) [48]	China	28	Both	49	Prospective cohort	Hospitalized	0.04
Wei-Jie Guan et al. (2020) [49]	China	926	Both	45	Retrospective	General Population	0.001
Wei-Jie Guan et al. (2020) [49]	China	173	Both	52	Retrospective	General Population	0.081
Nikpouraghdam et al. (2020) [1]	Iran	2964	Both	55.5	Retrospective	Hospitalized	0.086
Nikpouraghdam et al. (2020) [1]	Iran	2964	Both	55.5	Retrospective	General Population	0.018

Tab. II. The estimated case fatality rate of COVID-19 in different subgroups.

Group	Pooled estimation (%)	95% CI	Q	I^2 (%)
General population	1.00	1.0-3.0	P < 0.001	94.3
Hospitalized patients	13.0	9.0-17.0	P < 0.001	95.6
ICU admitted	37.0	24.0-51.0	P < 0.001	97.8
Unknown	4.0	3.0-5.0	P < 0.001	97.8
≤ 50	3.0	0.0-6.0	P < 0.001	93.7
> 50	19.0	13.0-24.0	P < 0.001	98.1
Unknown	2.0	1.0-3.0	P < 0.001	99.8
Overall	10.0	8.0-11.0	P < 0.001	99.7

Results

Figure 1 depicts the study selection procedure. A total of 516 records were retrieved through electronic databases search, and 324 identified articles after removing 192 pieces due to duplication and irrelevance for the review purpose. The second stape 236 articles were excluded after the title and abstract screeded for the inclusion and exclusion criteria. Of the remaining 88 articles, 49 articles were excluded due to a lack of relevant information or not original articles. Finally, 39 articles reported CFR of COVID-19 were included in the final analysis (Fig. 1 and Table 1).

The Median and IQR(Interquartile range) of reported CFR rate were 8.7%(23.0-1.0). The Minimum and Maximum reported CFR were 0 and 70.6% respectivly (Fig. 2). The overall pooled estimated CFR of COVID-19 was 10.0% (95% CI: 8.0-11.0; P < 0.001, I^2 = 99.7) (Fig. 2). The pooled estimated CFR of COVID-19 among general population was 1.0% (95% CI: 1.0-3.0; P < 0.001, I^2 = 94.3), while in hospitalised patients 13.0% (95% CI: 9.0-17.0; P < 0.001, I^2 = 95.6) (Fig. 2). The pooled estimated CFR of COVID-19 in the patients admited to ICU was 37.0% (95% CI: 24.0-51.0; P < 0.001, I^2 = 97.8), and in patients younger than 50 years 3.0% (95% CI: 0.0-6.0; P < 0.001, I^2 = 99.2), while the CFR was 19.0% (95% CI: 13.0-24.0; P < 0.001, I^2 = 99.8) in patients older than 50 years (Fig. 2 and Table 2). Based

Fig. 2. The forest plot of estimated case fatality rate of COVID-19 in different subgroups.

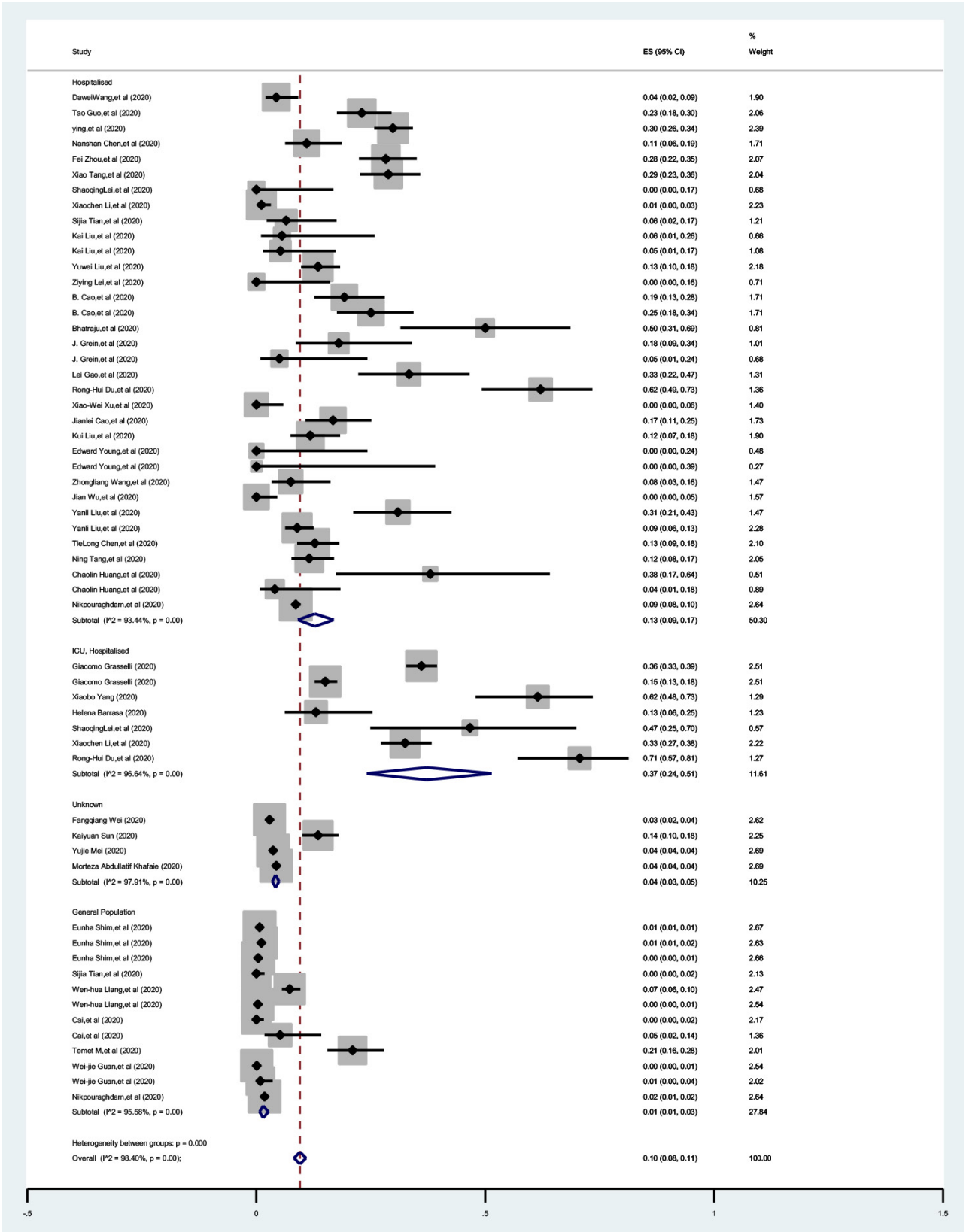
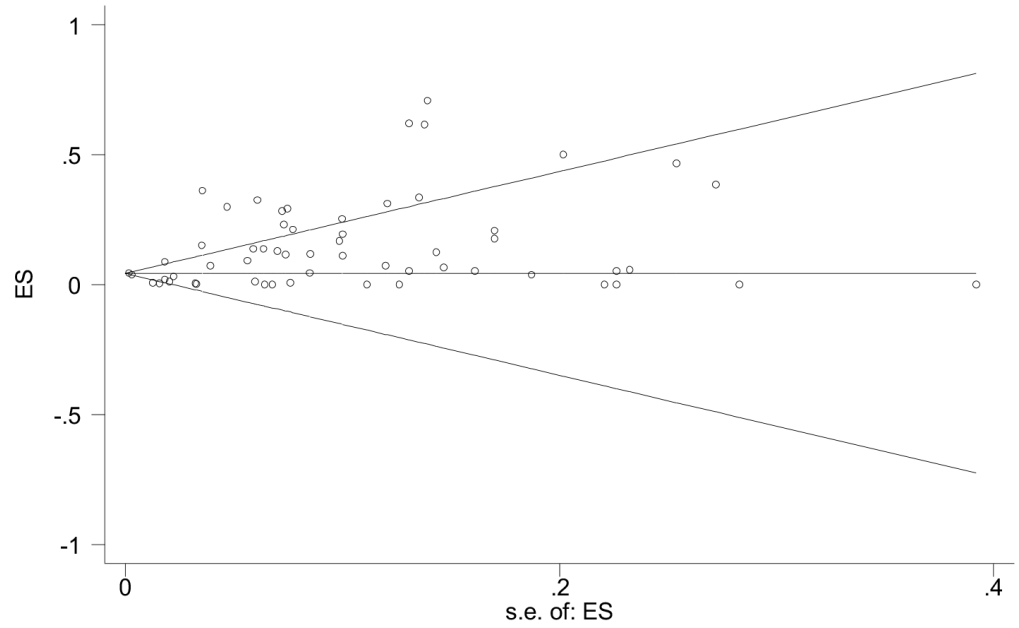


Fig. 3. The beggs funnel plot to assess publication bias.



on Beggs test there was no publication bias(P = 0.2), but the Eggers tests was shown the presence of publication bias (P < 0.001). Moreover, based on metaregresion regression analysis, ample size was not significantly associated with heatrogeneity of pooled estimated CFR (P = 0.31) (Fig. 3).

Discussion

The present study systematically reviewed the available literature to estimate the overall pooled CFR COVID-19 and specific subpopulations in patients admitted in hospital, ICU, and old. Based on 39 studies that fulfilled this study, the overall estimated pooled CFR of COVID-19 was 10.0%. The pooled CRF was only 1.0% in the general population, while 29% in patients admitted in ICU and 15% in hospitalized patients.

Although there is limited information on COVID-19 CFR, some primary studies have been reported CFR in different countries with various target populations. For example, the studies reported from Italy have indicated a 9.26% CFR of COVID-19 [47, 50]. Moreover, studies reported from Spain and France have reported 6.16 and 4.21% CFR, respectively [47, 50]. Furthermore, a study reported from Iran shown that 7.9% of CFR, while the study reported from Turkey indicated 2.0% CFR of COVD-19 [47, 50]. Compared to the previous studies cited above, our meta-analysis finding, based on primary studies reported from different countries, indicated CFR with a wide range. This difference between our CFR with its broad range and the previous study could be due to the target population difference.

Moreover, it might be due to case/death finding and reporting capacity between the countries where the primary studies were reported. Furthermore, case and death reporting in some countries might be influenced by political decisions. Thus, these probable reasons could affect the overall estimation of CFR, which could impact the actual epidemiological feature of the disease. CFR of COVID-19 ranges between 4 and 11% among hospitalized adult patients in different countries based on previous studies [51]. The present study showed that high (13%) CFR in hospital admitted patients. The present study was also revealed that CFR in patients admitted to ICU was 37%. In contrast to our findings, a case series study reported from Seattle indicated high CFR (50%) among critically ill patients [32]. Moreover, a study reported from Washington state the highest CFR (67%) in patients admitted to ICU. Thus the health background of patients admitted to ICU could be an essential factor related to death [52]. For example, among patients admitted to ICU in Washington, 86% have comorbidities such as chronic kidney disease and congestive heart failure [52]. High CFR among patients admitted to ICU is mainly attributable to comorbidities and old age, which exacerbate the morbidity that leads to poor outcomes in patients admitted to ICU. Patients with comorbidities and old age demand great attention to recover from COVID-19, and more evidence requires better understanding to inform health care [32].

The present meta-analysis revealed a significant difference in CFR in the age group younger than 50 years and older (3.0 *vs* 19%). In Italy, CFR was 52.3 in patients more aged than 80 years and 35.6 in 70-79 years old [9]. Similarly, in Chinese, CFR was high among the most aging patients [53]. Besides CFR differences in age groups, the overall CFR reported from Italy (7.2%) is substantially higher than in China (2.3%) [9, 53]. The difference in CFR is not only related to age, rather other factors such as. Occupation, gender, and clinical

comorbid could be contributed to high CFR in the old age group. A better method to preventing possible misconceptions about age effect on CFR in COVID-19 patients direct age adjustment could be a solution.
Several factors could affect on mortality of COVID-19 in different settings due to health system capacity, age variation, the burden of chronic diseases, perception regarding COVID-19, and other unknown factors. For instance, the majority of COVID-19 confirmed cases in Italy are in old proportion. Moreover, most deaths due to COVID-19 in Italy are among geriatric, male patients with comorbidity [9]. In addition, the number of symptoms the cases shown is probably affected by death due to COVID-19. For example, some patients have only one or three main symptoms of COVID-19, but some patients reveal more than three symptoms which most probably affects the death due to COVID-19. Thus, advanced, in-depth analyses are required to explore the effect of the number of signs on fatalities associated with COVID-19.
Prior findings suggested that CFR of COVID-19 seems to be less deadly compared to Bird flu, Ebola, SARS, and MERS , However, it becomes a global economic and public health concern [47, 54]. In most patients, COVID-19 shows mild symptoms, which hid the burden of the disease and facilitate transmission in the community rapidly [47]. Thus, media should play a significant role in enhancing health literacy because the unique characteristics of COVID-19 make the general community at risk. Some undetected or delayed cases could probably lead to underestimation of CFR of COVID-19. Underestimation could be linked to the level of the general public and politicians' preparedness and mitigation.

Conclusions

The pooled estimate CFR of COVID-19 in this review is considerably high and differs between different patient groups. The CFR was higher in patients admitted in ICU and older than 50 years. Moreover, the present review results highlighted the need for transparency in testing and reporting policies and denominators used in CFR estimation. It is also necessary to report the case's age, sex, and comorbidity distribution of all patients, which is essential in comparing the CFR among different population segments.

Ethics statement

Ethics clearance was not sought because this review was based on published articles.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

YA and MS: conception of the idea, data analysis, Manuscript writing, HHT, AAGH and MJ: searching, data extraction, manuscript writing. All authors read and approved the final manuscript.

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Review

Can laboratory tests at the time of admission guide us to the prognosis of patients with COVID-19?

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Keywords

Coronavirus • Mortality • Prognosis • Laboratory tests

Summary

Introduction. *To enhance the COVID-19 patients' care and to optimize utilizing medical resources during the pandemic, relevant biomarkers are needed for prediction of the disease's progression. The current study was aimed to determine the factors that affect the mortality of COVID-19 patients admitted in Baharloo hospital in Iran.*

Methods. *in the current retrospective study, 56 survived patients and 56 patients who were died (a total of 112 cases) because of COVID-19 infection were randomly selected from those who were admitted to Baharloo hospital. Each patient who was diagnosed with COVID-19 and had recovered from it matched with each non-survived patient in the term of age. Laboratory tests of all these patients at the time of admission were recorded and compared. All analyses performed using spss version 22 by considering* $\alpha = 0.05$ *as a significant level.*

Results. *There was no statistical difference in the age and gender distribution between the two groups* ($p > 0.05$). *The prevalence of diabetes among survived patients was 37.5% and among non-survived patients was 26.8% and there was no statistical difference between two groups regarding this comorbidity* ($p = 0.22$). *Also, there was no statistical difference in the prevalence of hypertension and coronary heart diseases between two groups* ($p > 0.05$). *Lymphocyte percentage, blood oxygen level, and platelet (PLT) count was significantly higher in patients who had recovered* ($P < 0.05$).

Conclusions. *LDH level, Lymphocyte percentage, PLT count, and blood Oxygen saturation have associations with severe forms of COVID-19 infection and can be used as predictors to assess the patients who are suspected of infection with COVID-19 at the time of admission.*

Introduction

Since the emerging of novel Corona virus disease 2019 (COVID-19) in December, 2019, this virus has affected nearly 160 million people and caused about 3.25 million deaths worldwide. In Iran, more than 245,000 people are affected which has lead to 11000 deaths in the country up to 7 July 2020 [1]. The symptoms of the COVID-19 are wide from asymptomatic to severe forms of pneumonia and multi organ failure [2-4]. Fever, cough, and fatigue are the most common symptoms of COVID-19 [2]. Case fatality rate is 3.8% and 25.6% of the patients experience the severe forms of the disease [2, 5]. COVID-19 is a highly contagious disease. Human to human transmission is the main cause of COVID-19 transmission and close contact with infected patients may transmit the virus to others [6]. Secondary attack rate of this infection is about 35% [7] and the virus spreads rapidly in populations. Rapid increase in the number of patients impose excess burden on the health care systems and increases the costs [8]. To enhance the patients' care and to optimize utilizing medical resources during this pandemic, relevant biomarkers are needed for prediction of the disease's progression and actively monitoring illness severity at the early stage [2, 3].There are several studies on the factors which can predict the outcome in patients with COVID-19. Old age, low levels of lymphocytes, high levels of C reactive protein (CRP) and cardiac troponin, and D-Dimers levels higher than 1 μg/L were associated with poor prognosis in China [4, 9-11]. In a systematic review by Wynants et al, age, sex, computed tomography (CT) findings, lactate dehydrogenase (LDH), CRP, lymphocytes count, and presence of comorbidities were associated with the prognosis [12]. In previous studies on influenza, there had been differences between populations in the terms of the factors that have been related with mortality. Urea level in Mecedonia [13], CRP in Tunisia, and Creatinine in Taiwan were associated with mortality in patients with influenza . Such may be applicable in

patients with COVID-19 and there may be differences in prognostic factors in different populations. As there are no studies available on the prognostic factors of COVID-19 in Iranian population, the current study was aimed to determine the factors that affect the mortality of COVID-19 patients who were admitted in Baharloo hospital in Iran.

Materials and methods

Study population

Patients included in the current retrospective study were suspected of COVID-19 infection admitted in the Baharloo hospital. Baharloo hospital is a teaching hospital that located in Tehran and is affiliated to Tehran University of medical sciences medical school. This hospital has been COVID-19 referral center since the COVID-19 outbreak in Tehran. Inclusion criteria were: 1) clinical symptoms of COVID-19 such as fever, cough, fatigue, myalgia, dyspnea, chest pain, nausea, vomiting; 2) positive nasopharynx COVID-19 polymerase chain reaction (PCR) test; 3) lung imaging compatible with COVID-19 pneumonia. Patients who were diagnosed with bacterial pneumonia at the time of admission, those whose symptoms had started more than 7 days prior to admission and those whose medical records were incomplete were excluded from our study.

From those who were eligible to be included in our study, 56 patients who were died because of COVID-19 were randomly selected. Also the information of 56 patient who were recovered from the disease and were discharged from the hospital were selected as a control group. A code was dedicated to each patient and all data were recorded anonymously. We reviewed medical records of their recent admission because of COVID-19 infection. Demographic characteristics of patients such as age, gender, and their underlying diseases were recorded. Laboratory and clinical parameters such as blood's O2 Saturation, hemoglobin (Hb), white blood cell count (WBC), percentages of PMN and lymphocyte, platelet count, ESR, CRP, LDH, and serum vitamin D level at the time of admission to emergency department were extracted. The study design was approved by Tehran University of medical sciences ethical committee.

Statistical analysis

The discriptive analysis was performed using the mean (Standard Deviation) or frequency and percent for quantitative and qualitative variables, respectively. The differences in characteristics between survived and non-survived patients were examined using independent t-test for continuous variables and chi-squared test for categorical variables. All analysis performed using SPSS software version 22 by considering $\alpha = 0.05$ as a significant level.

Laboratory analysis

On the first admission day, 10 cc blood sample was obtained and sent to the hospital laboratory for CBC-diff (WBC count, Lymphocyte and PMN percents, Platelet count), LDH, CRP, ESR, and Vitamin D3 level. The automated hematology analyzer, Sysmex KX-21N, was applied for CBC-diff which counted cells and collected information on their size and structure (Lymphocyte, Neutrophil, Platelet). ESR test was made by Therma NE instrument; however, sometimes the western green tubes were used for measurement of sedimentation rate manually. CRP measurement was performed by immunoturbidimetry method using Hitachi 912 and LDH level was performed by enzymatic method using Hitachi 717. Vitamin D3 level was measured by high performance liquid chromatography (HPLC) method using Agilent instrument.

Results

In total 56 survived and 56 non-survived patients included in our study. Of these patients, 77 (68.8%) were male and 35 (31.3%) were female. In survived group 38 (67.9%) of cases were males and 18 (32.1%) of cases were females. In non-survived group 39 (69.6%) of cases were males and the 17 (30.4%) of cases were females. There was no significant difference in gender between two groups (P: 0.83).

The mean of ages among survived patients was 67.14 ± 10.54 and among death cases was 67.96 ± 14.60. There was no significant difference between two groups about age distribution (P = 0.73).

The prevalence of diabetes among among survided and non- survided patients were 37.5% and 26.5% respectively. There was no statistical difference between two group about this comorbidity(p = 0.22).Also there was no statistical difference in prevalence of hypertention and coronary heart diseases between two groups. More information has been shown in Table I.

Lymphocyte percentage was significantly higher in patients who had recovered from the disease as compared with the patients who died (22.76 *vs* 18%)(P = 0.001). PLT level in recovered patients was significantly higher than death cases (214,964 *vs* 167,196/microliter) (P = 0.003). LDH level was significantly higher in those who had not survived from COVID-19 infection compared to those who had recovered (587 vs 487 U/L) (P < 0.001). Also, Blood oxygen saturation was significantly higher in patients who survived COVID-19 compred to those who died (91 *vs* 82%)(P < 0.001). The more information about the Laboratory and clinical measures status in survived and non-survived patients was shown in Table II.

Discussion

COVID-19 pneumonia sometimes progress rapidly to Acute respiratory distress syndrome (ARDS) and even death. Unfortunately, until now, there is no definite treatment for the COVID-19 related illnesses. The

Tab. I. Comparison some factors among survived and non survived cases.

Variales	Total (n = 112)	Survived (n = 56)	Non-survived (n = 56)	P-value
Age group				
< 60	36 (32.1%)	17 (47.2%)	19 (52.8%)	0.68
> 60	76 (67.9%)	39 (51.3%)	37 (48.8%)	
Gender				
Males	77 (68.8%)	38 (50.6%)	39 (49.4%)	0.85
Females	35 (31.2%)	18 (51.4%)	17 (48.6%)	
O2 status				
< 93	66 (84.6%)	36 (54.5%)	30 (45.5%)	0.008
≥ 93	12 (15.4%)	12 (100%)	0(0.0%)	
Comorbidity				
Asthma	2 (1.8%)	0 (0.0%)	2 (100%)	0.15
Diabetes	36 (32.1%)	21 (37.5%)	15 (26.8%)	0.22
Hypertension	34 (30.4%)	19 (33.9%)	15 (26.8%)	0.411
Coronary artery disease	16 (14.3%)	6 (10.7%)	10 (17.9%)	0.28

Tab. II. Comparison of clinical and laboratory measures of survived and non-survived patients.

Variables	Total (n = 112)		Survived (n = 56)		Non-survived (n = 56)		P
	Mean	SD	Mean	SD	Mean	SD	
WBC count/ microliter	7510.18	4162.94	6470.58	3955.02	5257.14	1680.13	0.183
Neutrophil %	75.58	15.42	71.32	10.86	77.14	7.44	0.515
Lymphocyte %	**17.56**	**8.77**	**22.76**	**11**	**18**	**7.11**	**0.001**
Neutrophil / Lymphocyte	6.36	5.89	5.42	6.13	7.29	5.54	0.093
Haemoglobin (g/dL)	13.04	1.97	13.16	2.28	13.35	2.04	0.526
PLT/ microliter	**191080.35**	**85825.73**	**214964.28**	**89961.39**	**167196.42**	**74909.01**	**0.003**
ESR (mm/h)	66.13	29.19	60.58	23.22	58.71	27.18	0.397
CRP (mg/L)	59.32	45.06	55.5	28.63	72.85	22.31	0.101
LDH (U/L)	**664.71**	**445.86**	**487.352**	**142.92**	**587.14**	**161.84**	**< 0.001**
Vitamin D (ng/ml)	25.96	14.56	25.62	15.53	26.52	12.7	0.81
Blood's oxygen Saturation %	86.89	9.02	91	4.01	82.42	10.46	< 0.001

established laboratory markers to assess the illness severity are few and tentative [2, 14].

In the present study, some simple and available biomarkers are investigated and compared between survivor and non- survivor groups. Neutrophil and Lymphocyte counts, neutrophil to lymphocyte ratio, platelet count, LDH and CRP levels usually are economic, rapid and usable laboratory parameters that could straightforwardly discriminate between COVID patients with and without severe disease. Neutrophil count in severe COVID-19 cases were likely to be higher in contrast with lymphocyte count that were lower compared with non-severe patients in previous studies [15]. In MERS coronavirus leukocyte population change was found to be an important factor tied with severity and outcome of the patients [16]. COVID-19 infection causes dysregulation of immunological response and cytokine storm. This phenomenon enhances the neutrophil production and stimulates the lymphocyte apoptosis. On the other hand, severe viral infection may lead to bacterial co-infection, therefore neutrophil count would be raised [15]. NLR, absolute neutrophil count divided by absolute lymphocyte count, is a simple indicator. NLR is a predictor for mortality in malignancies, collagen vascular diseases, infectious diseases, acute coronary syndrome and intracranial hemorrhage. A research showed that higher NLR was tied with mortality in admitted COVID-19 patients [17] but there was no association between severity of the disease and NLR in our study, We found that Lymphocyte count was lower in those who experienced severe forms of the disease. The decrease of Lymphocyte count might be explained by the following mechanisms; direct invasion of lymphocyte through ACE-2 receptor by virus, destruction of lymphoproliferative systems (Spleen, Thymus) by COVID-19, apoptosis of lymphocyte with pro-inflammatory cytokines and suppression of lymphocytes proliferation by lactic acidosis in severe infection [18]. The present study found significant differences in Lymphocyte count between non-survivor and survivor groups ($P < 0.05$). Neutrophil to lymphocyte ratio in the survivors was less than non-survivor, however this difference was not significant ($P > 0.05$) . Platelet count (PLT) was significantly higher in those who had recovered from COVID-19 compared to those who had not in our study. Although, this novel coronavirus is

different from SARS, the mechanism of decrease in PLT count might be similar. Thrombocytopenia in COVID-19 might be explained by platelet activation and aggregation when the virus starts immunological damage of lung tissue. The platelet consumption is increased in the injured area. Disseminated intravascular coagulopathy (DIC) might also be induced by COVID-19 and culminates in thrombocytopenia [14, 19-21]. Moreover, the virus may involve bone marrow directly to lead in the thrombocytopenia [2]. LDH is related with cytokine and chemokine functions. It enhances the immune responsive cells (e.g., CD4+ T cells) and Gamma-Interferon production [22]. Suppression of LDH is linked with decreasing effect of the inflammatory mediators [23]. Previous studies indicated that high LDH levels in some infection such as EBV, PCP, influenza, H1N1 and even Zika virus were related to lung injury [22-25]. COVID-19 invades multiple organs (e.g., lung-intestines, liver, myocardium) through ACE 2 receptors. Therefore, high LDH level in COVID-19 patients might mean multiple organ damages not merely lung injury [22-26]. Our research showed that the LDH levels in non-survivors are significantly higher than the survivor group ($P < 0.005$). It might be due to the accelerating multi-organ failure in the former group as compared to the latter ($P < 0.001$). COVID-19 can directly involve multiple organs, trigger the severe inflammatory response, and produce cytokines (i.e., CRP, interleukins) [22, 23]. CRP activates the complement system and augments phagocytosis. CRP attaches to virus and prompt the phagocyte cells to eliminate microorganisms. These molecules can enhance the pro-inflammatory cytokines (IL1, IL6, Il8, TNF-a, CRP) effects [10, 27-29]. Statistically there was no significant difference in CRP between survival and non-survival groups in our study ($P = 0.101$), however CRP was higher in those who did not survive which may be clinically significant and means more inflammation due to severe infection [24]. The current study had some limitations, We focused on "death" as the index of severity of the disease but there are some other indicators such as admission in ICU that can be used as an indicator of severe form of the disease. Also the sample size in the current study was small and future studies are advised to evaluate the prognostic indicators of COVID-19 infection in larger Iranian populations.

Conclusions

Blood oxygen saturation, LDH level, Lymphocyte count and PLT count are reliable, low expense biomarkers for monitoring COVID-19 patients' outcome. Having these available biomarkers in the first day of admission, can be useful for early management of patients. To confirm these results and identification of other biomarkers in poor outcome patients, other studies are necessary.

The study has the following limitations. It is a unicentric retrospective observational study with a relatively small sample size. Biomarkers were measured only once at the time of admission, so we are unaware if the kinetics of biomarkers could improve or worsen the observed results. We provide several variables in our cohort; however, some variables may be missing, such as lung computed tomography scan information. Although viral presence was confirmed mainly by polymerase chain reaction assay, false positives and false negatives could be present.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: HH, HA. Data curation: All authors. Formal analysis: SA,ANA, YA and MK. Methodology: HA. Project administration: All authors. Writing – original draft: HA,HH. Writing – review & editing: HH, ANA. All authors read and approved the final version of the manuscript.

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Review

Prevention and control of coronavirus epidemic: role of clinical awareness and flow of accurate information

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Dear Editor,

The outbreak of novel coronavirus was originated in Wuhan city of China during December 2019 and was declared as a public health emergency of international concern by World Health Organization (WHO) [1]. As of October 15, 2020, over 38 million laboratory confirmed cases including 1 million deaths reported across the globe [2].

Countries are devising every possible effort to control the rising toll, however, the preventive measures currently in place have not found as effective as desired. The awareness on mode of transmission and risks in local settings must be reinforced among general public especially among those engaged in health care systems [3].

Control and prevention of coronavirus outbreak require scientific evidence based multiple approaches. First of all, it is important to reduced person to person transmission, reducing the infection among the close contacts and frontline health care workers to minimize the spread of virus in the community and within hospitals. Without appropriate protection, the frontline health care workers get infected and become a source of nosocomial and community transmission. Front line health workers should be able to know the clinical signs and symptoms. Several reports indicate that the majority of infected patients with life-threatened symptoms are those with underlying diseases such as diabetes, blood pressure, cardiovascular disease, pulmonary disorder, chronic liver disease, asthma and obesity [4]. Along with the clinical awareness every country must response at initial stages to track contact, self-isolation, quarantine, public health measures such as handwashing, cough etiquette, social distancing, proper use of face mask and other personal protection equipment whenever needed [5].

The health care workers for the first time in their lives are going to use the PPE, if they don't know how to used PPE properly such type of incidence will surely be happen. There is no any communication amongst the epidemiologist, virologist and front line health care physicians' worldwide to get benefit from the experience of each other.

Varieties of deficiencies have been reported in the preparedness program against coronavirus outbreak prevention, especially in South East Asian countries including Pakistan, India, Bangladesh and Afghanistan [6]. Due to the miss behavior of health authorities with the patients, creating panic and fear on media, many confirmed patients escaped from various hospitals in India and Pakistan [7, 8]. Many coronavirus positive cases committed suicide after jumping off the hospitals in Pakistan [9], India, Saudi Arabia, France, Britain, Germany, and Italy due to panic, stress, confusion created by media, insufficient medical facility and misbehaves [10]. Such types of issues require urgent solution otherwise it will become worrisome in coming days. This is the time to win the trust of public with meaningful approach. Without awareness and financial help of the people it would become difficult if the virus gets hold in the rural areas of the region where more than 10 family members lived in single room.

On the other hand flow of misinformation is another major problem in containing the coronavirus outbreak worldwide. Fear based messaging on social media can make a patient feel that he/she is responsible for coronavirus infection. The messaging must be positive every time and convey the message that more than 98% patients recovered from the infection [11]. Misinformation and conspiracy theories floating on the social media have generated panic and confusion among the general public and create hurdle in the outbreak response activities [12]. Fake information regarding the origin of virus to be a synthetic or mutated strain engineered in a laboratory further complicates the control efforts [13]. Through scientific evidence, it has been proven that the SARS-CoV-2 originated in nature and transmitted to humans through a zoonotic event in the recent past [14]. It is already confirmed that at present there is no any treatment in the form of antiviral or vaccine available for coronavirus. In such situation the used home remedies such as garlic, beetroots, lemon juice, Onion, sodium chloride with citric acid, alcohol and many other type of treatment options circulating on social media. However, many of these products are harmless but some are even proved to be very dangerous. Such type of misinformation results in the further public confusion and leading to greater transmission of deadly virus such as reports from Africa on home treatment of HIV infected patients resulted in exacerbated the transmission of HIV and costing more than 300,000 lives [15]. More than 728 individuals have died in Iran after ingesting alcohol, as fake remedies for the new coronavirus spread across social media in Iran [16]. Likewise in India, fake information circulating on social media claimed that drinking of cow urine and applying cow dung on the body can kill coronavirus [17]. In India more than eleven people hospitalized by using poisonous fruit of Datura plant as a treatment of coronavirus [18]. In Thailand, a fake

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news circulating on social media that Vitamin D pills are an effective for the prevention of coronavirus [19]. In England the Director of National Health Services (NHS) described the linking of 5G mobile networks [20] transmitting coronavirus as the worst kind of fake news circulating on social media. In Australia similar fake news circulating on social media that the coronavirus is transmitted from the petrol pumps [21]. Some social media news claiming that coronavirus can be transmitted through Mosquitoes [22]. Supreme leader of Iran said the united states of America created a special version of coronavirus for Iran [23, 24].

Worldwide, it is reported that coronavirus was created by human without any scientific evidence. The medical scientists are still struggling to understand the virus, the social, electronic and print media has already reporting the various dangerous effects of the virus along with variety of treatment options without any scientific evidence which in turn create panic and confusion amongst the public [25]. Government and media must utilize the opinions of the experts such as epidemiologist, Virologist and public health professional to deliver the authentic and accurate information which will be surely helpful in reducing the panic amongst the general public. If medical authorities sensibly educate and resolve the public issues, the containment of the virus would become much easier. Government official, media and health authorities across the globe must inform the general public about the reality regarding the coronavirus epidemic and educate them how to stay away from the coronavirus infection [26].

Coronavirus pandemic is a global health crisis, so collective efforts are needed to deal with such crisis. Information for the control and treatment of coronavirus at local, national and, international forums must be provided using authentic source like CDC, WHO or FDA. Accurate clinical, epidemiological and laboratory findings can result in better planning and implementations of awareness, control and prevention strategies.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors equally contributed to this paper.

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Review

Age-related risk factors and severity of SARS-CoV-2 infection: a systematic review and meta-analysis

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Keywords

COVID-19 pandemic • Symptoms and comorbidities • Systematic review • Age-related risk factors • Correlation analysis

Summary

Objectives. *We aimed to estimate the prevalence of reported symptoms and comorbidities, and investigate the factors associated with age of the SARS-CoV-2 infected patients.*
Methods. *We performed a systematic review with meta-analysis (PROSPERO registration: CRD42020182677) where the databases (PubMed, SCOPUS, EMBASE, WHO, Semantic Scholar, and COVID-19 Primer) were searched for clinical studies published from January to April, 2020. Initially, the pooled prevalence of symptoms and comorbidity of COVID-19 patients were estimated using random effect model and the age –related factors were identified performing multivariate analysis [factor analysis].*
Results. *Twenty-nine articles with 4,884 COVID-19 patients were included in this study. Altogether, we found 33 symptoms and 44 comorbidities where the most frequent 19 symptoms and 11 comorbidities were included in the meta-analysis. The fever (84%), cough/dry cough (61%), and fatigue/weakness (42%) were found more prevalent while acute respiratory distress syndrome, hypertension and diabetes were the most prevalent comorbid condition. The factor analysis showed positive association between a cluster of symptoms and comorbidities with patients' age. The symptoms comprising fever, dyspnea/shortness of breath, nausea, vomiting, abdominal pain, dizziness, anorexia and pharyngalgia; and the comorbidities including diabetes, hypertension, coronary heart disease, COPD/lung disease and ARDS were the factors positively associated with COVID-19 patient's age.*
Conclusion. *As an unique effort, this study found a group of symptoms (fever, dyspnea/shortness of breath, nausea, vomiting, abdominal pain, dizziness, anorexia and pharyngalgia) and comorbidities (diabetes, hypertension, coronary heart disease, COPD/lung disease and ARDS), associated with the age of COVID-19 infected patients.*

Introduction

The COVID-19 pandemic caused by Severe Acute Respiratory Virus 2 (SARS-CoV-2) is a serious public health crisis in the history of humanity. Originated in Wuhan, China, SARS-CoV-2 has spread to every corner of the world within a few months. As of March 22, 2021, over 123 million confirmed cases and 2.72 million deaths have been reported from over 219 countries [1].
As the virus is moving fast, various clinical spectrum and differential clinical outcomes are unfolding across different geographic locations. Several symptoms have been reported which includes fever, cough, myalgia, sputum production, headache, hemoptysis, diarrhea, and dyspnea [2]. The severity of COVID-19 has been reported to be linked with various host factors including diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease (COPD), malignancy, and chronic liver disease [2]. While susceptibility to COVID-19 covers all age groups, people with compromised immune systems and or having comorbidity are at a higher risk [3, 4]. A few review studies investigated symptoms and comorbidities of the COVID-19 infected patients with a shorter time-frame [3, 5-8]. The mortality rate is high in older COVID-19 patients with organ dysfunctions comprising shock, acute respiratory distress syndrome (ARDS), acute cardiac injury, and acute kidney injury [9]. However, there is a scarce information regarding the relationship between symptoms, comorbidities, and age of the COVID-19 patients. The objective of this study was to estimate the prevalence of all reported symptoms and comorbidities, and then identified the risk factors associated with age of COVID-19 infected patients.

Methods

The PRISMA-P-2009 guidelines was followed in our systematic review and meta-analysis (PROSPERO registration: CRD42020182677) [10].

Data sources and search strategy

The major databases, such as PubMed, SCOPUS, EMBASE, WHO, Semantic Scholar, and COVID-19

Tab. I. Search strategy used in different databases.

PubMed	SCOPUS/EMBASE	WHO/Semantic Scholar
ALL ("COVID-19" OR "COVID-2019" OR "severe acute respiratory syndrome coronavirus 2" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "nCoV" OR "SARS-CoV-2" OR "2019nCoV" OR "coronavirus") AND ALL ("clinical for epidemiological characterization" OR "Symptom" OR "Symptoms") AND ALL ("comorbidity" OR "comorbidities" AND full text[sb] AND ("2019/12/31"[PDat] : "2020/04/30"[PDat]) AND Humans[Mesh]	ALL ("COVID-19" OR "COVID-2019" OR "severe acute respiratory syndrome coronavirus 2" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "nCoV" OR "SARS-CoV-2" OR "2019nCoV" OR "coronavirus") AND ALL ("clinical for epidemiological characterization" OR "Symptom" OR "Symptoms") AND ALL ("comorbidity" OR "comorbidities") AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (PUBYEAR , 2020)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re"))	("COVID-19" OR "COVID-2019" OR "severe acute respiratory syndrome coronavirus 2" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "nCoV" OR "SARS-CoV-2" OR "2019nCoV" OR "coronavirus") AND ("clinical or epidemiological characterization" OR "Symptom" OR "Symptoms") AND ("comorbidity" OR "comorbidities")

Primer were searched to include peer-reviewed and pre-proof research articles. The mortality starts falling at the end of April 2020 [11] and we limited our review within initial period to high mortality period. Also, our literature search strategy covered almost hundred percent of the COVID-19 symptoms and comorbidities, and the overall sample size for our data analysis was sufficiently large [n = 4,884]. Therefore, we restricted our search language in only English literature within the time period January to April, 2020.

The search terms used included: "COVID-19" OR "COVID-2019" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "2019nCoV" OR "nCoV" OR "SARS-CoV-2" OR "coronavirus" AND "clinical for epidemiological characterization" OR "Symptom" OR "Symptoms" AND "comorbidity" OR "comorbidities". Some articles were manually retrieved from Google Scholar and other databases. We also searched the reference lists of the selected publications. MMR, BB, and MJU independently screened the titles and abstracts of the articles and checked full-text eligibility (Tab. I).

Inclusion/exclusion criteria

Research articles were selected if they reported clinical characteristics (both symptoms and comorbidities) of the COVID-19 patients. The inclusion criteria for studies were: clinical investigations or consecutive cases; focused on infected patients; reported at least ten cases and considered all age-groups from any countries. Studies were excluded if they were: grey literature, case report, and secondary studies; specific to children or pregnant women; less than 10 small sample; and only reported symptoms or comorbidities. A standardized form was used to extract data from eligible studies. Disagreements were resolved through discussion with co-reviewers. For each study, publication details, research design and the participants' characteristics with major findings were recorded.

Data quality assessment and analysis

The quality of each study was assessed by ZF using Joanna Briggs Institute (JBI) guidelines [12]. A set of eight questions was used for the quality assessment. Random effect model was used to estimate the prevalence of all reported symptoms and comorbidities in the COVID-19 patients. Heterogeneity was assessed using the Cochran Q and the I^2 statistic [13, 14]. We performed Egger test ($p < 0.001$) to examine the presence of publication bias and small-study effects. Multivariate analysis [multivariable factor analysis (MFA)] was performed to examine the correlation/association among symptoms and comorbidities with the patients' age [15, 16]. All statistical analyses were conducted by Stata version 15 (Stata Corp, College Station, TX) using the metaprop, metabias; and R-programming language using the FactoMineR package.

Supplementary Table S1 have provided in the supplementary file. Please see supplementary file.

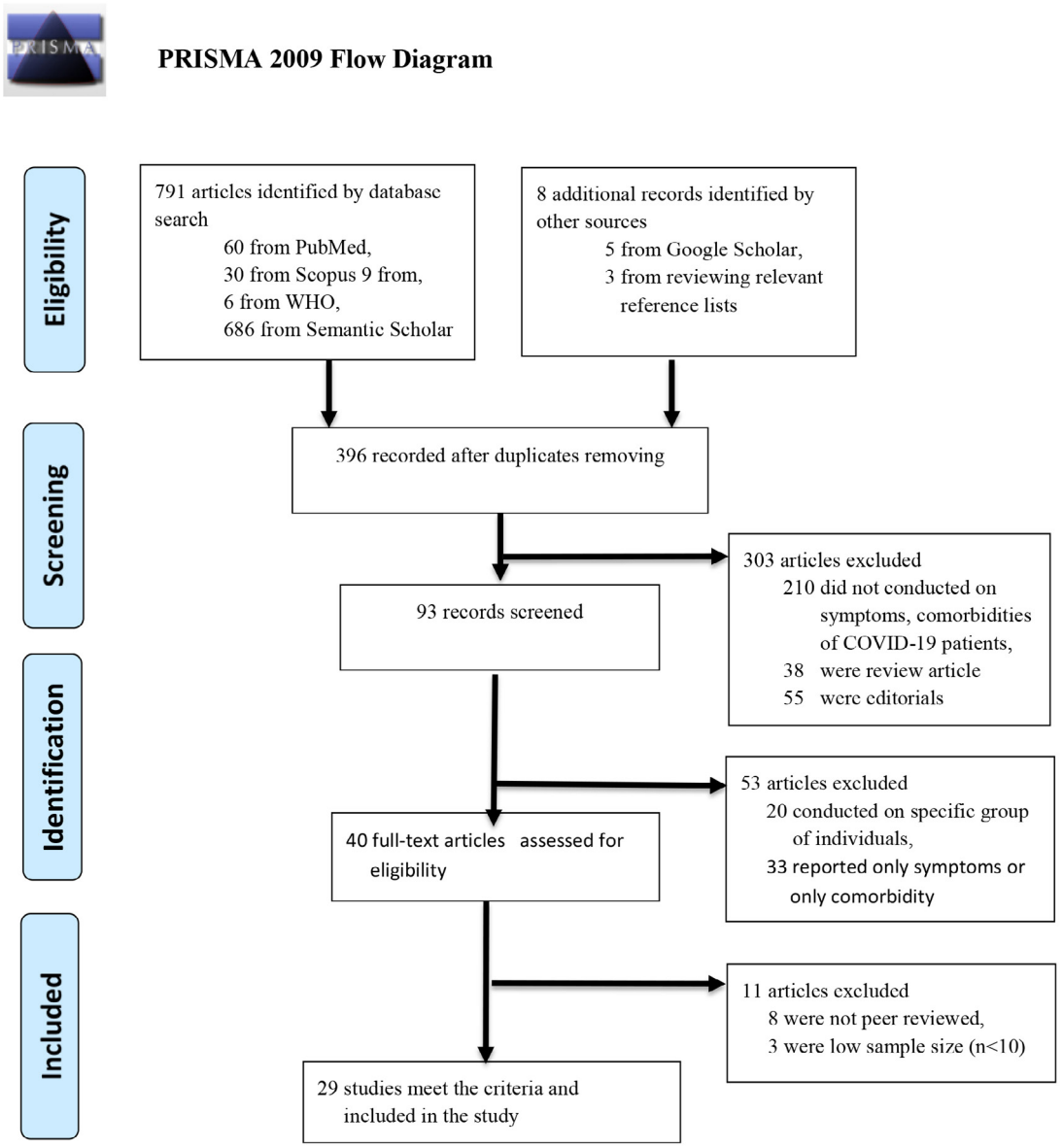
Results

A total of 799 articles (databases: 791, other sources: 8) were retrieved. Of them, 403 articles were removed due to duplication and irrelevance. Furthermore, 303 review articles, editorials, case reports, and irrelevant study populations were excluded. Fifty-three articles were excluded as they failed to meet all inclusion criteria. Finally, eleven articles were excluded due to not peer-reviewed and small sample sizes, resulting in the selection of 29 articles for our review. The PRISMA flow diagram visualizes the screening process of selected studies (Fig. 1).

Supplementary Table S1 summarizes the characteristics of the selected studies and 83% of selected studies for this meta-analysis were reported from China. Five studies were conducted in the USA, India, Spain, and South Korea. The overall sample size was 4,884 COVID-19 patients, with an age range of 10 to 92 years. Among the patients, 2,675 (55%) were male, and 2,208 (45%) were female. The sample size ranged from 12 to 1,099 patients, where most studies (79%) had a retrospective research design.

Altogether, 33 symptoms and 43 comorbidities were found. Almost all the studies reported fever (proportion of

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for the study selection process.



patients ranging from 25 to 100%), cough/dry cough (22-92%) and myalgia or muscle ache (3-63%) as common symptoms of COVID-19. Other reported symptoms were: headache (3-66%); diarrhea (3-48%); fatigue/weakness (9-85%); dyspnea/shortness of breath (1-88%); sputum production or expectoration (4-42%); vomiting (1-19%); nausea (4-27%); chest tightness (7-55%); and sore throat (5-32%). For the comorbidities, about 93% and 86% of studies reported two comorbidities: diabetes (2 to 35%) and hypertension (8-50%). Other prevalent comorbidities were chronic obstructive pulmonary disease (COPD)/ lung infection (0.2-38%); cardiovascular disease (5-23%); chronic liver disease (1-29%); malignancy (1-7%); coronary heart disease (1-33%); cerebrovascular disease (1-19%); chronic renal disease (1-8%); chronic kidney disease (1-29%); and Acute respiratory distress syndrome (ARDS) (17-100%). The less reported symptoms and comorbidities were presented in Supplementary Table S1.

Meta-analysis of symptoms and comorbidities

We meta-analysed 19 symptoms and 11 comorbidities, using random effect models that were reported in at least five selected articles (Tab. II and Supplementary Figs S2-S31). Meta-analysis showed a higher prevalence of fever (pooled prevalence: 84, 95% confidence interval (CI): 80-88%) and cough/dry cough (61, 95% CI: 55-67%); followed by fatigue/weakness (42, 95% CI: 34-51%); dyspnea/shortness of breath (39, 95% CI: 27-51%); headache and diarrhea (12, 95% CI: 8-17%); sore throat (15, 95% CI: 11-20%); myalgia/muscle ache and sputum production/expectoration (24, 95% CI: 18-30%); rhinorrhea (13, 95% CI: 4-26%); chest tightness (25, 95%

CI: 15-31%); and anorexia (26, 95% CI: 16-38%). The less prevalent symptoms were: chest pain (3%), nausea (8%), vomiting (6%), abdominal pain (4%), dizziness (5%), pharyngalgia (7%), and hemoptysis (2%).

The most prevalent comorbidities were ARDS (61, 95% CI: 15-97%), hypertension (23, 95% CI: 18-28%), and diabetes (12, 95% CI: 9-15%), followed by cardiovascular disease (10, 95% CI: 7-13%); coronary heart disease (7, 95% CI: 3-12%); cerebrovascular disease (6, 95% CI: 2-08%); COPD/lung disease (3, 95% CI: 02-50%); chronic liver disease (05, 95% CI: 03-07%); chronic Renal disease (0.01, 95% CI: 00%-03%); chronic Kidney disease (05, 95% CI: 02-10%); and malignancy (03, 95% CI: 02-04%).

There was a high heterogeneity (I^2 ranged from 85 to 97%, Cochran Q-statistic $p < 0.001$) in all the prevalence of symptoms, except chest pain ($I^2 = 0\%$, Cochran Q-statistic $p < 0.95$); abdominal pain ($I^2 = 22.89\%$, Cochran Q-statistic $p < 0.26$); dizziness ($I^2 = 64.21\%$, Cochran Q-statistic $p < 0.002$); and haemoptysis ($I^2 = 63.48\%$, Cochran Q-statistic $p < 0.01$). In the case of comorbidities, the heterogeneity was found higher in almost all the comorbidities (I^2 ranged from 68.06 to 98.01%, Cochran Q-statistic $p < 0.001$) (Tab. II).

Symptoms and comorbidity factors associated with age of COVID-19 infected Patients

Nineteen symptoms and 11 comorbidities were categorized into: symptom group and comorbidity group to determine the association between symptoms/comorbidities and age of the COVID-19 patients (Fig. 2). In factor analysis, the correlation circle represented between/within-group integration with the patients' age. The longer vectors indicated more influential than others, and the vectors that were close to each other with the same direction indicated a highly positive association. Vectors that were the opposite direction showed a negative association, and the vectors with an almost 90-degree angle demonstrated no association. The first principal component showed 31.59% variation and the second one showed 20.45% variation in the dataset.

Tab. II. Overall prevalence summary for clinical symptoms and comorbidities of the COVID-19 patients.

Clinical characteristics (symptoms)	No. reports	No. patients	Pooled prevalence	Test for Heterogeneity		Egger's test
				I^2 (%)	P-value	
Fever	29 (100%)	4,115	0.84 (0.80-0.88)	90.670	< 0.001	< 0.001
Cough/dry cough	29 (100%)	3,039	0.61 (0.55-0.67)	93.400	< 0.001	0.382
Fatigue/Weakness	21 (72.41%)	1,627	0.42 (0.34-0.51)	96.320	< 0.001	0.107
Dyspnoea/shortness of breath	18 (62.06%)	920	0.39 (0.27-0.51)	97.370	< 0.001	< 0.001
Headache	22 (72.86%)	448	0.12 (0.09-0.16)	89.980	< 0.001	0.109
Diarrhoea	22 (72.86%)	474	0.12 (0.08-0.17)	93.720	< 0.001	0.004
Sore throat	9 (31.03%)	348	0.15 (0.11-0.20)	84.990	< 0.001	0.266
Myalgia/muscle ache	25 (86.20%)	925	0.24 (0.18-0.30)	95.000	< 0.001	< 0.001
Rhinorrhoea	5 (17.24%)	48	0.13 (0.04-0.26)	88.010	< 0.001	0.088
Sputum production/expectoration	15 (51.72%)	1,066	0.24 (0.19-0.30)	92.310	< 0.001	0.956
Chest tightness	11 (37.93%)	462	0.25 (0.15-0.31)	88.440	< 0.001	0.527
Chest pain	5 (17.24%)	15	0.03 (0.01-0.04)	0.000	< 0.95	0.878
Nausea	12 (41.37%)	238	0.08 (0.04-0.12)	91.780	< 0.001	0.023
Vomiting	14 (48.27%)	209	0.06 (0.03-0.09)	88.330	< 0.001	0.096
Abdominal pain	6 (20.68%)	42	0.04 (0.03-0.06)	22.890	< 0.26	0.431
Dizziness	6 (20.68%)	71	0.05 (0.03-0.08)	64.21	< 0.002	0.132
Anorexia	7 (24.13%)	339	0.26 (0.16-0.38)	94.470	< 0.001	< 0.001
Pharyngalgia	6 (20.68%)	86	0.07 (0.04-0.13)	88.030	< 0.001	0.017
Haemoptysis	7 (24.13%)	47	0.02 (0.01-0.04)	63.480	< 0.01	0.005
Comorbidity						
Diabetes	27 (93.10)	539	0.12 (0.09-0.15)	83.09	< 0.001	0.009
Hypertension	25 (86.20)	1,096	0.23 (0.18-0.28)	93.24	< 0.001	0.149
Cardiovascular disease	15 (51.72)	212	0.1 (0.07-0.13)	73.96	< 0.001	0.031
Coronary heart disease	10 (34.48)	141	0.07 (0.03-0.12)	92.21	< 0.001	0.007
Cerebrovascular disease	10 (34.48)	100	0.06 (0.02-0.08)	90.77	< 0.001	0.004
COPD/lung disease	21 (72.41)	136	0.03 (0.02-0.05)	86.67	< 0.001	< 0.001
Chronic liver disease	15 (51.72)	96	0.05 (0.03-0.07)	78.23	< 0.001	< 0.001
Chronic renal disease	9 (31.03)	32	0.01 (0.00-0.03)	54.63	< 0.001	0.003
Chronic kidney disease	6 (20.68)	41	0.05 (0.02-0.10)	86.69	< 0.001	0.036
Malignancy	15 (51.72)	82	0.03 (0.02-0.04)	68.06	< 0.001	< 0.001
ARDS**	4 (13.79)	111	0.61 (0.15-0.97)	98.01	< 0.001	0.301

** ARDS reported in four studies and we include this study into our analysis because it showed higher prevalence rate.

In symptom group, fever, dyspnea/shortness of breath, nausea, vomiting, abdominal pain, dizziness, anorexia, and pharyngalgia were found positively associated with the COVID-19 patients' age. In contrast, sore throat, headache, rhinorrhea, myalgia/muscle ache, fatigue, and hemoptysis were negatively associated with age. Similarly, in the comorbidity group, diabetes, hypertension, coronary heart disease, COPD/lung disease, and ARDS were in the same direction and positively associated with the age of the COVID-19 infected patients. The symptoms like chest tightness/pain and the comorbidities, including chronic liver and kidney diseases, showed no association with the patients' age.

Considering group integration, the fever, dyspnea/shortness of breath, dizziness, pharyngalgia, and anorexia in the symptom group were positively associated with diabetes, ARDS, and kidney, cardiovascular, and liver diseases in comorbidity group. The symptoms like diarrhea, nausea, vomiting, and abdominal pain were positively associated with hypertension, coronary heart disease, and COPD/lung disease. The symptoms of sore throat, headache, rhinorrhea, myalgia/muscle ache, fatigue, and hemoptysis were positively associated with cerebrovascular disease (Fig. 2).

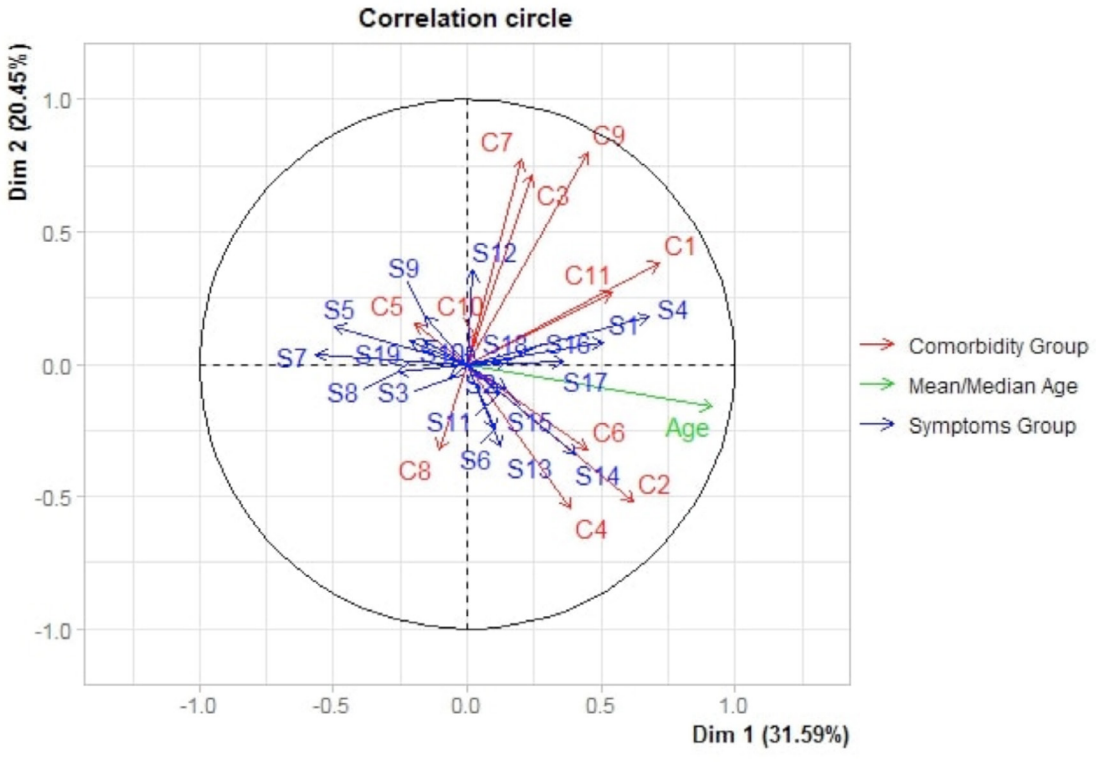
Table III summarizes the quality assessment of the selected studies. In 16 (55%) studies, participant recruitment method was appropriate, while the method was unclear in 45% studies. Thirteen (45%) studies had a sample size of more than 100, and about 96% of studies reported the subjects and design in detail. Validated methods were used in all studies, where the measurement was reliable, and the response rate was 100% (Tab. III).

The Egger test of symptoms – fever, dyspnea/shortness of breath, diarrhea, myalgia/muscle ache, nausea, anorexia, pharyngalgia, and hemoptysis – were found significant ($p < 0.05$), which suggested the presence of small-study effects. The comorbidities- diabetes, cardiovascular disease, cerebrovascular disease, COPD/lung disease, chronic liver disease, chronic renal disease, chronic kidney disease, and malignancy were found significant ($p < 0.05$) by the Egger's test, that recommended the presence of small-study effects.

Discussion

We aimed to estimate the prevalence of all reported symptoms and comorbidities, and investigate the factors associated with age of patients tested positive in COVID-19. In our selected 29 studies, the ratio

Fig. 2. Group association of symptoms and comorbidities with age of the COVID-19 patients (*Symptom Group*: S1: Fever, S2: Cough/Dry cough, S3: Fatigue, S4: Dyspnea/Shortness of breath, S5: Headache, S6: Diarrhea, S7: Sore Throat, S8: Myalgia/Muscle Ache, S9: Rhinorrhea, S10: Sputum Production/Expectoration, S11: Chest tightness, S12: Chest pain, S13: Nausea, S14: Vomiting, S15: Abdominal Pain, S16: Dizziness, S17: Anorexia, S18: Pharyngalgia, S19: Haemoptysis. *Comorbidity Group*: C1: Diabetes, C2: Hypertension, C3: Cardiovascular Disease, C4: Coronary heart disease, C5: Cerebrovascular disease, C6: COPD/Lung disease, C7: Chronic liver disease, C8: Chronic Renal disease, C9: Chronic Kidney disease, C10: Malignancy, C11: ARDS).



Tab. III. Quality assessment of the selected studies.

Authors	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriately?
Wan et al. [17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhang et al. [18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Xu et al. [19]	Not Clear	No	Yes	Yes	Yes	Yes	Yes	Yes
Zhu et al. [20]	Not Clear	No	Yes	Yes	Yes	Yes	Yes	Yes
Chen et al. [21]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Liu et al. [22]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Chen et al. [23]	Not Clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mo et al. [24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liu et al. [25]	Not Clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jin et al. [26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang et al. [27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yuan et al. [28]	Not Clear	No	Yes	Yes	Yes	Yes	Yes	Yes
Guan et al. [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liu et al. [30]	Not Clear	No	Yes	Yes	Yes	Yes	Yes	Yes
Zhou et al. [31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Huang et al. [2]	Not Clear	No	Yes	Yes	Yes	Yes	Yes	Yes
Chen et al. [32]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Du et al. [33]	Not clear	No	Yes	Yes	Yes	Yes	Yes	Yes
Xu et al. [34]	Yes	No	Yes	Yes	Yes	Yes	Not Clear	Yes
Goyal et al. [35]	Not Clear	Yes	Yes	Yes	Yes	Yes	Not Clear	Yes
Barrasa et al. [36]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Yan et al. [37]	Yes	No	Not Clear	Yes	Yes	Yes	Yes	Yes
Gupta et al. [38]	Not Clear	No	Yes	Yes	Yes	Yes	No	Yes
Yang et al. [39]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Han et al. [40]	Not Clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kim et al. [41]	Yes	No	Yes	Yes	Yes	Yes	Not Clear	Yes
Wang et al. [42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shi et al. [43]	Not Clear	No	Yes	Yes	Yes	Yes	Yes	Yes
Yang et al. [44]	Not Clear	No	Yes	Yes	Yes	Yes	Yes	Yes

of infection was reported higher in males than in females (100:82.5), and this result is consistent with previous studies [2, 5, 27, 45]. It is generally assumed that males are more likely to be infected by bacteria and viruses than females, because of the women's robust innate and adaptive immune responses [3, 46]. Moreover, males are more vulnerable to infectious disease because of different patterns of occupation, social communication, and lifestyle than females. Furthermore, in many developing countries, women are housewives who stay at home and have little contact with others [47].

We found 33 symptoms and 43 comorbidities in the studies, and our meta-analysis included most reported 19 symptoms and 11 comorbidities. Fever, cough/dry cough, fatigue, dyspnea, anorexia, chest tightness, myalgia, sore throat, rhinorrhea, headache, and diarrhea were highly prevalent symptoms where the others symptoms were found rarely. All studies reported fever (84%) and cough/dry cough (61%) as symptoms consistent with relevant studies across the countries [19, 23, 25, 48]. Previous studies reported hypertension as the most common comorbidity [3, 6, 7], but our study suggests three major comorbidities – acute respiratory distress syndrome (61%), hypertension (23%), and diabetes (12%). Acute respiratory distress syndrome was found a higher prevalence rate (61%) as reported in three studies in China and one in outside China [28, 32, 36, 44]. We observed that the symptoms like anorexia (26%), chest tightness (25%) and rhinorrhea (13%), and one comorbidity, i.e., acute respiratory distress syndrome (61%) were examined with significant prevalence, but they were under-reported in the published systematic reviews [5, 6, 49, 50].

Human aging is associated with declines in adaptive and innate immunity, and it loses the body's ability to protect against infections [51-53]. Virologists and clinicians agree that the older adults are more vulnerable to COVID-19, and the patient's age can strongly be associated with symptoms and comorbidities [30, 54-57]. Our multivariate analysis revealed that a cluster of symptoms, including fever, dyspnea/shortness of breath, nausea, vomiting, abdominal pain, dizziness, anorexia, and pharyngalgia, as well as a cluster of comorbidities, including diabetes, hypertension, coronary heart disease, COPD/lung disease, and ARDS, were positively associated with the age of COVID-19 infected patients. The Centers for Disease Control and Prevention (CDC) suggested that the older adults are more likely to be asymptomatic and they are at greater risk of requiring hospitalization or dying if they are diagnosed with COVID-19 [58]. The comorbid conditions (e.g. hypertension, heart problems, diabetes) and disease symptoms were more severe in the elderly age than any other age groups [59-63]. In a study, Wu Z and the authors reported that the COVID-19 infected elderly aged above 80 years had a higher case fatality rate (14.8 *vs* 8.0%) than 70-80 years aged peoples [64]. The World Health Organization (WHO) reported that older people with pre-existing medical conditions including asthma, diabetes, and heart disease appear to be more vulnerable to becoming severely ill with the virus and this findings supports to many other studies [65-68].

During literature search, we were limited to only in English texts within the time frame January to April, 2020. The majority of the studies were found in China, and only five from other countries. More studies outside of China could add value in prevalence estimation. We found no data for <10 years children and thus, more studies are warranted in the child COVID-19 patients. Lastly, a few studies were found low sample size.

Conclusions

This review study is the unique effort of its kind that estimated all frequent symptoms and comorbidities, and determines the age related risk factors of the COVID-19 patients. We found a cluster of symptoms and comorbidities that were the age associated risk factors of patients infected in COVID-19. Thus, in very early stages of SARS-CoV-2 infection, if a patient exhibits any of the symptoms within the cluster, this patient should be isolated and the necessary actions should be taken. Our findings also suggest a prioritize vaccination by age groups and older people with underlying conditions. Finally, policymakers should develop a comprehensive mass media campaign to educate the general population about these symptoms and comorbidities.

Data availability statement

The full list of data and the data entries for all included studies is provided in the manuscript as a supplementary file. No additional supporting data is available.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MMR contributed to conceptualization, design and supervision of the study. MMR, BB and ZF

contributed to the screening of studies for inclusion and data extraction. MMR, BB, MJU and MABC searched the databases. MMR and ZF contributed to the analysis and interpretation of the data. MMR, BB and MH contributed to drafting and formatting of the manuscript. MMR, MH, MABC, MSH, MHS, MZI, ER and MJU contributed to supervision, editing and checking of the manuscript. All authors contributed to the reviewing for important intellectual context and approved of the manuscript to be submitted.

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Supplementary Material

S1. Characteristics of studies that evaluated the age related risk factors of COVID-19 patients.

Authors	Publication Date	Country & Location	Study Design	Mean/ Median Age	Patient No. (n)	Male (n)	Female (n)	Gender	Fever	Cough / Dry cough	Fatigue	Dyspnoea/ Shortness of breath	Headache	Diarrhoea
Wan et al.	21.3.2020	Chongqing, China	N/M	47	135	72	63	Both	0.89	0.77	0.33	0.13	0.33	0.13
Zhang et al.	18.2.2020	Wuhan, China	N/M	57	140	71	69	Both	0.79	0.64	0.64	0.31	N/M	0.13
Xu et al.	19.2.2020	Zhejiang, China	Retrospective	41	62	35	27	Both	0.77	0.81	0.52	N/M	0.34	0.08
Zhu et al.	13.3.2020	Anhui, China	Retrospective	46	32	15	17	Both	0.84	0.66	0.16	N/M	0.03	0.03
Chen et al.	16.02.2020	Wuhan, China	Retrospective	56	21	17	4	Both	0.99	0.80	0.85	0.52	0.10	0.20
Liu et al.	9.02.2020	Shenzhen, China	N/M	60	12	8	4	Both	0.83	0.92	N/M	N/M	N/M	0.17
Chen et al.	26.03.2020	Wuhan, China	Retrospective	62	274	171	103	Both	0.91	0.68	0.50	0.44	0.11	0.28
Mo et al.	16.3.2020	Wuhan, China	Retrospective, single center	54	155	86	69	Both	0.81	0.63	0.73	0.32	0.10	0.05
Liu et al.	07.02.2020	Hubei, China	Retrospective	57	137	61	76	Both	0.82	0.48	0.32	0.19	0.10	0.08
Jin et al.	24.03.2020	Zhejiang, China	Retrospective	46	651	331	320	Both	0.84	0.67	0.18	N/M	0.10	N/M
Wang et al.	17.03.2020	Wuhan, China	Retrospective, single center	56	138	75	63	Both	0.99	0.59	0.70	0.31	0.07	0.10
Yuan et al.	19.03.2020	Hubei, China	Retrospective	60	27	12	15	Both	0.78	0.59	N/M	0.41	N/M	N/M
Guan et al.	28.02.2020	China (30 provinces)	Cohort	47	1099	639	460	Both	0.89	0.68	0.38	N/M	0.14	0.04
Liu et al.	27.03.2020	Hainan, China	Retrospective	68	56	31	25	Both	0.76	0.36	0.09	N/M	N/M	N/M
Zhou et al.	12.03.2020	Wuhan, China	N/M	51	254	115	139	Both	0.84	0.39	0.52	0.04	0.11	N/M
Huang et al.	24.01.2019	Wuhan, China	Cohort	49	41	30	11	Both	0.98	0.76	0.44	0.55	0.08	0.03
Chen et al.	29.01.2019	Wuhan, China	Retrospective, single center	55.5	99	67	32	Both	0.83	0.82	N/M	N/M	0.08	0.02
Du et al.	3.04.2020	Wuhan, China	Retrospective	66	85	62	23	Both	0.92	0.22	0.59	0.71	0.05	0.19
Xu et al.	28.02.2020	Guangzhou, China	N/M	50	90	39	51	Both	0.78	0.63	0.21	N/M	0.04	0.06
Goyal et al.	17.04.2020	New York, USA	Retrospective	62	393	238	155	Both	0.77	0.79	N/M	0.57	N/M	0.24
Barrasa et al.	1.04.2020	Vitoria, Spain	N/M	63	48	27	21	Both	1.00	0.73	N/M	0.88	N/M	N/M
Yan et al.	12.4.2020	USA	Cross sectional	48.5	59	29	29	Both	0.70	0.66	0.81	0.54	0.66	0.48
Gupta et al.	6.04.2020	New Delhi, India	Retrospective, Observational	40	21	14	7	Both	0.43	0.43	N/M	N/M	0.14	N/M
Yang et al.	21.02.2020	Wenzhou, China	Retrospective cohort	45	149	81	68	Both	0.77	0.58	N/M	0.01	0.09	0.07
Han et al.	15.04.2020	Wuhan, China	Retrospective	62.5	206	91	115	Both	0.67	0.26	0.45	N/M	N/M	0.33
Kim et al.	6.04.2020	South Korea	Cohort	40	28	15	13	Both	0.25	0.29	0.11	N/M	0.25	0.11
Wang et al.	15.03.2020	Wuhan, China	Retrospective, single-centre	69	339	166	173	Both	0.92	0.53	0.40	0.41	0.04	0.13
Shi et al.	24.02.2020	Wuhan, China	Retrospective	49.5	81	42	39	Both	0.73	0.59	0.09	0.42	0.06	0.04
Yang et al.	21.02.2020	Wuhan, China	Retrospective, single-centre, Observational	60	52	35	17	Both	0.98	0.77	N/M	0.64	0.06	N/M

N/M: Not Mentioned

S1 (Continued). Characteristics of studies that evaluated the age related risk factors of COVID-19 patients.

Authors	Sore Throat	Myalgia/ Muscle Ache	Rhinorrhea	Cough/ Sputum Production	Chest tightness	Chest pain	Nausea	Vomiting	Abdominal Pain	Dizziness	Anorexia	Pharyngalgia	Hemoptysis	Others	No. of Symptoms
Wan et al.	N/M	0.33	N/M	0.09	N/M	N/M	N/M	N/M	N/M	N/M	N/M	0.18	0.03	Loss of appetite-4.4%, Palpitation-3.7%, Retching-3%	13
Zhang et al.	N/M	N/M	N/M	N/M	0.31	N/M	0.17	N/M	0.06	N/M	0.17	N/M	N/M	N/M	9
Xu et al.	N/M	0.52	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	0.03	N/M	7
Zhu et al.	N/M	0.16	N/M	0.16	0.09	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	8
Chen et al.	N/M	0.40	N/M	N/M	0.55	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	8
Liu et al.	N/M	0.33	N/M	N/M	N/M	N/M	0.17	0.17	N/M	N/M	N/M	N/M		Chill- 42%	7
Chen et al.	N/M	0.22	N/M	0.30	0.38	N/M	0.09	0.06	0.07	0.08	0.24	0.04	0.03	N/M	16
Mo et al.	N/M	0.61	N/M	N/M	0.39	0.04	0.04	0.04	0.02	0.02	0.32	N/M		N/M	14
Liu et al.	N/M	0.32	N/M	0.04	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	0.05	Heart palpitation-7%	10
Jin et al.	0.15	0.11	N/M	0.35	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	0.02	Nasal Obstruction-6%,	9
Wang et al.	N/M	0.35	N/M	0.27	N/M	N/M	0.10	0.04	N/M	0.09	0.40	0.17	N/M	N/M	13
Yuan et al.	N/M	0.11	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	4
Guan et al.	0.14	0.15	N/M	0.34	N/M	N/M	0.05	0.05	N/M	N/M	N/M	N/M	0.01	Conjunctival congestion-1%, Nasal congestion-5%, Chils-11.5%, Throat congestion-2%, Tonsil sweling-2%, Rash-0.2%	17
Liu et al.	N/M	N/M	N/M	N/M	0.07	N/M	N/M	0.17	N/M	N/M	N/M	N/M	N/M	Nasal congestion-5%,	6
Zhou et al.	0.06	0.34	N/M	0.42	0.26	N/M	N/M	N/M	N/M	0.07	N/M	N/M	N/M	N/M	10
Huang et al.	N/M	0.44	N/M	0.28	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	0.05	N/M	9
Chen et al.	0.05	0.11	0.04	N/M	N/M	0.02	0.01	0.01	N/M	N/M	N/M	N/M	N/M	N/M	10
Du et al.	N/M	0.17	N/M	0.38	N/M	0.02	N/M	0.05	0.04	N/M	0.57	0.02	N/M	N/M	14
Xu et al.	0.26	0.28	N/M	0.12	N/M	N/M	0.06	0.02	N/M	N/M	N/M	N/M	N/M	Chills-7%	11
Goyal et al.	N/M	0.19	N/M	N/M	N/M	N/M	0.19	0.19	N/M	N/M	N/M	N/M	N/M	N/M	7
Barrasa et al.	N/M	0.04	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	Malaise-44%	5
Yan et al.	0.32	0.63	0.31	N/M	N/M	N/M	0.27	N/M	N/M	N/M	N/M	N/M	N/M	Nasal obstruction 47.5%, Anosmia 68%, Ageusia 71%	13
Gupta et al.	0.24	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	5
Yang et al.	0.14	0.03	N/M	0.32	0.10	0.03	0.01	0.01	N/M	N/M	N/M	N/M	N/M	Chill-14%, Snotty-3%	14
Han et al.	N/M	0.21	N/M	N/M	0.24	N/M	N/M	0.12	0.04	N/M	N/M	0.06	N/M	Poor apitite-34%	11
Kim et al.	0.29	0.25	0.07	0.21	N/M	N/M	N/M	N/M	0.04	N/M	N/M	N/M	N/M	N/M	10
Wang et al.	N/M	0.05	N/M	0.28	0.26	N/M	0.04	N/M	N/M	0.04	0.28	0.04	N/M	N/M	13
Shi et al.	N/M	N/M	0.26	0.19	0.22	N/M	N/M	0.05	N/M	0.02	0.01	N/M	N/M	N/M	12
Yang et al.	N/M	0.12	0.06	N/M	N/M	0.02	N/M	0.04	N/M	N/M	N/M	N/M	N/M	Malaise-35%, Arthralgia-2%	10

N/M: Not Mentioned

S1 (Continued). Characteristics of studies that evaluated the age related risk factors of COVID-19 patients.

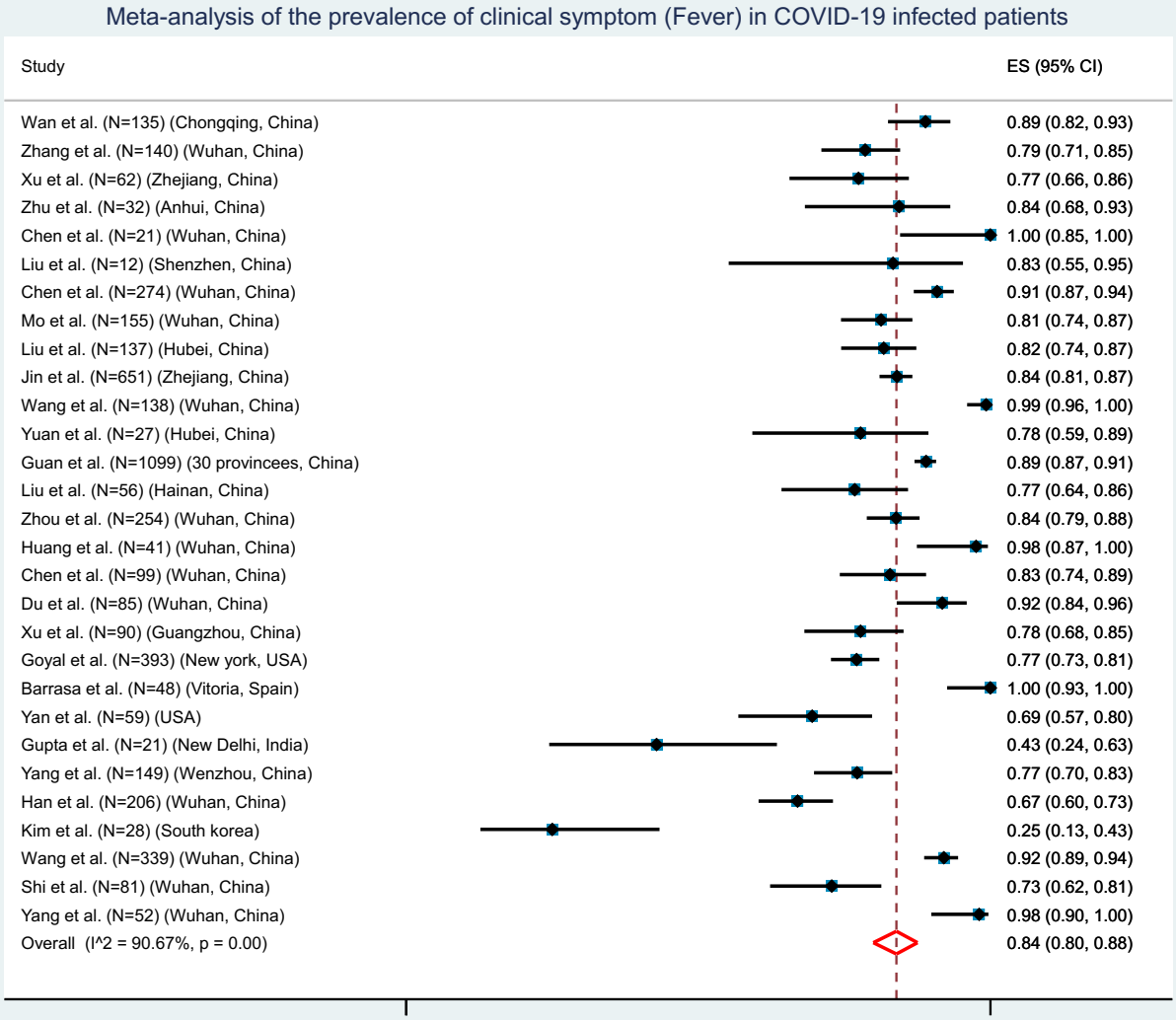
Authors	Diabetes	Hypertension	Cardiovascular Disease	Coronary heart disease	Cerebrovascular disease	COPD /Lung disease	Chronic liver disease	Chronic Renal disease	Chronic Kidney disease	Malignancy	ARDS	Others	No. of Comorbidities
Wan et al.	0.09	0.10	0.05	N/M	N/M	0.007	0.02	N/M	N/M	0.03	N/M	N/M	6
Zhang et al.	0.12	0.30	N/M	0.05	N/M	0.014	0.06	0.01	N/M	N/M	N/M	Gastric ulcer & Hyperlepedemia-5%, Thyroid disease-3.6%, Urolithiasis-2.1%, Arrhythmia-3.6%, Cholilithiasis-4.3%	12
Xu et al.	0.02	0.08	N/M	N/M	0.02	0.020	0.11	0.02	N/M	N/M	N/M	N/M	6
Zhu et al.	0.13	0.22	N/M	0.06	0.03	0.060	0.06	0.03	N/M	N/M	N/M	Mental disorder- 3%, Tumor-6%	9
Chen et al.	0.14	0.24	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	2
Liu et al.	0.08	0.25	N/M	0.33	N/M	0.080	N/M	0.08	N/M	N/M	N/M	Bacterial co infection-17%, Pneumonia-100%,	7
Chen et al.	0.17	0.34	0.08	N/M	0.01	0.070	N/M	N/M	0.01	0.03	N/M	HBV infection-4%, Metabolic arthritis & Autoimmune disease & Gastro Intestinal disease- 1%	11
Mo et al.	0.10	0.24	0.10	N/M	0.05	0.030	0.05	0.04	N/M	0.05	N/M	Tuberculosis-2%, HIV-1%	10
Liu et al.	0.10	0.10	0.07	N/M	N/M	0.015	N/M	N/M	N/M	0.02	N/M	N/M	5
Jin et al.	0.07	0.15	N/M	0.01	N/M	0.002	0.04	0.01	N/M	0.01	N/M	Immunosuppression-0.17%,	8
Wang et al.	0.10	0.31	0.15	N/M	0.05	0.030	0.03	N/M	0.03	0.07	N/M	HIV infection-1%	9
Yuan et al.	0.22	0.19	0.11	N/M	N/M	N/M	N/M	N/M	N/M	N/M	0.41	Tumor & Cerebral infraction & Chronic gastric- 4%	9
Guan et al.	0.07	0.15	N/M	0.03	0.01	0.010	N/M	0.01	N/M	0.01	N/M	Hepatitis B Infection-2%, Immune deficiency-0.2%,	9
Liu et al.	0.07	0.17	N/M	0.11	N/M	N/M	0.06	N/M	0.03	N/M	N/M	Persistent arterial fibrilliation-6%,	6
Zhou et al.	0.10	0.25	0.05	0.07	N/M	0.020	0.01		N/M	0.01	N/M	HIV infection-0.4%,	8
Huang et al.	0.20	0.15	0.15	N/M	N/M	0.020	0.02	N/M	N/M	0.02	N/M	N/M	6
Chen et al.	N/M	N/M	N/M	N/M	N/M	N/M	N/M	0.03	N/M	N/M	0.17	Acute Respiratory Injury-8%, Septic shock-4%, Pneumonia-1%	5
Du et al.	0.22	0.38	0.08	0.12	N/M	0.020	0.06	N/M	0.04	0.07	N/M	N/M	8
Xu et al.	0.06	0.19	0.03	N/M	N/M	0.010	N/M	N/M	N/M	0.02	N/M	Tuberculosis-2%,	6
Goyal et al.	0.25	0.50	N/M	0.14	N/M	0.050	N/M	N/M	N/M	N/M	N/M	Asthama-12.5%, Obesity-35%	6
Barrasa et al.	0.19	0.44	N/M	0.10	N/M	0.380	N/M	N/M	N/M	N/M	1.00	Obesity-48%, Immunosuppression-3%	7
Yan et al.	0.09	0.14	0.05	N/M	N/M	0.050	N/M	N/M	N/M	0.04	N/M	Allergic rhinitis-34%, Sinus disease 3%	7
Gupta et al.	0.14	0.24	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	N/M	Anxity-5%, Hypothyroidism-5%, Migrane-5%, Obstructive sleep aponea-5%	6
Yang et al.	N/M	N/M	0.19	N/M	0.19	N/M	N/M	N/M	N/M		N/M	Respiratory system disease - 0.67%, Digestive system disease- 5%, Endocrine disease- 6%	5
Han et al.	0.10	0.27	N/M	N/M	0.08	0.040	N/M	N/M	N/M	N/M	N/M	N/M	4
Kim et al.	0.07	N/M	N/M	N/M		N/M	0.04		N/M	0.04	N/M	Obesity-18%, Asthama-4%	5
Wang et al.	0.16	0.41	0.16	N/M	0.06	0.060	0.01	N/M	0.04	0.04	N/M	Autoimmune disease-1.5%	9
Shi et al.	0.12	0.15	0.10	N/M	0.07	0.110	0.09	0.04	N/M	0.05	N/M	N/M	8
Yang et al.	0.35	N/M	0.23	N/M	N/M	N/M	0.29	N/M	0.29	N/M	0.67	Urinary tract infection-2%, Gastrointestinal haemorrhage-4%	7

N/M: Not Mentioned

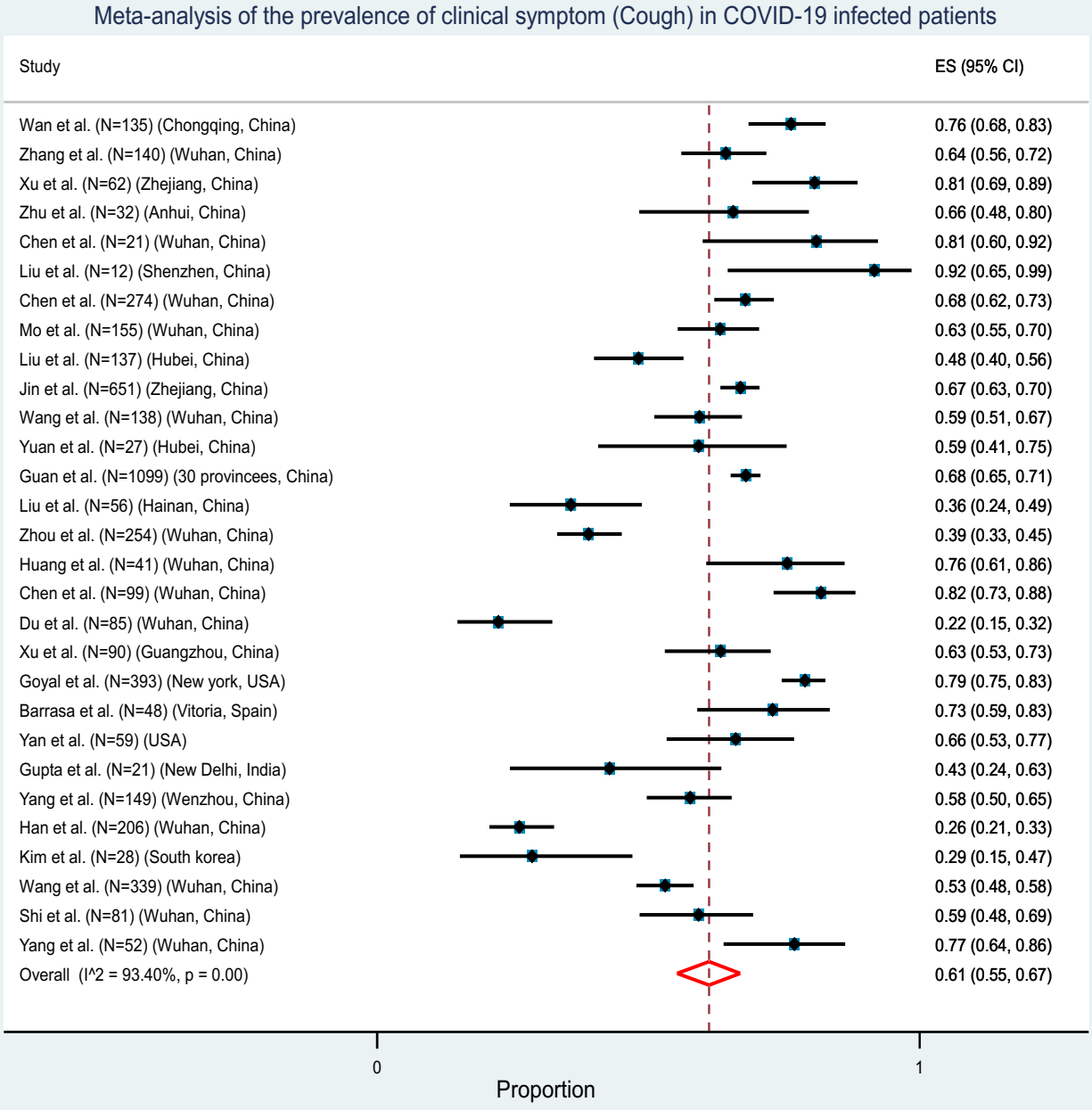
Pooled estimation of the symptoms and comorbidities

Symptoms

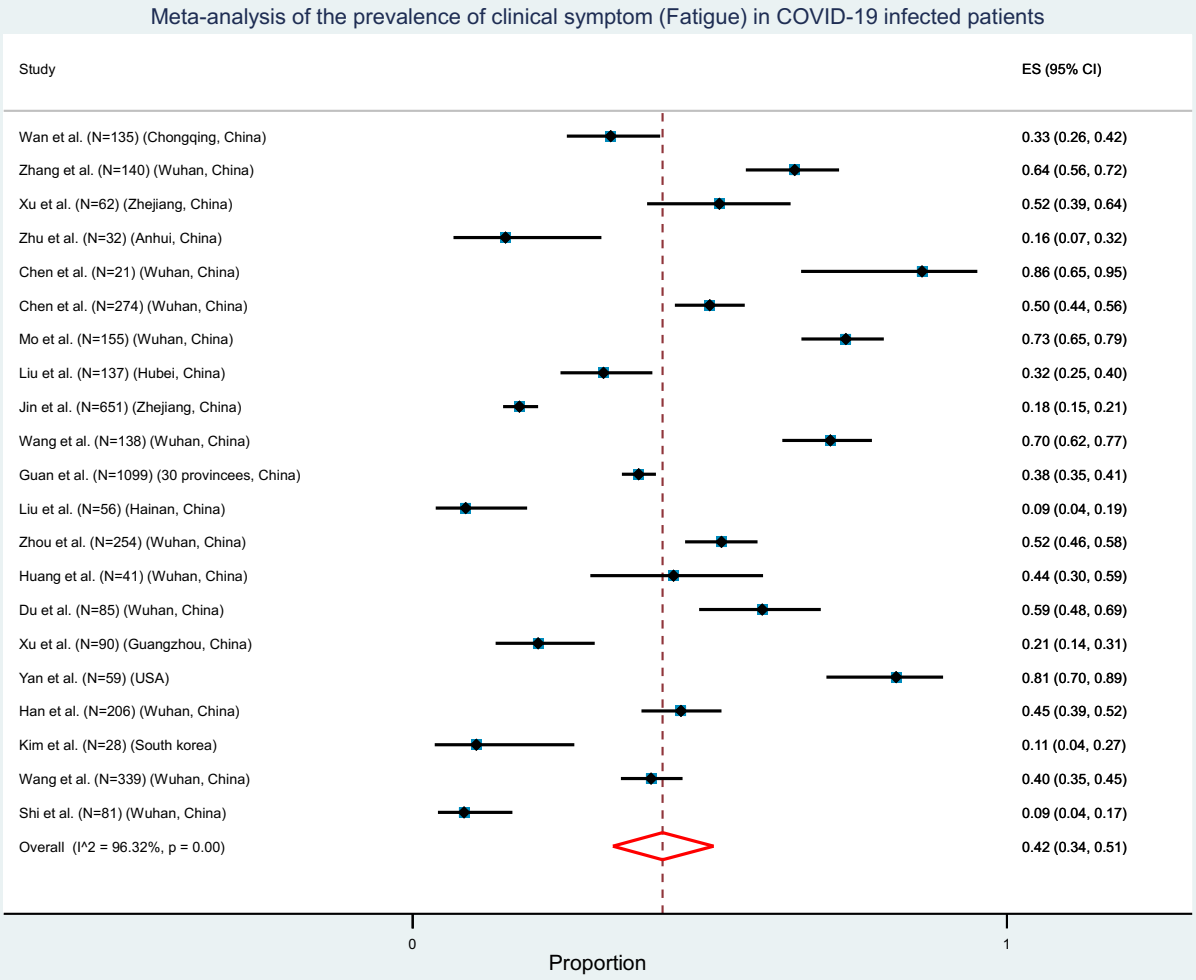
S2. Fever



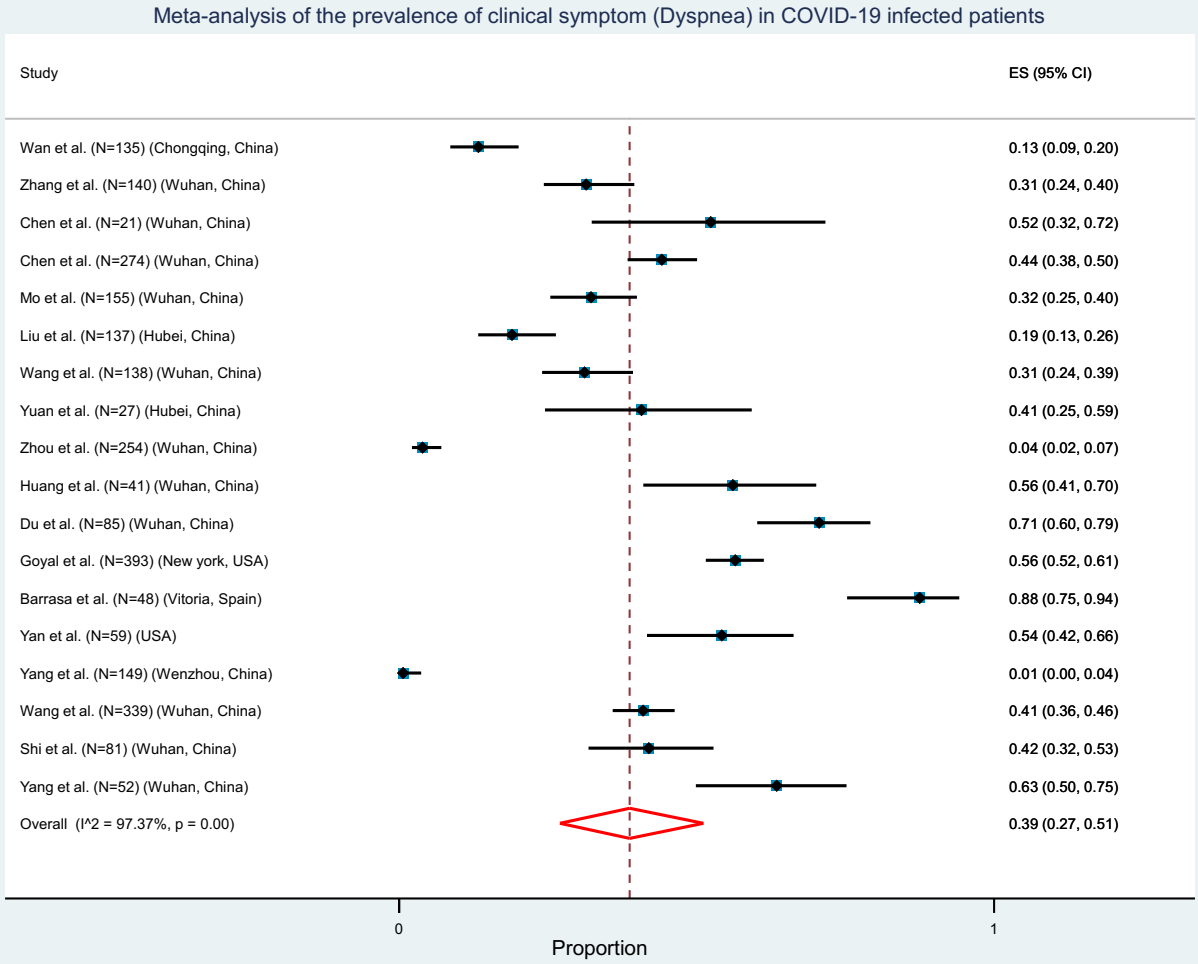
S3. Cough / Dry Cough



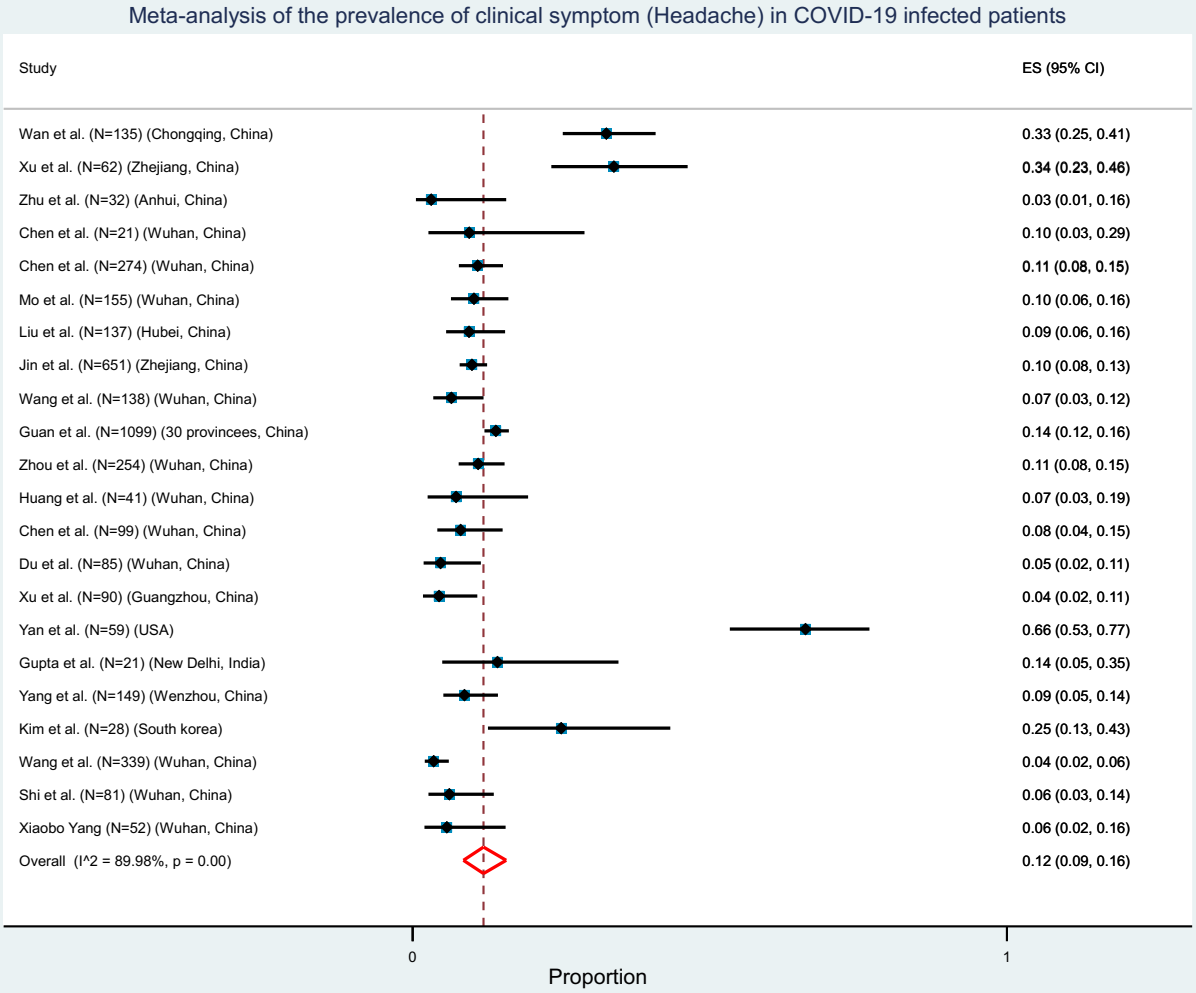
S4. Fatigue/Weakness



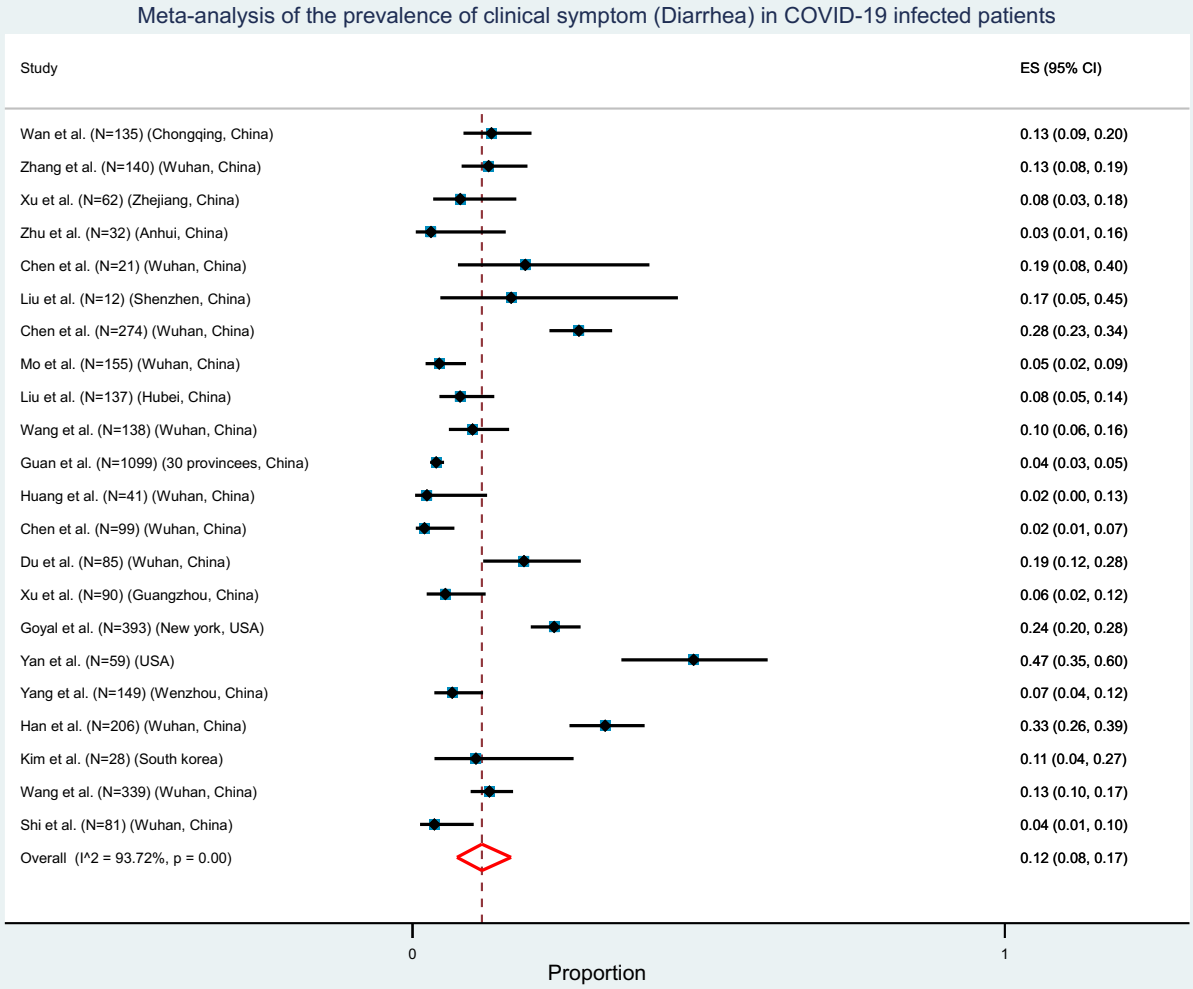
S5. Dyspnea/Shortness of breath



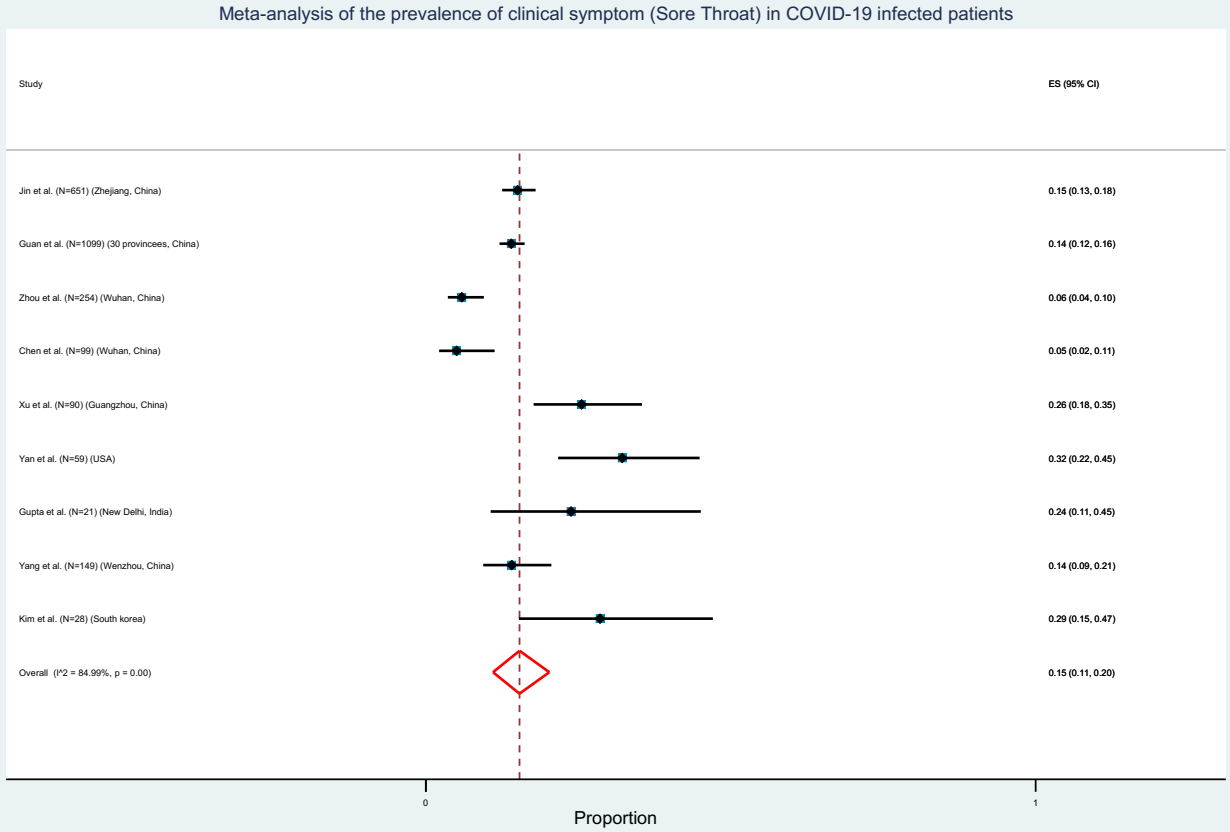
S6. Headache


Meta-analysis of the prevalence of clinical symptom (Headache) in COVID-19 infected patients
Study
ES (95% CI)
Wan et al. (N=135) (Chongqing, China) 0.33 (0.25, 0.41)
Xu et al. (N=62) (Zhejiang, China) 0.34 (0.23, 0.46)
Zhu et al. (N=32) (Anhui, China) 0.03 (0.01, 0.16)
Chen et al. (N=21) (Wuhan, China) 0.10 (0.03, 0.29)
Chen et al. (N=274) (Wuhan, China) 0.11 (0.08, 0.15)
Mo et al. (N=155) (Wuhan, China) 0.10 (0.06, 0.16)
Liu et al. (N=137) (Hubei, China) 0.09 (0.06, 0.16)
Jin et al. (N=651) (Zhejiang, China) 0.10 (0.08, 0.13)
Wang et al. (N=138) (Wuhan, China) 0.07 (0.03, 0.12)
Guan et al. (N=1099) (30 provincees, China) 0.14 (0.12, 0.16)
Zhou et al. (N=254) (Wuhan, China) 0.11 (0.08, 0.15)
Huang et al. (N=41) (Wuhan, China) 0.07 (0.03, 0.19)
Chen et al. (N=99) (Wuhan, China) 0.08 (0.04, 0.15)
Du et al. (N=85) (Wuhan, China) 0.05 (0.02, 0.11)
Xu et al. (N=90) (Guangzhou, China) 0.04 (0.02, 0.11)
Yan et al. (N=59) (USA) 0.66 (0.53, 0.77)
Gupta et al. (N=21) (New Delhi, India) 0.14 (0.05, 0.35)
Yang et al. (N=149) (Wenzhou, China) 0.09 (0.05, 0.14)
Kim et al. (N=28) (South korea) 0.25 (0.13, 0.43)
Wang et al. (N=339) (Wuhan, China) 0.04 (0.02, 0.06)
Shi et al. (N=81) (Wuhan, China) 0.06 (0.03, 0.14)
Xiaobo Yang (N=52) (Wuhan, China) 0.06 (0.02, 0.16)
Overall (I^2 = 89.98%, p = 0.00) 0.12 (0.09, 0.16)
0
1
Proportion

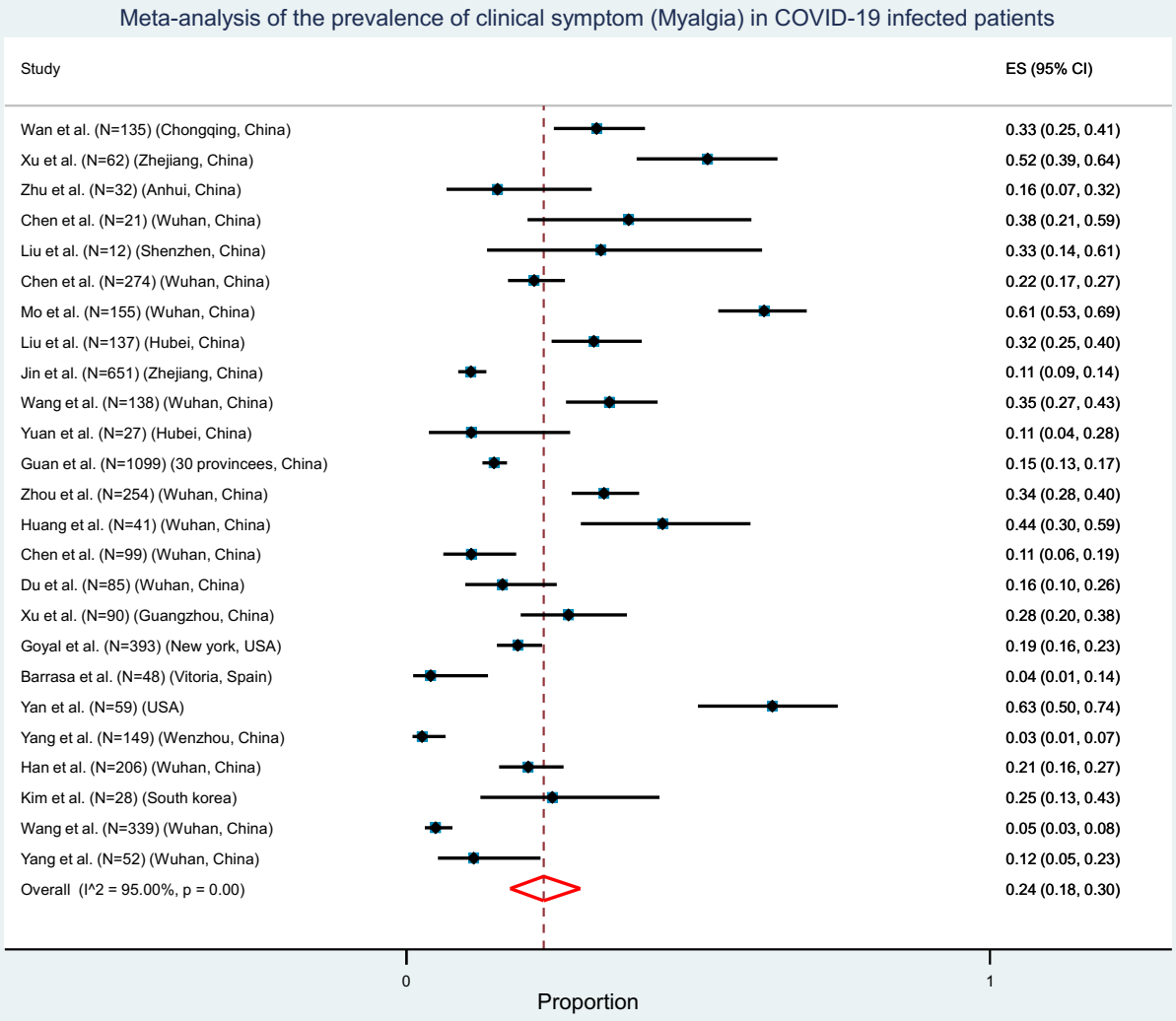
S7. Diarrhea


Meta-analysis of the prevalence of clinical symptom (Diarrhea) in COVID-19 infected patients
Study
ES (95% CI)
Wan et al. (N=135) (Chongqing, China) 0.13 (0.09, 0.20)
Zhang et al. (N=140) (Wuhan, China) 0.13 (0.08, 0.19)
Xu et al. (N=62) (Zhejiang, China) 0.08 (0.03, 0.18)
Zhu et al. (N=32) (Anhui, China) 0.03 (0.01, 0.16)
Chen et al. (N=21) (Wuhan, China) 0.19 (0.08, 0.40)
Liu et al. (N=12) (Shenzhen, China) 0.17 (0.05, 0.45)
Chen et al. (N=274) (Wuhan, China) 0.28 (0.23, 0.34)
Mo et al. (N=155) (Wuhan, China) 0.05 (0.02, 0.09)
Liu et al. (N=137) (Hubei, China) 0.08 (0.05, 0.14)
Wang et al. (N=138) (Wuhan, China) 0.10 (0.06, 0.16)
Guan et al. (N=1099) (30 provincees, China) 0.04 (0.03, 0.05)
Huang et al. (N=41) (Wuhan, China) 0.02 (0.00, 0.13)
Chen et al. (N=99) (Wuhan, China) 0.02 (0.01, 0.07)
Du et al. (N=85) (Wuhan, China) 0.19 (0.12, 0.28)
Xu et al. (N=90) (Guangzhou, China) 0.06 (0.02, 0.12)
Goyal et al. (N=393) (New york, USA) 0.24 (0.20, 0.28)
Yan et al. (N=59) (USA) 0.47 (0.35, 0.60)
Yang et al. (N=149) (Wenzhou, China) 0.07 (0.04, 0.12)
Han et al. (N=206) (Wuhan, China) 0.33 (0.26, 0.39)
Kim et al. (N=28) (South korea) 0.11 (0.04, 0.27)
Wang et al. (N=339) (Wuhan, China) 0.13 (0.10, 0.17)
Shi et al. (N=81) (Wuhan, China) 0.04 (0.01, 0.10)
Overall (I^2 = 93.72%, p = 0.00) 0.12 (0.08, 0.17)
0
1
Proportion

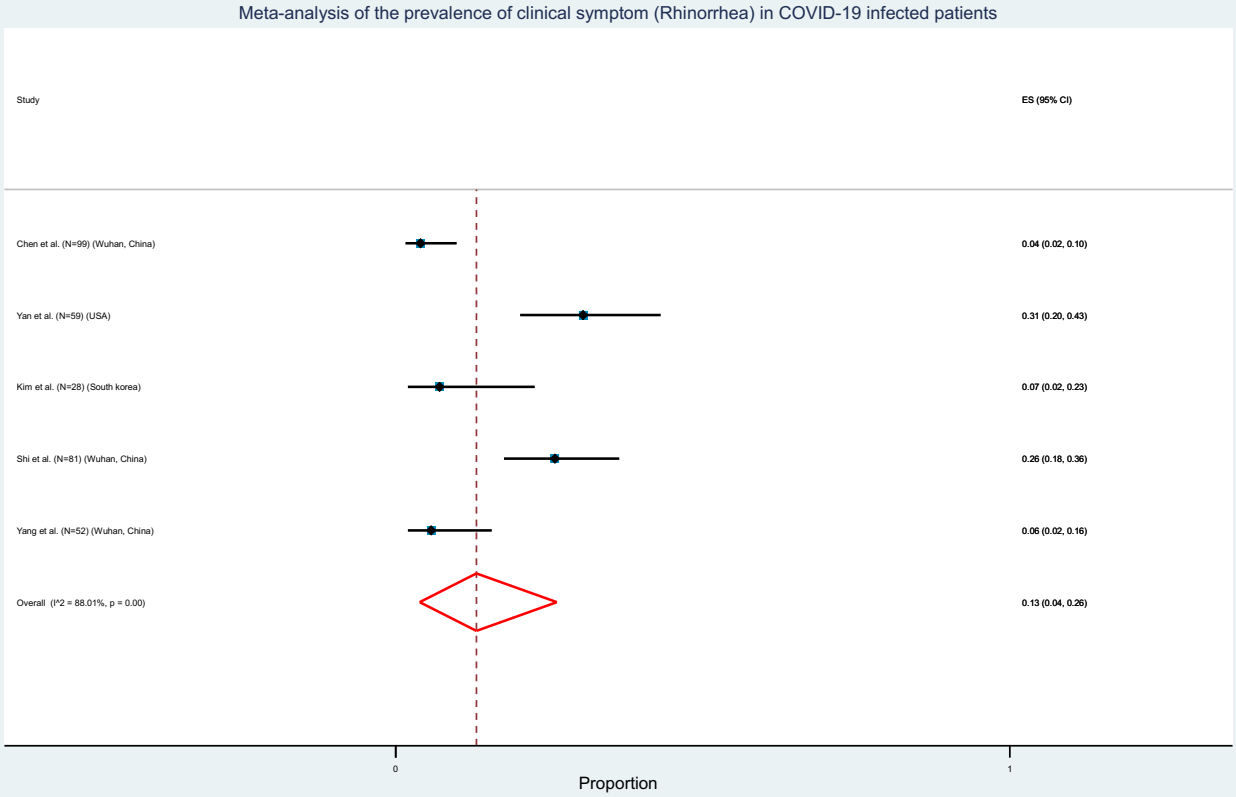
S8. Sore Throat



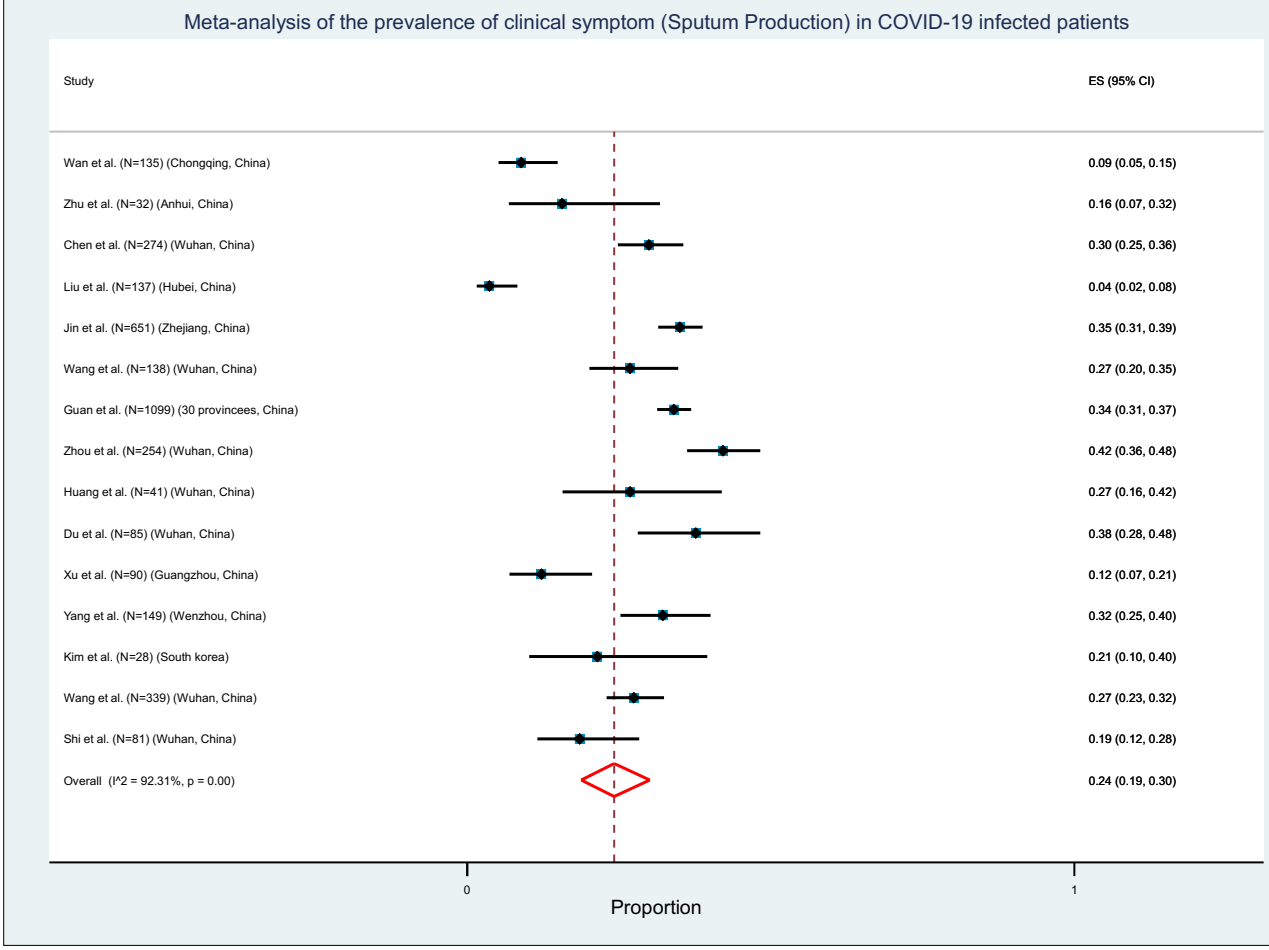
S9. Myalgia/Muscle Ache



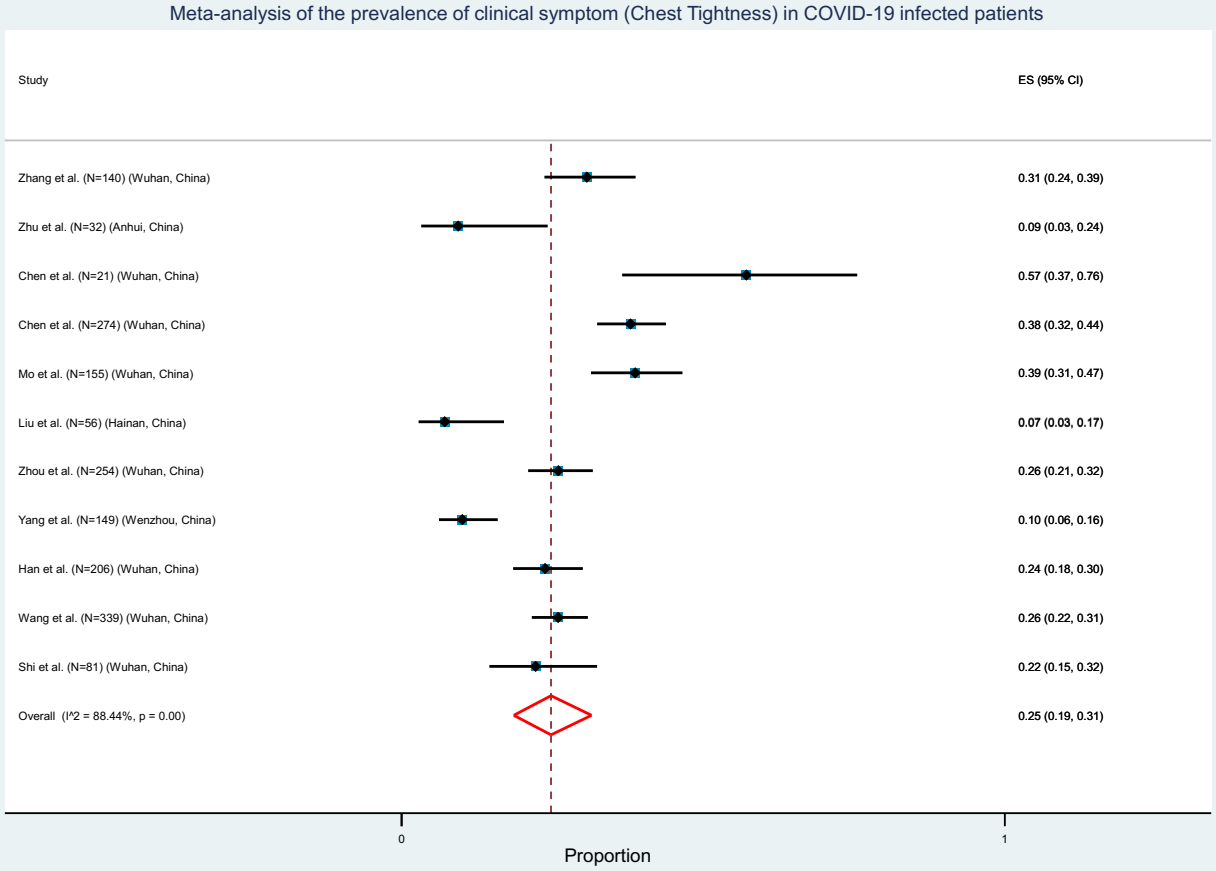
S10. Rhinorrhea



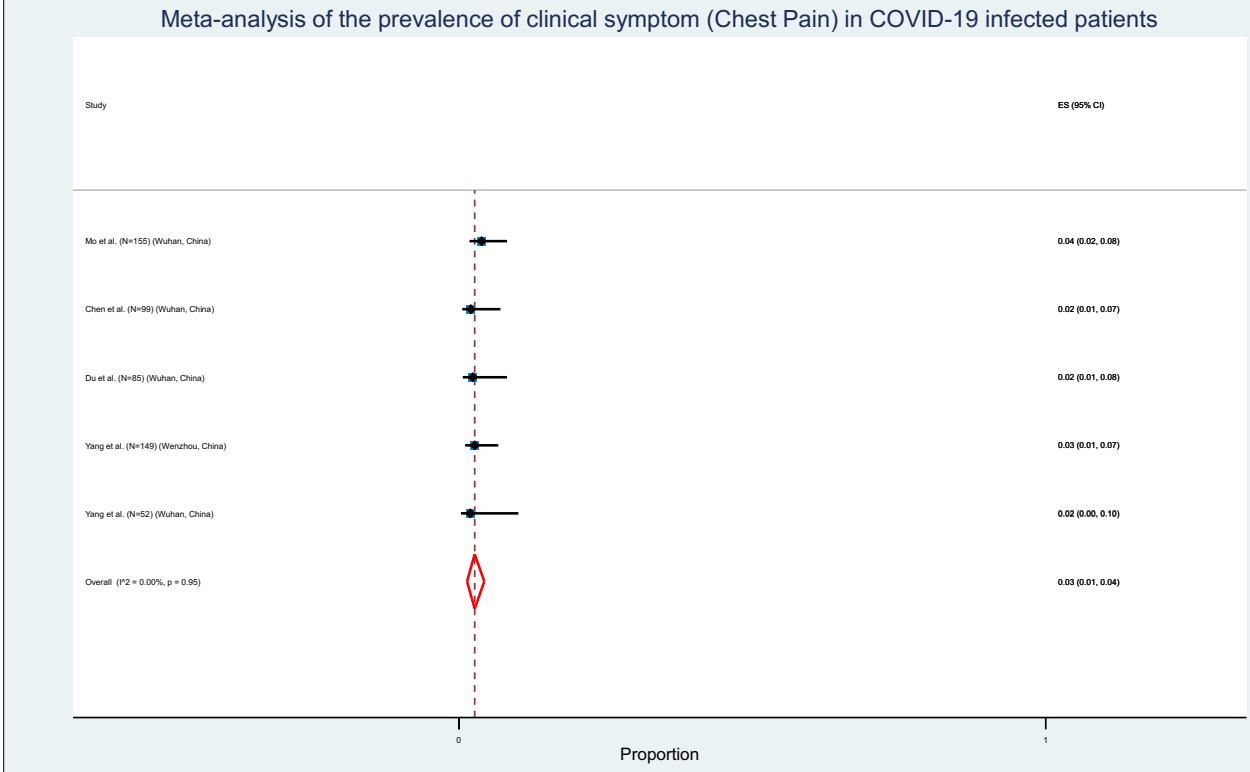
S11. Sputum Production/Expectoration



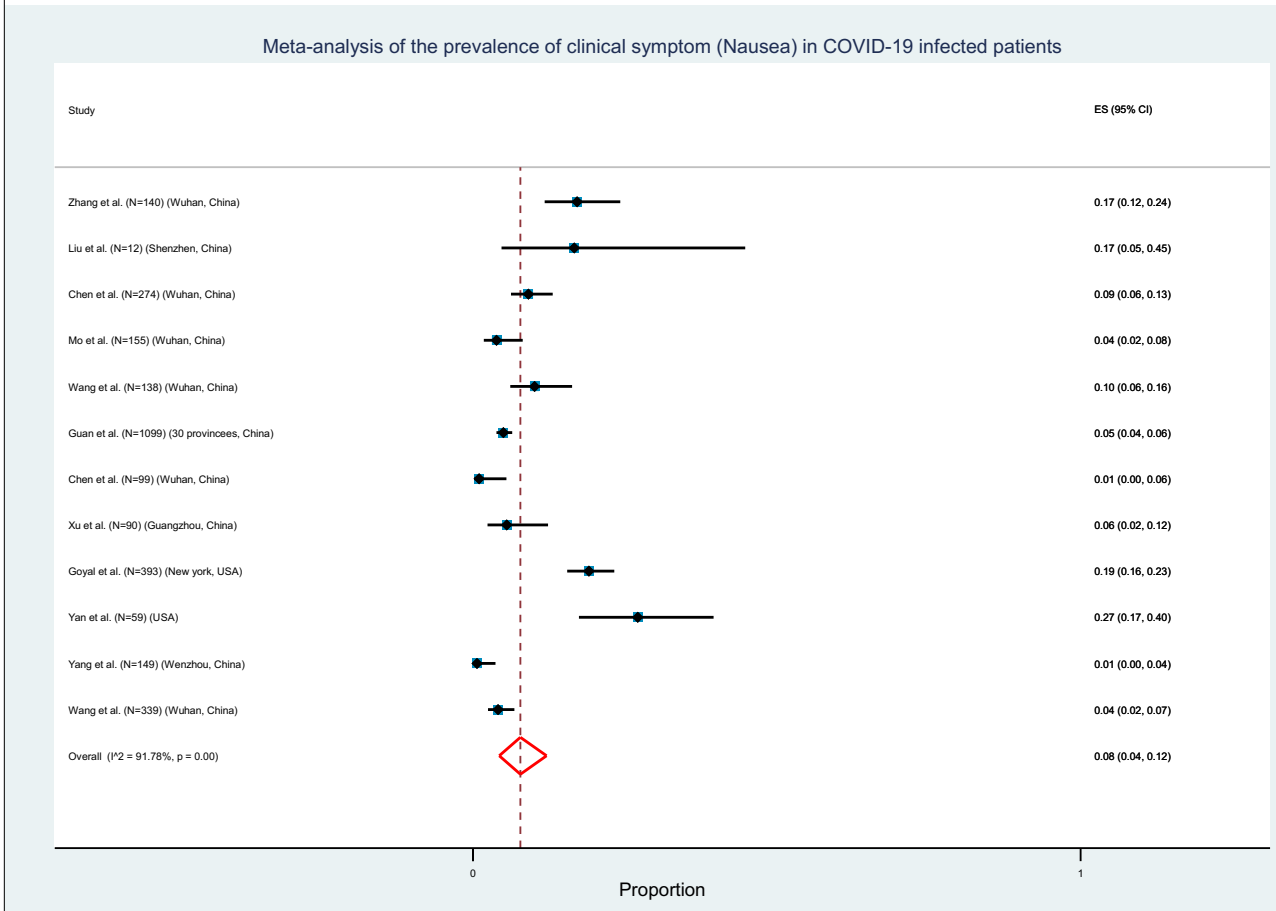
S12. Chest tightness



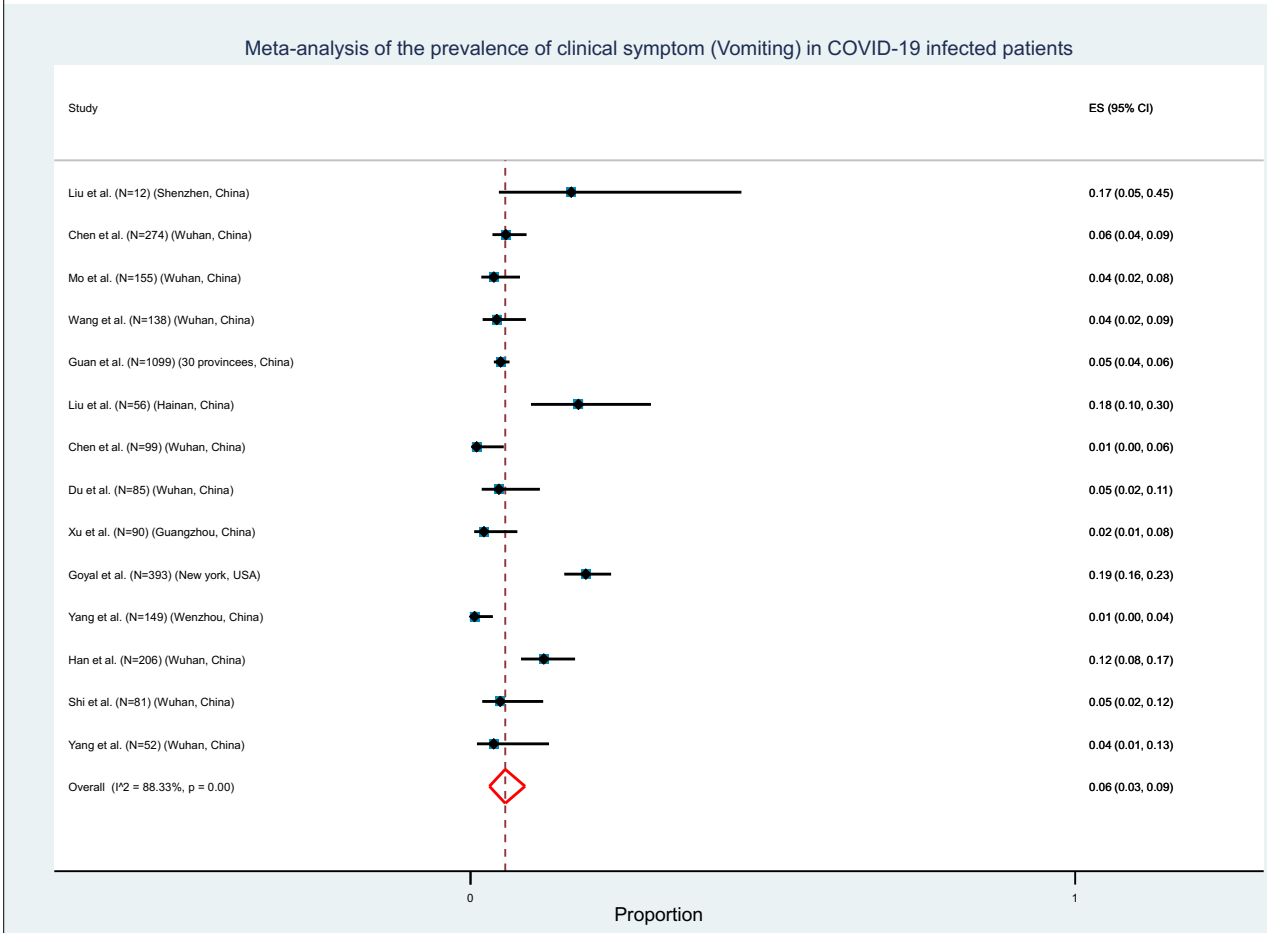
S13. Chest pain



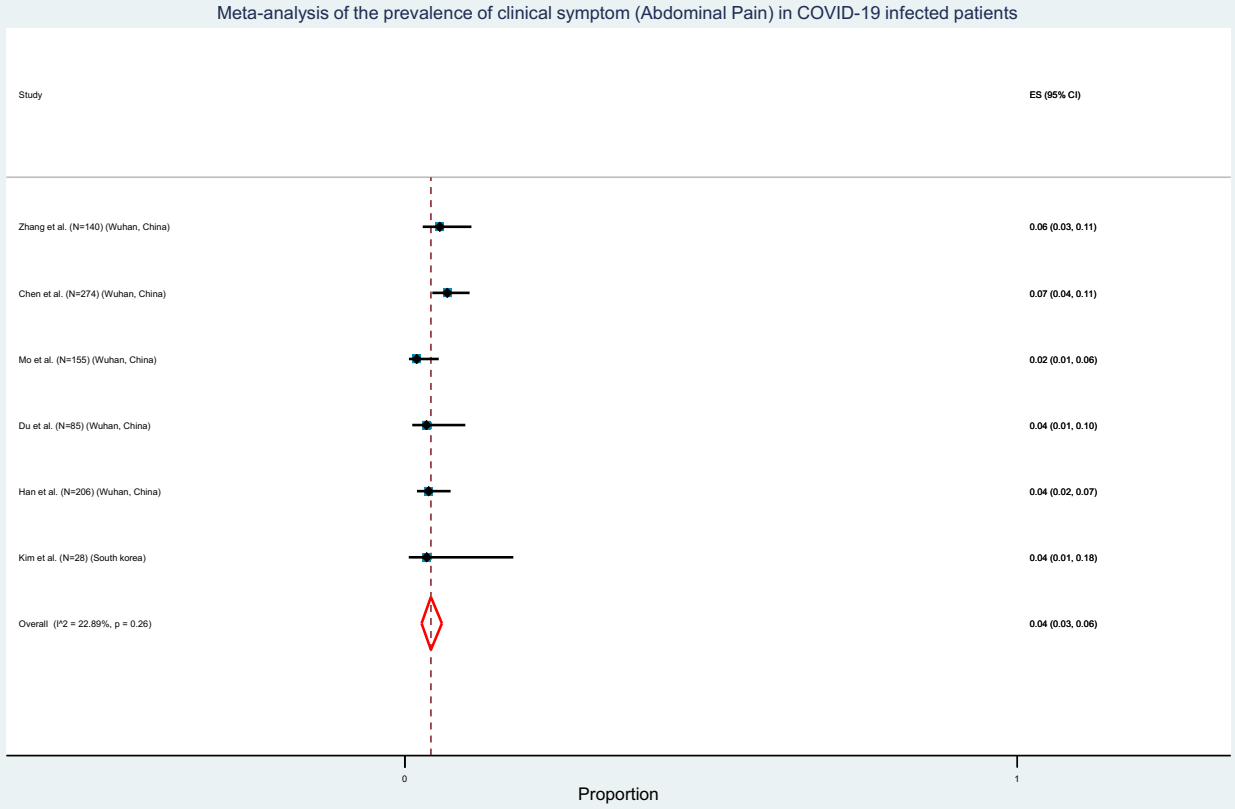
S14. Nausea


Meta-analysis of the prevalence of clinical symptom (Nausea) in COVID-19 infected patients
Study
ES (95% CI)
Zhang et al. (N=140) (Wuhan, China)
0.17 (0.12, 0.24)
Liu et al. (N=12) (Shenzhen, China)
0.17 (0.05, 0.45)
Chen et al. (N=274) (Wuhan, China)
0.09 (0.06, 0.13)
Mo et al. (N=155) (Wuhan, China)
0.04 (0.02, 0.08)
Wang et al. (N=138) (Wuhan, China)
0.10 (0.06, 0.16)
Guan et al. (N=1099) (30 provincees, China)
0.05 (0.04, 0.06)
Chen et al. (N=99) (Wuhan, China)
0.01 (0.00, 0.06)
Xu et al. (N=90) (Guangzhou, China)
0.06 (0.02, 0.12)
Goyal et al. (N=393) (New york, USA)
0.19 (0.16, 0.23)
Yan et al. (N=59) (USA)
0.27 (0.17, 0.40)
Yang et al. (N=149) (Wenzhou, China)
0.01 (0.00, 0.04)
Wang et al. (N=339) (Wuhan, China)
0.04 (0.02, 0.07)
Overall (I^2 = 91.78%, p = 0.00)
0.08 (0.04, 0.12)
0
1
Proportion

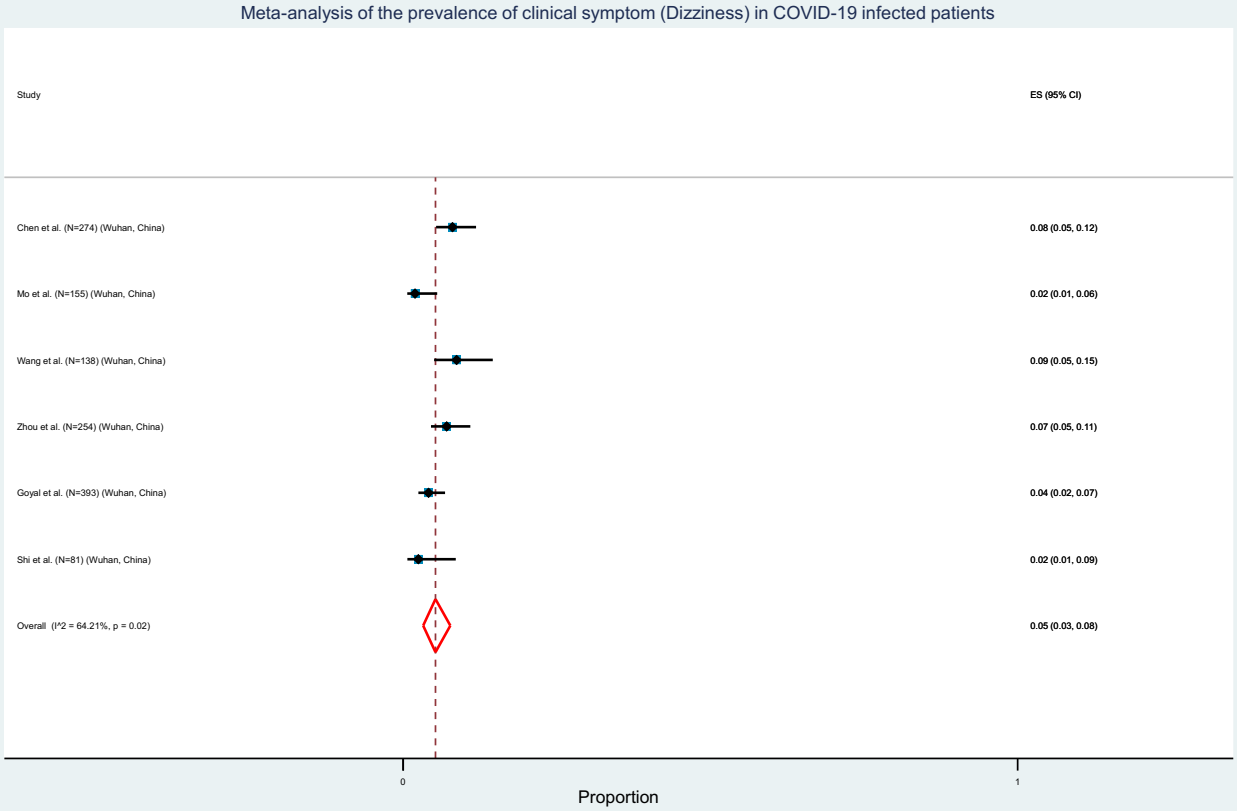
S15. Vomiting



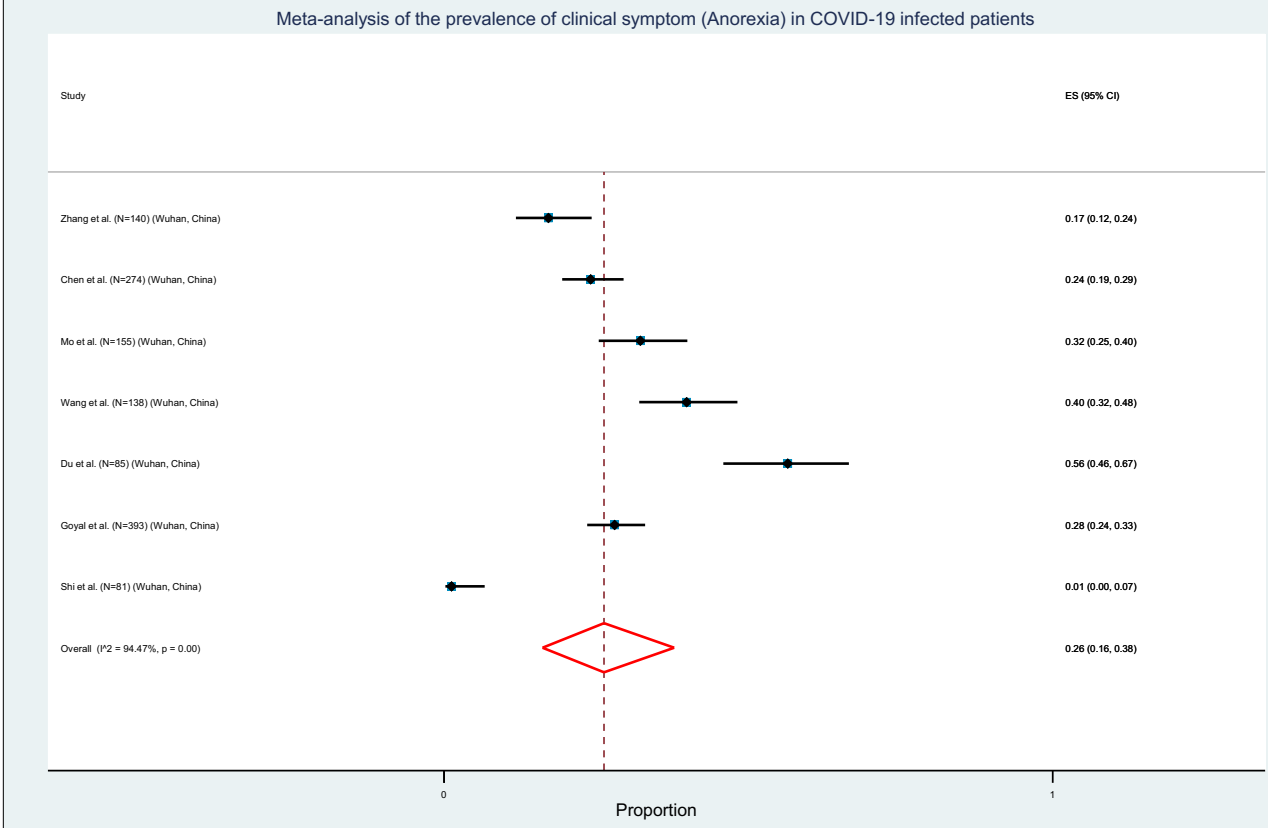
S16. Abdominal Pain



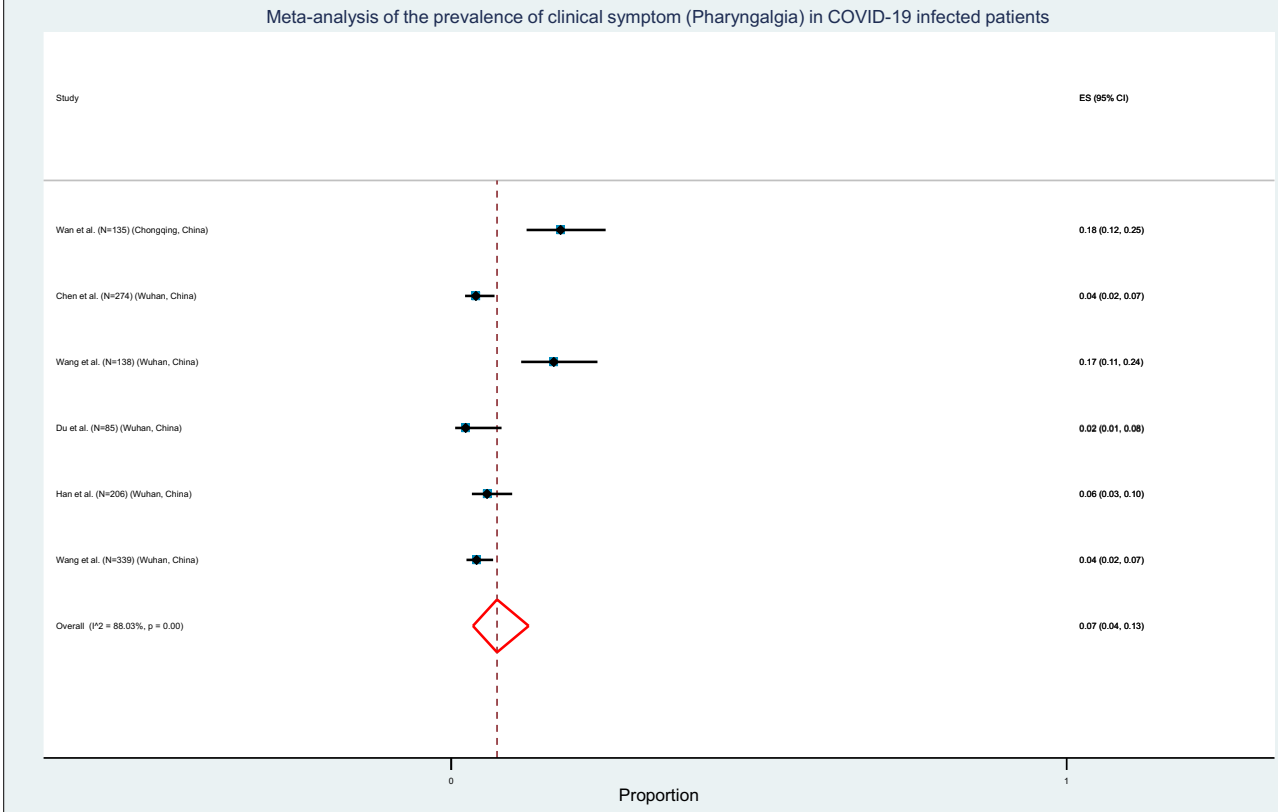
S17. Dizziness



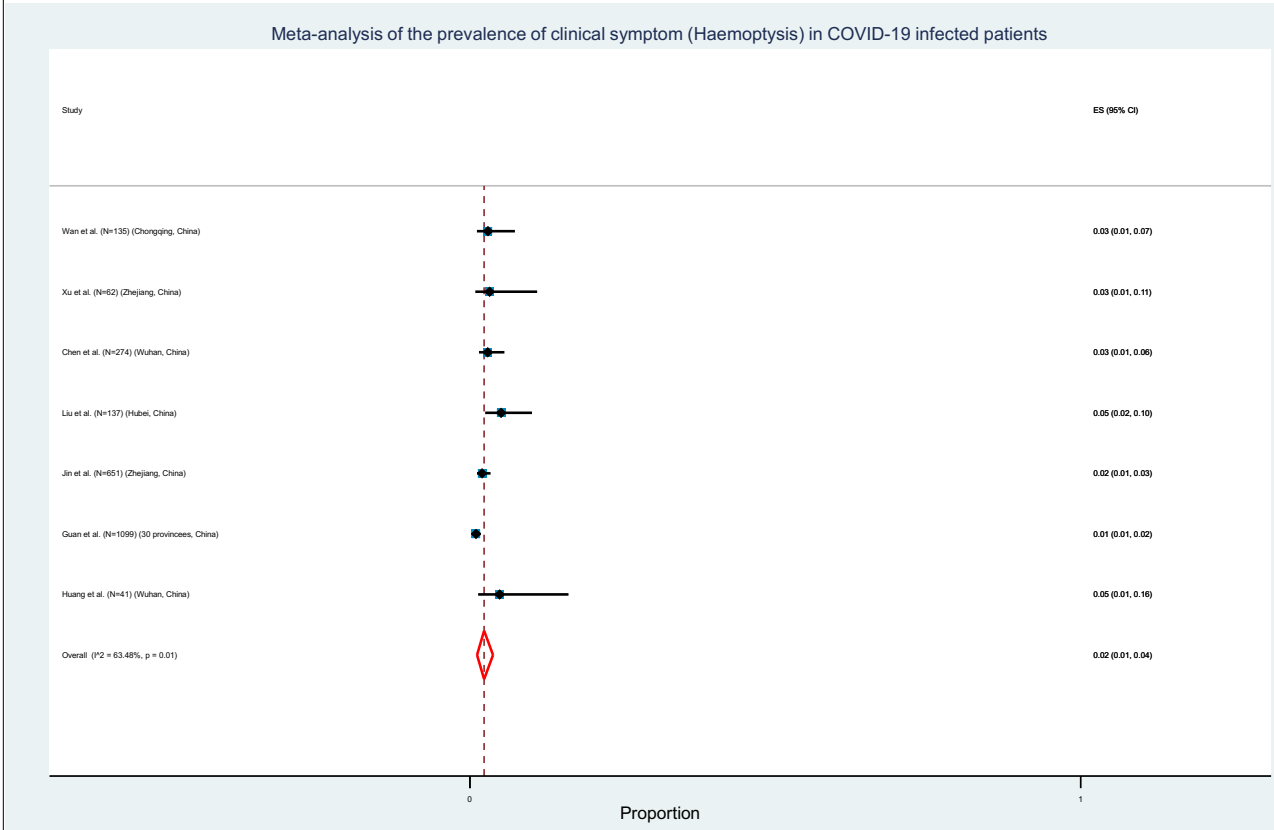
S18. Anorexia



S19. Pharyngalgia

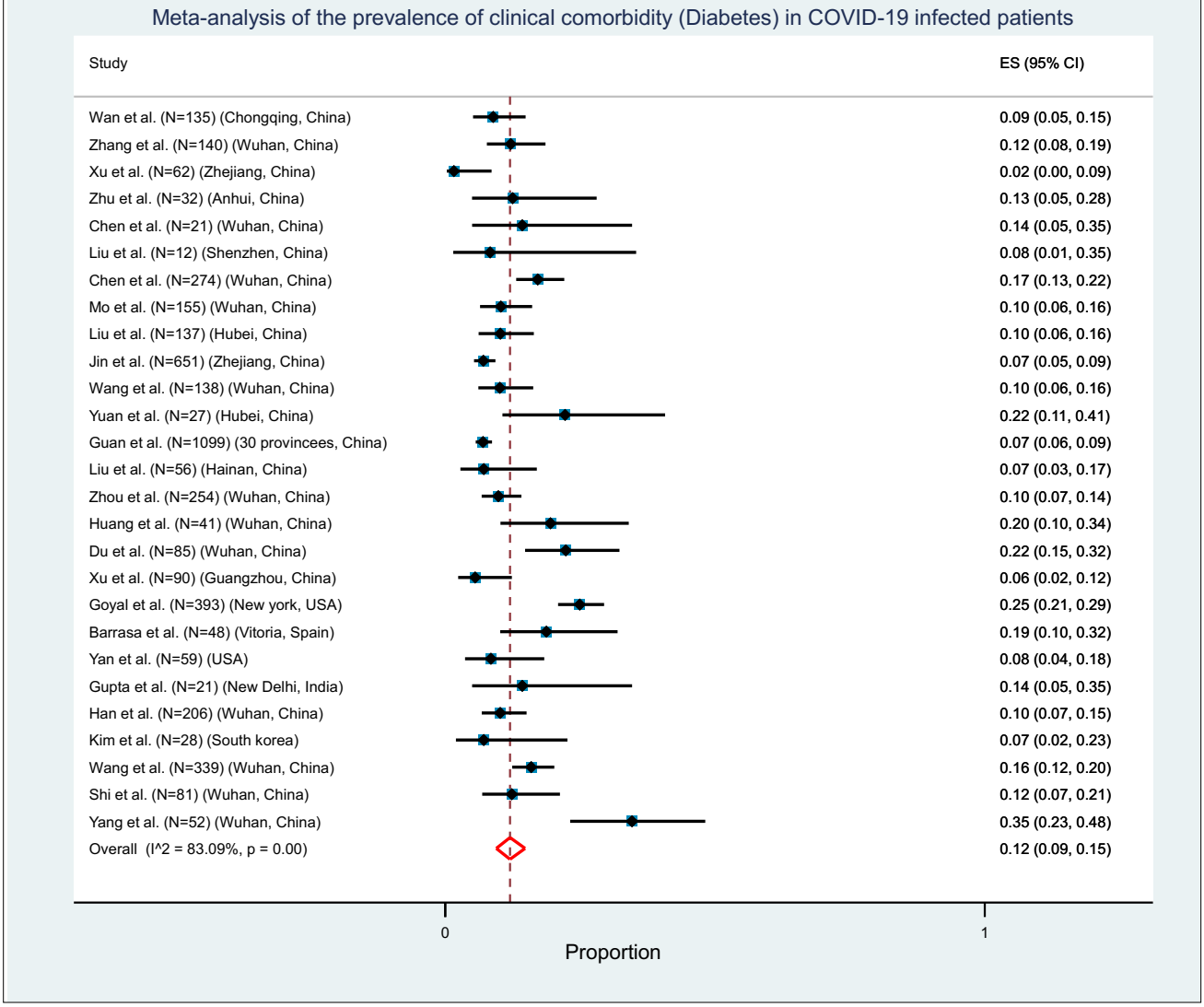


S20. Haemoptysis

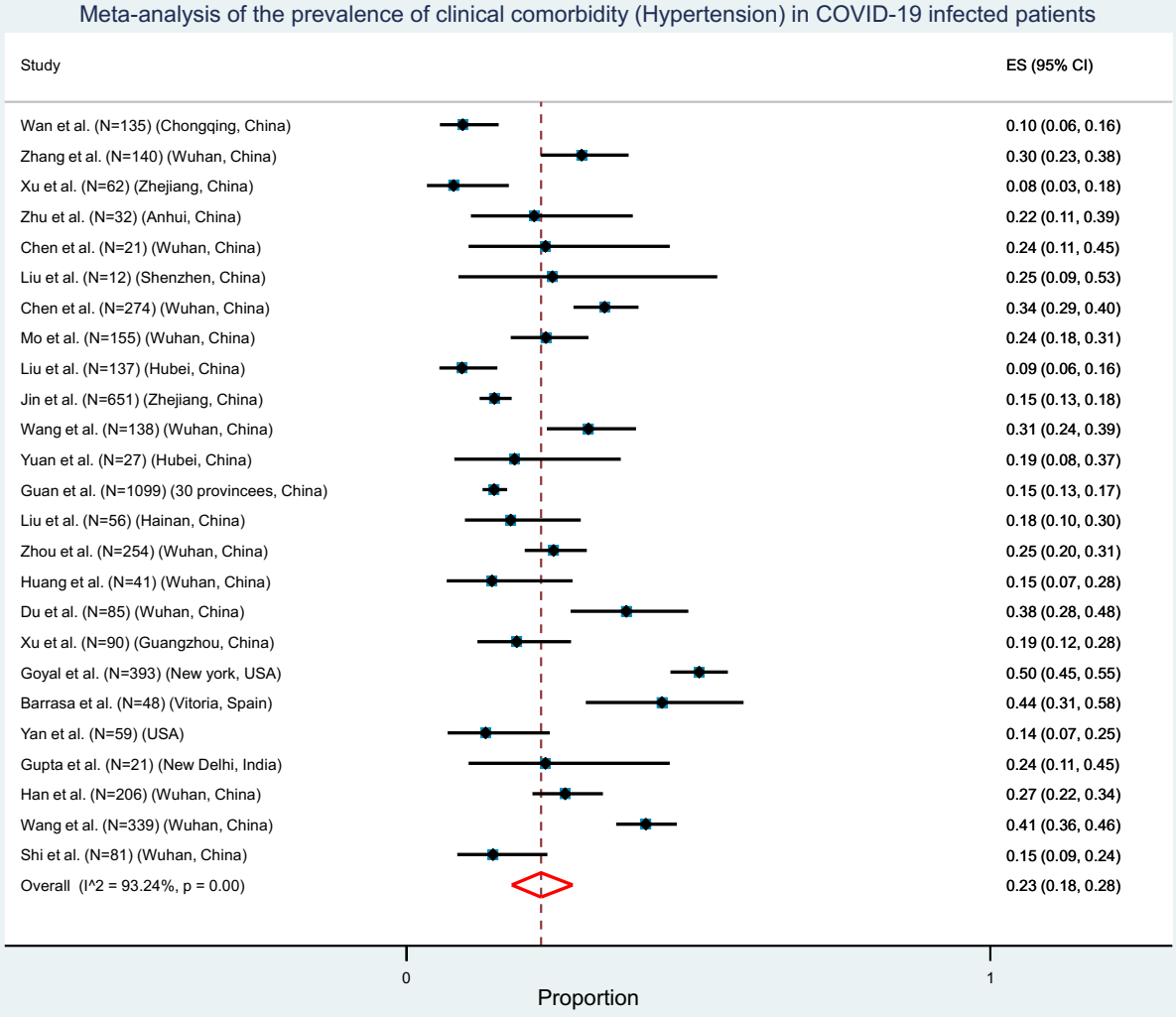


Comorbidity

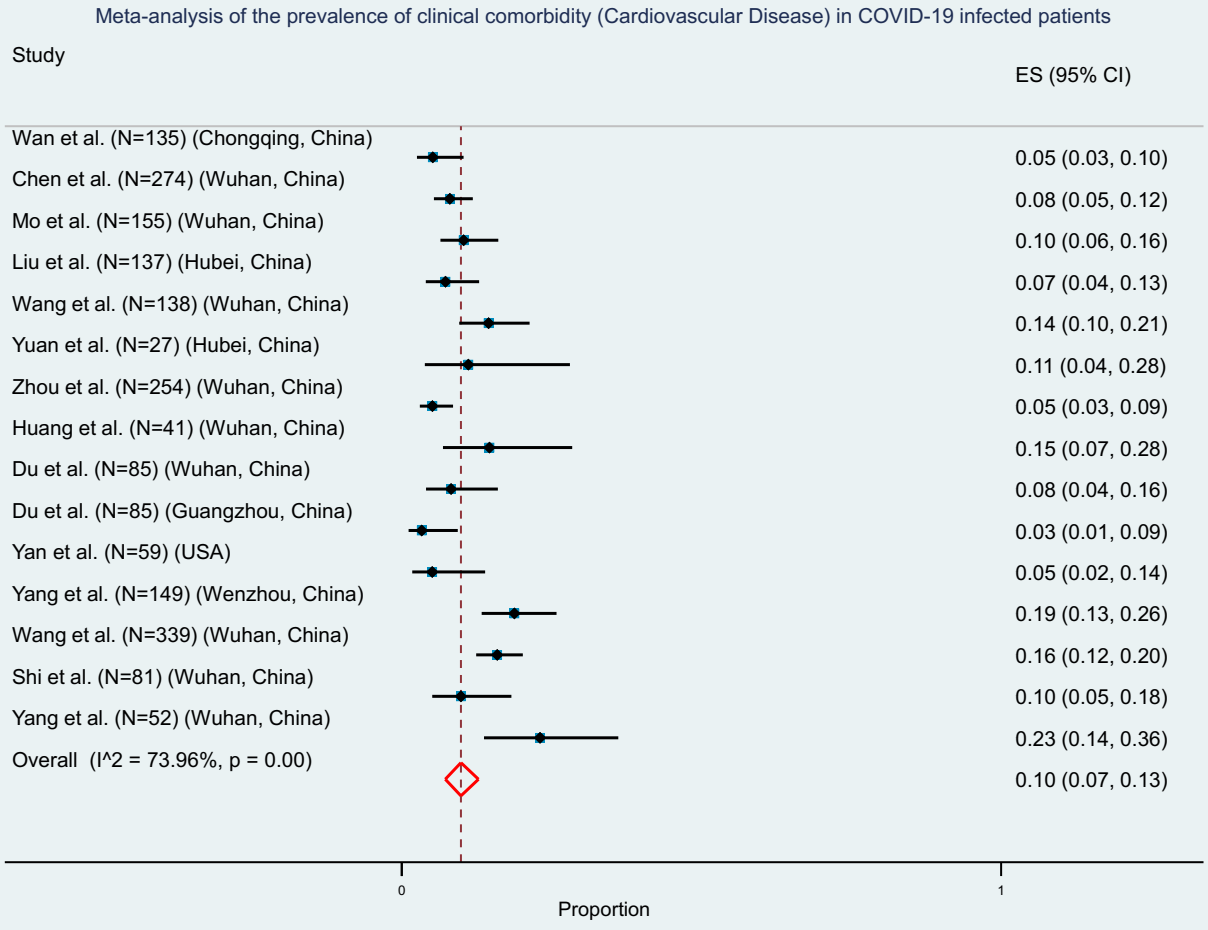
S21. Diabetes



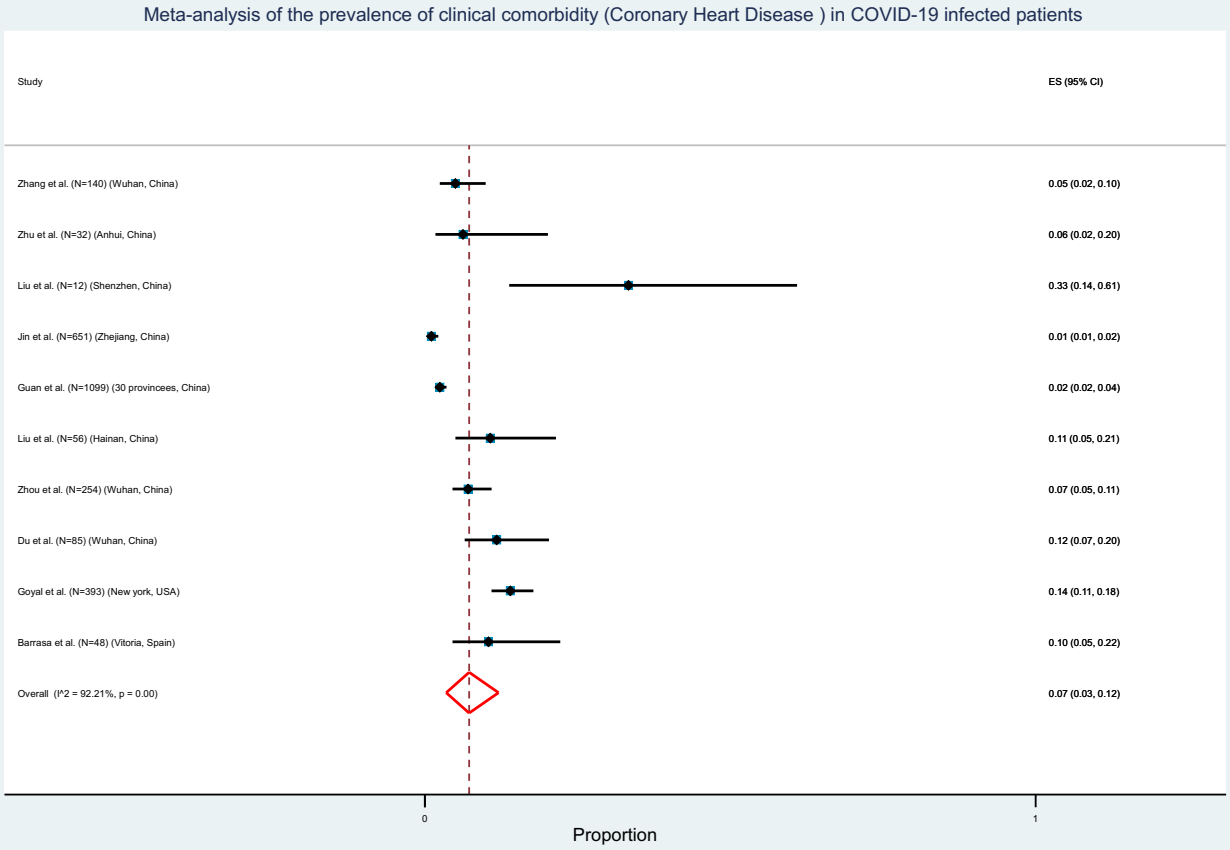
S22. Hypertension



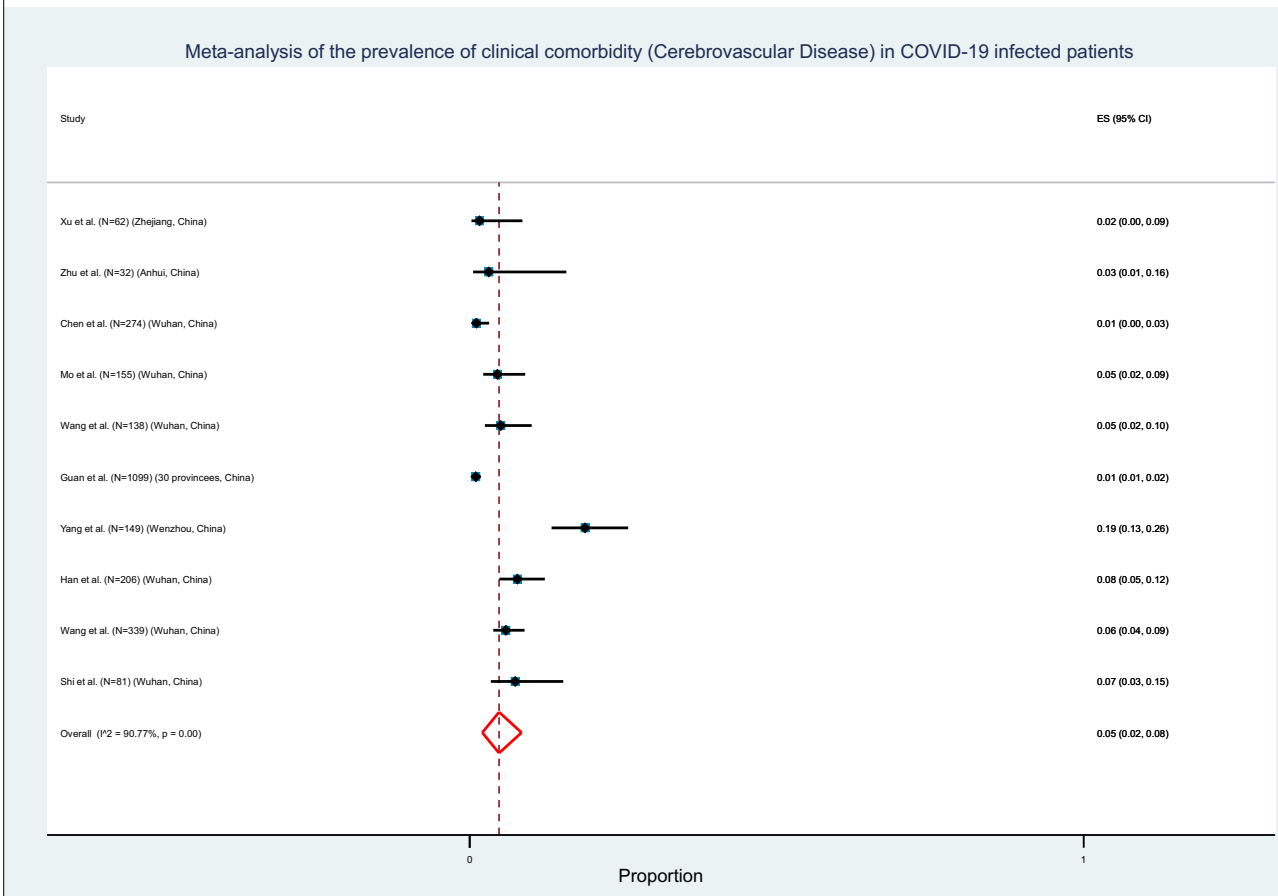
S23. Cardiovascular Disease



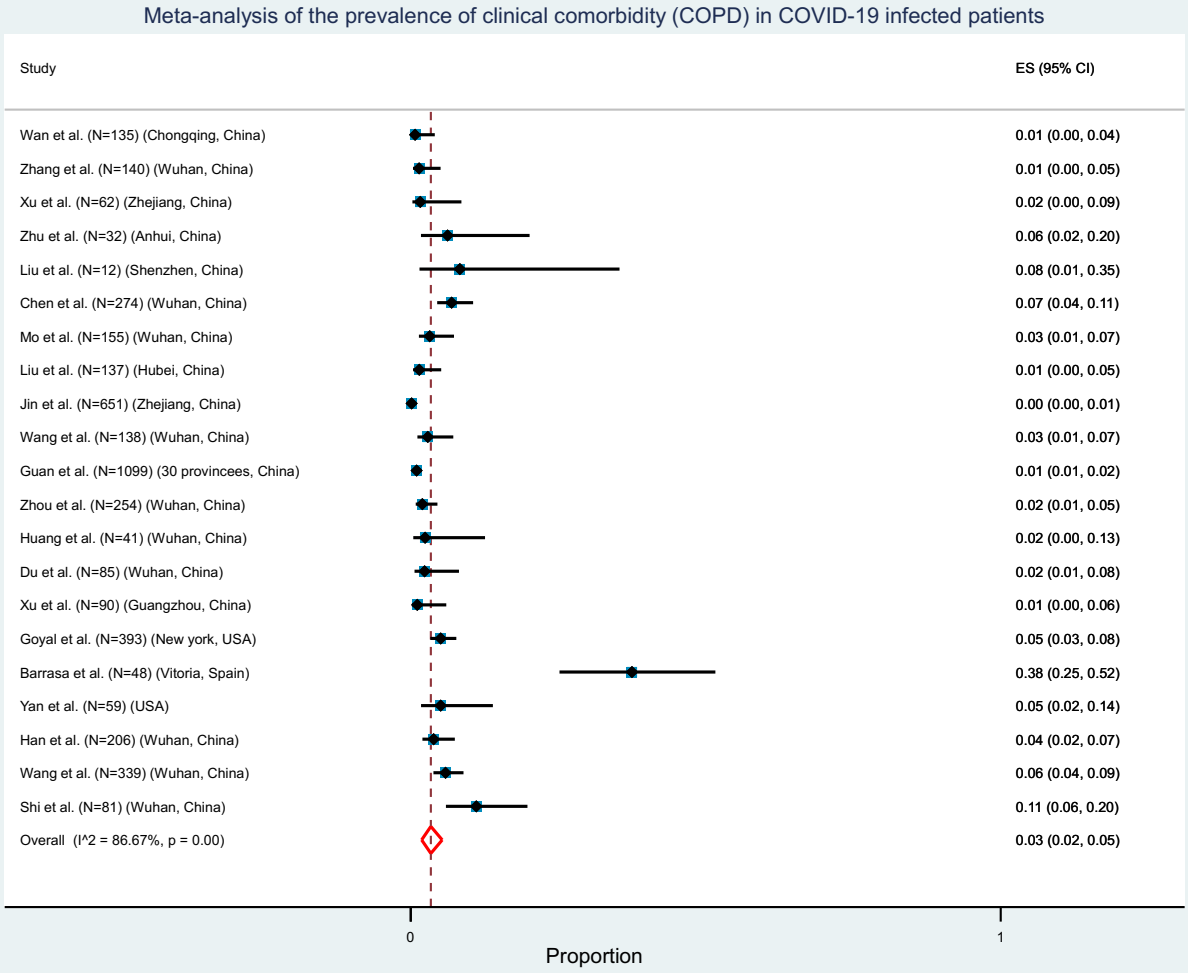
S24. Coronary heart disease



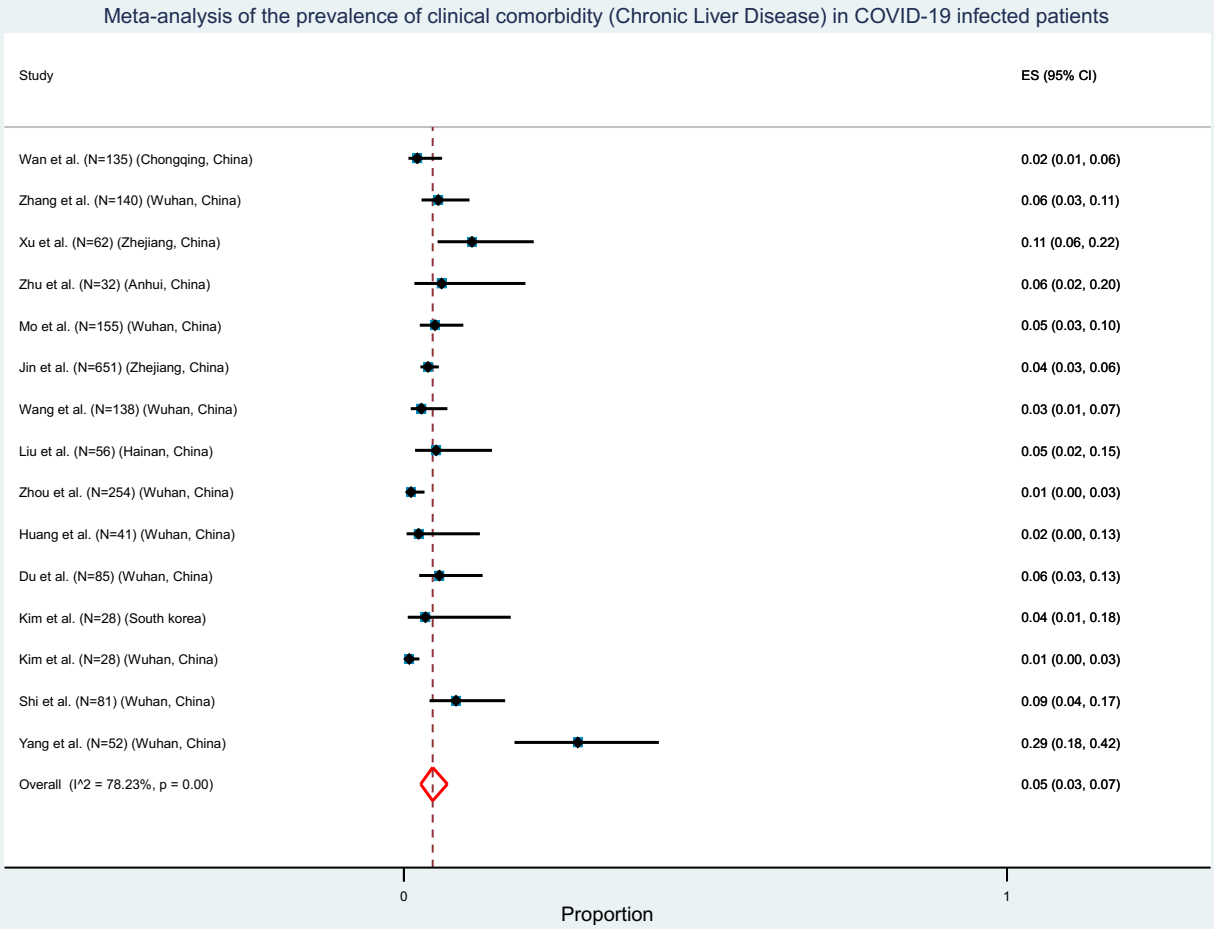
S25. Cerebrovascular disease



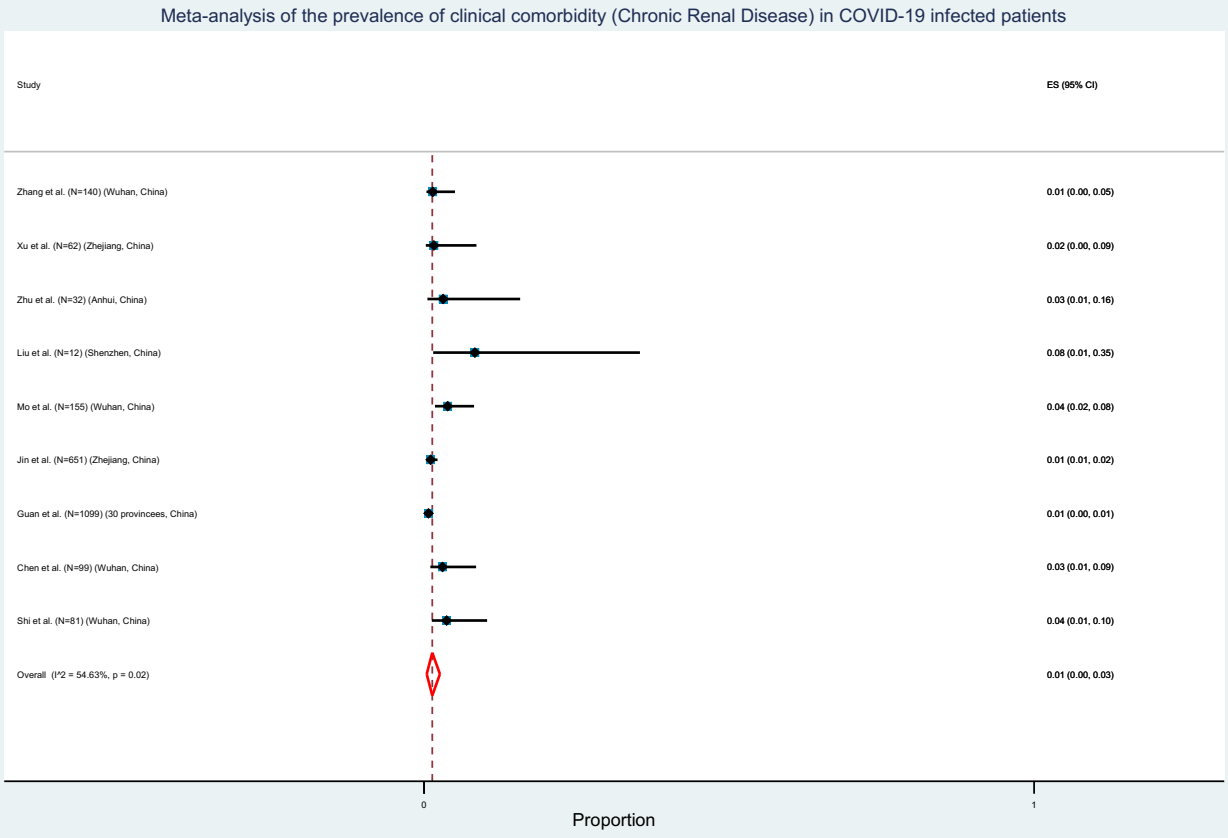
S26. COPD/Lung disease



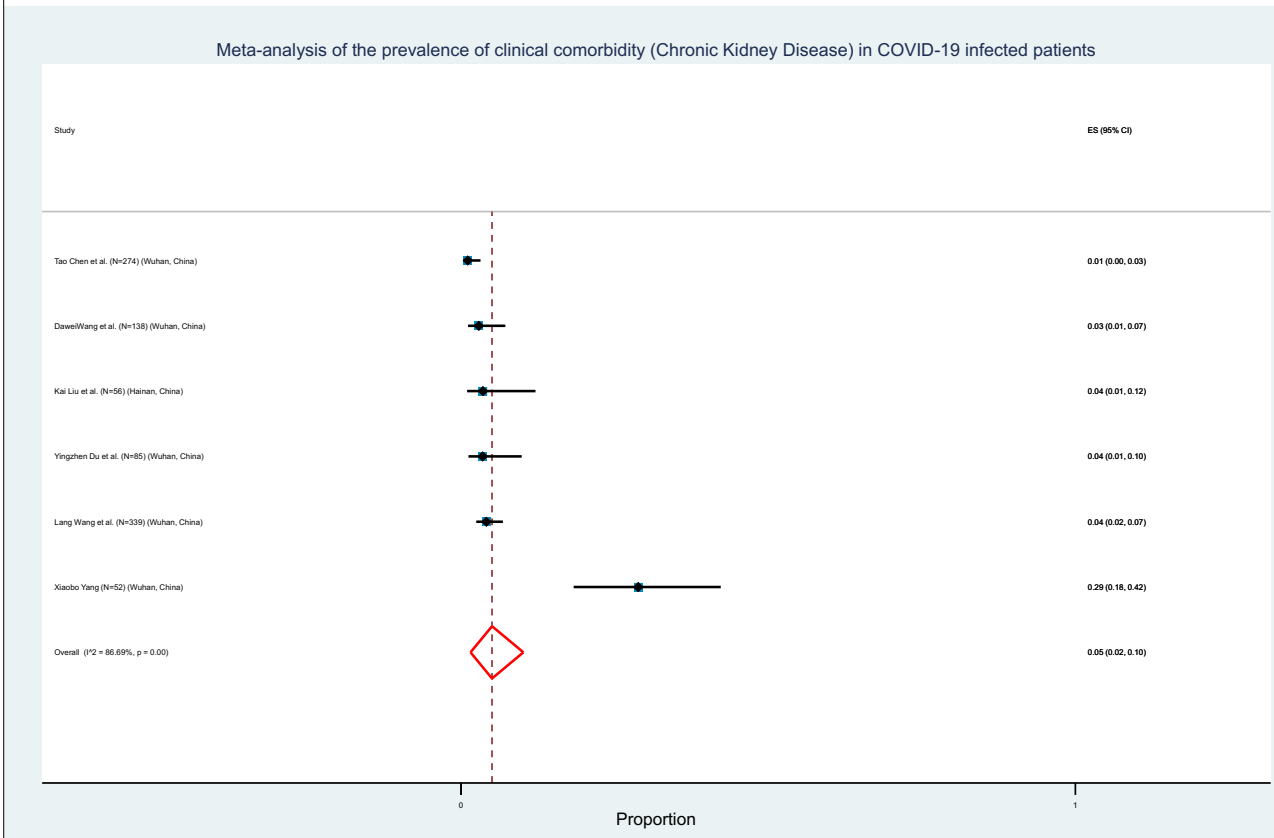
S27. Chronic liver disease



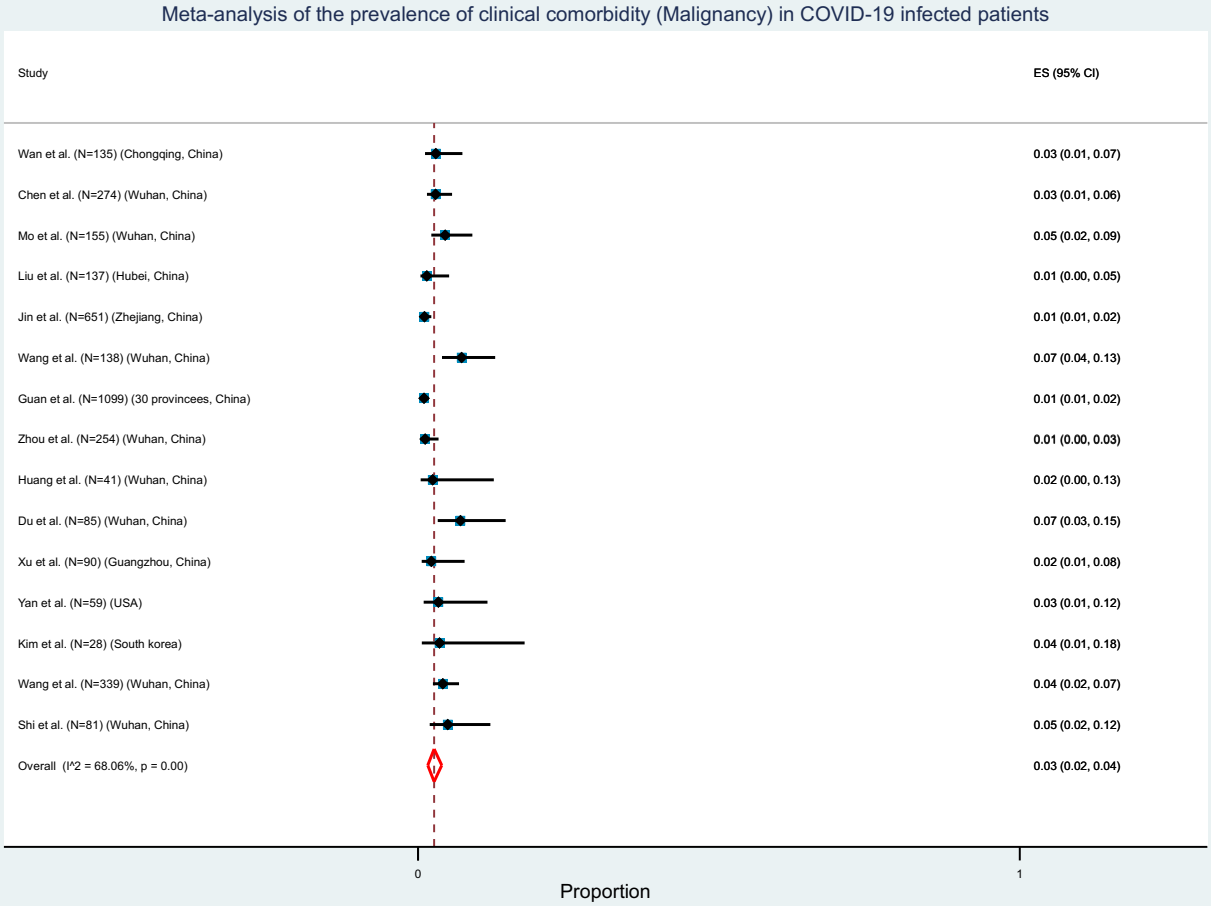
S28. Chronic Renal disease



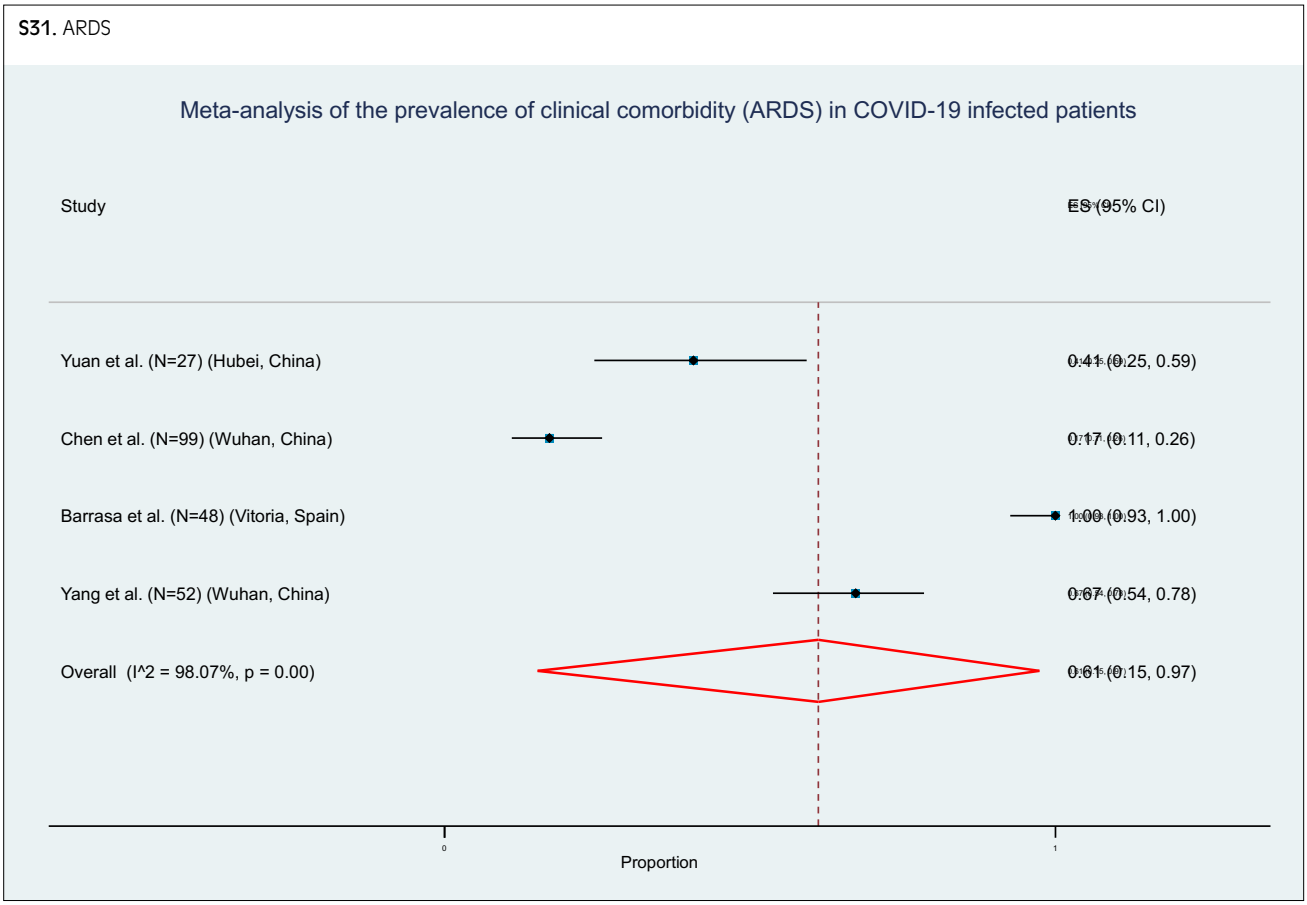
S29. Chronic Kidney disease



S30. Malignancy



S31. ARDS


Meta-analysis of the prevalence of clinical comorbidity (ARDS) in COVID-19 infected patients
Study
ES (95% CI)
Yuan et al. (N=27) (Hubei, China)
0.41 (0.25, 0.59)
Chen et al. (N=99) (Wuhan, China)
0.17 (0.11, 0.26)
Barrasa et al. (N=48) (Vitoria, Spain)
1.00 (0.93, 1.00)
Yang et al. (N=52) (Wuhan, China)
0.67 (0.54, 0.78)
Overall (I^2 = 98.07%, p = 0.00)
0.61 (0.15, 0.97)
0
1
Proportion

Research paper

Seroprevalence of antibodies to cytomegalovirus in pregnant women in the Apulia region (Italy)

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[1] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy; [2] VisMederi srl, Siena, Italy

Keywords

Cytomegalovirus • Pregnancy • Apulia region • Italy • Seroprevalence

Summary

Introduction. *Cytomegalovirus is ubiquitous and easily transmitted by contact. Following the first infection, the virus becomes latent and periodic reactivation could occur due to immunosuppression. If the infection is acquired in pregnancy, especially in the first trimester, the foetal consequences could be serious. The present study was conducted to assess the serological profile of pregnant women with respect to cytomegalovirus in Apulia from 2016 to 2019.*
Methods. *Serum samples were tested by commercial ELISA kit for the detection of specific IgM and IgG antibodies against cytomegalovirus.*
Results. *The data showed that most of the pregnant women (70.8%), especially those of ≥ 40 years of age (80.6%), has antibodies against cytomegalovirus, though these do not confer fully protective immunity against infection by different strains nor can prevent the re-activation of the latent one. Conversely, most of the youngest women are seronegative (44.4% in women < 25 years of age) and vulnerable during pregnancy.*
Conclusions. *Currently, cytomegalovirus screening for pregnant women is not mandatory in Italy. Considering that congenital cytomegalovirus is the leading non-genetic cause of sensorineural hearing loss, it would be extremely useful and cost-saving to screen women of childbearing age and women at early stage of pregnancy for cytomegalovirus infection in addition to increase awareness of cytomegalovirus infection and consequences among pregnant women, health care workers and the public.*

Introduction

Congenital infections are caused by pathogens able to infect the placenta and damage the foetus. The most common are toxoplasmosis, rubella, cytomegalovirus (CMV), herpes simplex and others grouped traditionally as TORCH complex. These infections represent a major public health concern, nevertheless it seems to be poor awareness of CMV infection among pregnant women, health care workers and the public [1-3]. Prenatal screening for toxoplasmosis and rubella is usually performed at the early stage of pregnancy in Italy.
CMV, formally designated human herpesvirus 5, belongs to the *Herpesviridae* family, is ubiquitous and transmitted by contact through infected body fluids such as urine, saliva, genital secretions and breast milk. Following the first infection, the virus becomes latent and periodic reactivation could occur due to immunosuppression (i.e. stress and pregnancy) [4-8].
The worldwide seroprevalence is roughly 60-90%, however there are some differences according to geographical areas, socioeconomic level and ethnic groups [5, 9]. Low prevalence is reported in countries as North America and United Kingdom, while most of the European countries has a prevalence of 80% meaning that most of the European women has been infected by CMV [9].
During pregnancy the transmission of CMV to the fetus may occur in two setting: "primary infection" and "non-primary infection". The first one occurs when seronegative women contract the infection during pregnancy; the second one occurs when a woman with prior immunity to CMV experiences a re-activation of the virus from latency or an infection by different strains [10, 11].
Seronegative women who become pregnant have a 4-fold higher risk to transmit the infection to the fetus if they are infected during pregnancy [12], as the likelihood of placental transmission appears to be higher among women with primary infection (approximately 30-50%) [10, 13]. The risk of transmission to the fetus is higher in the late stage of pregnancy (58-78% of infection transmitted in the third trimester versus 30-45% in the first trimester), although the likelihood of long-term sequelae is lower (24-26% in the first trimester versus 2.5-6% after 20 weeks of pregnancy) [11, 14, 15].
Most of the infants affected by congenital CMV (cCMV) are asymptomatic, while only 10% shows symptoms at birth, of whom a high proportion (40-60%) will develop long-term sequelae such as sensorineural hearing loss (SNHL) and neurodevelopmental difficulties. Among asymptomatic infants at birth, 6-23% could develop SNHL later making of cCMV the leading non-genetic cause of SNHL [10, 11].
The cCMV prevalence in Italy is one of the lowest, ranging from 0.15% in infants born to women ≥ 24 years old to 0.51% in infants born to women < 24 years old, suggesting that old age of the mother may be a "protective factor" against cCMV [9].

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CMV screening for pregnant women is not mandatory in Italy, while it is a routine test in 8 European countries and Israel [16]. Regarding Apulia region, a large region in Southern Italy, some useful information on hygienic measures aimed at avoiding CMV infection are included in a document dedicated to pregnant women [17, 18].
The present study was conducted to assess the serological profile of pregnant women with respect to CMV in Apulia from 2016 to 2019.

Materials and methods

Study population

Serum samples of pregnant women were collected from August 2016 to December 2019 in the province of Bari, the regional capital city with the highest population density in Apulia. Serum samples were anonymously collected in compliance with Italian ethics law and stored at the Molecular Epidemiology laboratory of the University of Siena, Italy. For each serum sample, information on age, state of pregnancy, gestational week, place and year of sampling was available.
Assuming an overall CMV IgG prevalence of 64.2% [19], a precision of the estimate of 5% and a confidence interval of 95%, a sample size of 354 serum samples was required.
A total of 360 samples, available at the sera bank, were stratified by age group (< 25, 25-29, 30-34, 35-39, ≥ 40 years of age) (Tab. I). The mean age was 32.6 ± 5.4 years (age range 17-46 years).
According to the USA National Institutes of Health's (NIH) definition, samples were stratified by trimester of pregnancy (Tab. II): first trimester from week 1 to week 12, second trimester from week 13 to week 28, third trimester from week 29 to week 40 [20].

Tab. I. Study population by age group; Apulia, Southern Italy 2016-2019.

Age group	N	%
< 25	27	7.5
25-29	76	21.1
30-34	120	33.3
35-39	101	28.1
≥ 40	36	10.0
Total	360	100

Tab. II. Study population by trimester of pregnancy; Apulia, Southern Italy 2016-2019.

Trimester	N	%
1°	140	38.9
2°	174	48.3
3°	46	12.8
Total	360	100

Serological assay

Specific IgM and IgG antibodies against CMV were detected by commercial ELISA kits (Enzywell Cytomegalovirus IgM and Enzywell Cytomegalovirus IgG; DIESSE, Siena, Italy). Testing was performed according to manufacturer's instructions. Samples were considered positive for IgM and IgG when the ratio between the optical density (OD) of the sample and that of the cut-off was > 1.2, and negative when the ratio between the OD of the sample and that of the cut-off was < 0.8. Samples with a borderline result (± 20% of the cut-off) were retested, in accordance with the manufacturer's instructions. For CMV IgG ELISA, IgG concentration was determined and expressed in IU/ml. Samples with CMV IgG concentration > 1.2 IU/ml were considered as immune, as indicated by manufacturer's instructions.

Statistical analysis

Mean age of subjects was calculated along with standard deviation (SD). IgM and IgG prevalence rates were calculated along with the corresponding 95% confidence intervals (95% CI). Geometric mean titres (GMTs) with corresponding 95% CI were calculated for IgG positive samples. Chi-square test and One-Way ANOVA test were used to compare prevalence rates and GMTs, respectively. Statistical significance was set at $p < 0.05$, two tailed.

Results

Out of 360 samples, 8 and 10 samples tested borderline for CMV IgM and IgG, respectively. After retest, only one sample still tested borderline for IgM.
255 samples (70.8%, 65.8-75.5 95% CI) tested positive for CMV IgG, while 105 (29.2%, 24.5-34.2 95% CI) were negative. No significant differences in prevalence rates or GMTs were found by age group (Tab. III).
Considering the CMV IgG prevalence by trimester of pregnancy, 47.8% (32.9-63.0 95% CI) of samples

Tab. III. CMV IgG prevalence (reported as number and %, 95% CI) of positive and negative samples by age group. IgG titres of positive samples are reported as GMT (95% CI).

CMV IgG	Positive			Negative	
Age groups	N	% (95% CI)	GMT (95% CI)	N	% (95% CI)
< 25	15	55.6 (35.3-74.5)	14.0 (11.8-16.5)	12	44.4 (25.5-64.7)
25-29	60	78.9 (68.1-87.5)	12.8 (11.2-14.5)	16	21.0 (12.5-31.9)
30-34	82	68.3 (59.2-76.5)	12.9 (11.7-14.3)	38	31.7 (23.5-40.8)
35-39	69	68.3 (58.3-77.2)	12.2 (11.0-13.6)	32	31.7 (22.8-41.7)
≥ 40	29	80.6 (64.0-91.8)	14.5 (12.3-17.0)	7	19.4 (8.2-36.0)

collected during the third trimester of pregnancy was positive, significantly lower when compared to the first (79.3%, 71.6-85.7 95% CI) and the second (70.1%, 62.7-76.8 95% CI) ones ($p < 0.001$). However, no significant differences were found for GMTs by trimester.

Three samples (0.8%, 0.2-2.4 95% CI) tested positive for CMV IgM, one in the first trimester (≥ 40 years old age group) and 2 in the second one (1 in 35-39 and 1 in ≥ 40 years old age group). One sample (0.3%, 0.0-1.5 95% CI) collected in the second trimester (25-29 years old age group) tested CMV IgM borderline. All these samples were CMV IgG positive.

Discussion

In this study a high proportion (70.8%) of pregnant women from the province of Bari had antibodies against CMV showing that almost two-thirds of pregnant women included in this study have been infected by CMV. Considering the gestational period, we found a high proportion of women in the first and second trimester of pregnancy with CMV IgG antibodies (79.3 and 70.1%, respectively), while in the third trimester a lower (47.8%) proportion of women resulted positive to CMV. We do not have a clear explanation for this difference, and it is known that although the risk of CMV transmission to the fetus is higher in late pregnancy, the probability of long-term sequelae is lower in case of infection in the later stage of pregnancy than during the first trimester [11, 14, 15].

In our study, 29.2% of pregnant women were seronegative to CMV, with the younger age group (< 25 years) being more susceptible to CMV infection during pregnancy (44.4%) compared to the oldest age group (≥ 40 years old, 19.4%). In a multicentre survey conducted in 4 Italian regions it was found that the frequency of cCMV infection was higher in children born to women younger than 24 years old than those born to older women [21]. Seronegative women at the beginning or during pregnancy have the greatest risk to transmit CMV infection to the foetus. Roughly 40% of the women with primary infection during pregnancy transmits CMV to the foetus and approximately 10% of the infected infants shows the disease [22]. In Italy CMV prevalence in pregnant women increases with age [23] and together to a relatively high age at first pregnancy (mean age > 31.1 years) [24] it may represent a "protective factor" against cCMV [9] infection of new-born. A study conducted in 1993 focusing on infants and children reported that CMV infection was endemic in the area of Bari, was mostly acquired in early childhood once the maternal immunity waned in the first year of life [25]. Other Italian studies performed on women of childbearing age and healthy subjects from 3 to 18 years old reported a seroprevalence of 79.9 [21] and 64.2% [23] respectively. Noteworthy, the latter found a prevalence significantly higher in females and subjects resident in the South of Italy [23].

Our findings show a higher prevalence of CMV antibodies in pregnant women than what reported from different Italian areas such as the Province of Trento (64.2%) [19], the urban area of Northern Italy (68.3%) [26] and Sicily (65.87%) [27], as well as in some European countries as in Belgium (53.9%) [28] and in London (54.4%) [29], but considerably lower than in Iran (97.69%) [30], Saudi Arabia (98.7%) [31], and Brazil (97.5%) [32].

Notably, one sample in the first trimester of pregnancy in the ≥ 40 age group and two samples in the second trimester in the 35-39 and ≥ 40 age groups tested IgM and IgG positive. These finding could suggest recent primary infection, however further investigations should be needed [33].

This study has some limitations. The serum samples are convenience samples and may not be fully representative of the Apulia region or other Italian regions.

The presence of IgM provides an indication of recent infection, however the lack of baseline serum sample did not allow to assess seroconversion, if any.

For these samples no information on maternal and/or foetal outcomes was available so further analysis could not be performed.

Conclusions

In conclusion, our study highlights that most of the pregnant women, especially those of ≥40 years of age, has antibodies against CMV, though these do not confer fully protective immunity against infection by different strains nor can prevent the re-activation of the latent one. On the other hand, most of the youngest women are seronegative and vulnerable during pregnancy. It is acknowledged that educational and hygienic measures represent an important primary prevention strategy able to effectively reduce the rate of maternal primary infection during pregnancy and cCMV infection [18].

Considering that cCMV is the leading non-genetic cause of SNHL, whose prevalence is much higher than that of Down syndrome and spina bifida [8], as well as of other congenital anomalies and long-term sequelae in new-borns, it would be extremely important, useful and cost-saving to screen women of childbearing age and women at early stage of pregnancy for CMV infection [26, 27, 34]. In addition, increase in the awareness of CMV infection, as for other diseases representing a threat during pregnancy [35, 36], is needed to reduce the risk of congenital infection through counselling about appropriate hygienic measure to prevent infection.

Vaccination may represent the most effective way of preventing CMV infection. Despite vaccine development has been in process since the 1970s and significant progress has been made, no vaccine is yet available mainly due to the ability of CMV to evade immune mechanisms and virus genetic diversity [37]. In addition to the screening actively offered to all pregnant women, seroepidemiological studies are an important tool for monitoring not only of vaccine preventable

diseases [35, 36, 38, 39] but also of other infections that represent a potential threat for pregnant women and new-borns [40-42].

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization, CMT; formal analysis, SM; investigation, CMT, SM; resources, CMT; writing, original draft preparation, CMT; writing, review and editing, SM, SV, EM; visualization, SM; project administration, CMT.
All authors have read and agreed to the published version of the manuscript.

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Research paper

Influenza vaccination coverage and obstacles in healthcare workers (HCWs) and the follow up of side effects: a multicenter investigation in Iran

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Keywords

Influenza • Vaccination • Healthcare workers

Summary

Introduction. *Seasonal influenza is an annual common occurrence in cold seasons; but the COVID-19 pandemic is also currently ongoing. These two diseases can't be distinguished from their symptoms alone; therefore, the importance of preventing influenza by vaccination is more than ever. Due to the high exposure of hospital personnel, widespread influenza vaccination of these high-risk groups seems to be a necessity. This Study conducted to determine vaccination coverage in the personnel of four tertiary referral collegiate hospitals in 2019 and to further investigate individual obstacles for Influenza vaccination.*

Methods. *In this cross-sectional descriptive study, 637 personnel were selected randomly from distinctive hospitals in a list-wised. Ones vaccinated filled the side effects questionnaire and who not vaccinated filled the vaccination obstacles questionnaire. The study was approved by the ethics committee of Tehran University of Medical Sciences with this reference number: IR.TUMS.IKHC.REC.1398.218*

Results. *The mean vaccination coverage was 29.4% and the coverage difference among centers was not statistically significant ($p = 0.192$). The following items had the most impact on personnel decision: confidence about one's immune system ($p < 0.05$), the experience of side effects from previous vaccinations ($p = 0.011$), attitude about vaccination in colleagues ($p = 0.021$) and work experience ($p < 0.05$). About 23% of vaccinated individuals reported side effects following vaccination and the most common side effect was mild cold symptoms with 12.3% prevalence.*

Conclusion. *The results of the current study revealed that influenza vaccination coverage among HCWs is not satisfactory in Iran. Hospital authorities and infection control units should plan to remove the obstacles of influenza vaccination.*

Introduction

Influenza, also known as "the flu" is an infectious disease caused by the influenza virus, leading to an acute respiratory illness affecting the upper and/or lower respiratory tract [1]. Receiving an influenza vaccination, as CDC confirms, is the major public health measure for the prevention of influenza virus infection [2] and thus, vaccination has to be considered one of the most crucial actions which have to be taken to immunize healthcare workers who are highly in exposure to various threatening viruses.

Influenza epidemics are a familiar annual event, but currently in the absence of widespread use of vaccine for novel coronavirus, the COVID-19 pandemics also circulate in parallel with seasonal influenza [3, 4]. WHO concerns many healthcare systems are already reached to their limits and may not be able to deal with influenza. Unfortunately, the two diseases can't be distinguished from their symptoms alone, and laboratory tests are needed. Therefore, the importance of preventing influenza infection is certainty these years more than ever. The most effective way to avoid influenza infection is through vaccination [3].

Based on a rapid evidence appraisal identifying the public health need for healthcare worker (HCW) influenza immunization and the international independent expert group confirmed in 2019 the need to support policy-making for health worker vaccination to support pandemic preparedness in countries in line with the WHO global influenza vaccine strategy. However, some studies are indicating that the majority of healthcare workers are not usually immunized based on different reasons [5]. Some of the barriers to acceptance of influenza vaccination among HCWs are fear of vaccine side-effects (especially influenza-like symptoms), perceived ineffectiveness of

the vaccine, insufficient time, or inconvenience [6, 7]. Other factors included perceived low likelihood of contracting influenza, perceived low threat compared to other infectious diseases, avoidance of medications, and fear of needles [8]. In response to these perceptions, healthcare facilities have adopted programmatic strategies to improve vaccination uptake in HCWs including the participation of senior personnel or opinion leaders as role models, removing administrative barriers, e.g. costs, providing on-site vaccination delivery service at convenient times that are easily accessible by HCWs [5, 9]. Several studies have highlighted that the vaccinated and non-vaccinated HCWs had opposing perceptions about the risks and benefits of the vaccination and degree of its benefits [10, 11].

Despite the importance of identifying and breaking these barriers in increasing vaccination coverage of HCWs, there have been limited studies countrywide, investigating the vaccine coverage rate among HCWs and identifying barriers to get vaccinated among them [7, 12]. Therefore, in this study, we are trying and aiming to help the governors and motivate them to work things out to define a new priority for immunizing HCWs who are highly vulnerable for transmitting the disease. The other contribution of the current paper is to analyze adverse effects of vaccination and exploiting the scope of its effectiveness in HCWs.

Methods

In this cross-sectional descriptive study, some personnel of distinctive hospitals (four tertiary referral collegiate hospitals in Tehran, Iran) were selected randomly in a list-wised fashion. Moreover, a pre-designed questionnaire was taken from listed HCWs regarding their attitude of vaccination and their confidence about their immune system capabilities, vaccination history, number of flu episodes in the past year as well as the scope and severity of symptoms if present, underlying diseases, fear from side effects and injection, side effects regarding vaccination, and their demographic data as well as their working experience.

Another questionnaire was additionally taken from vaccinated HCW regarding the side effects they have experienced following their current influenza vaccination.

Research Ethics

In this study no intervention was done, and no cost imposed on the participants. Researchers, in all stages, were adhered to the principles of the Helsinki manifesto and the Ethics Committee of Tehran University of Medical Sciences. Ethics Code: IR.TUMS.IKHC.REC.1398.218.

Results

From 637 listed individuals as healthcare workers across four hospitals, 477 were female and 160 were males. Vaccination coverage across all hospitals was 29.4% with the median age of 36.88 and 34.15 years in vaccinated and non-vaccinated groups respectively. The vaccination coverage was significantly different between sex groups with 35.85% and 27.31% for males and females respectively ($p = 0.041$). Vaccination coverage in these four hospitals was 24.41, 27.51, 34.29, and 34.33%. Vaccination coverage among different centers was not statistically significant ($p = 0.192$).

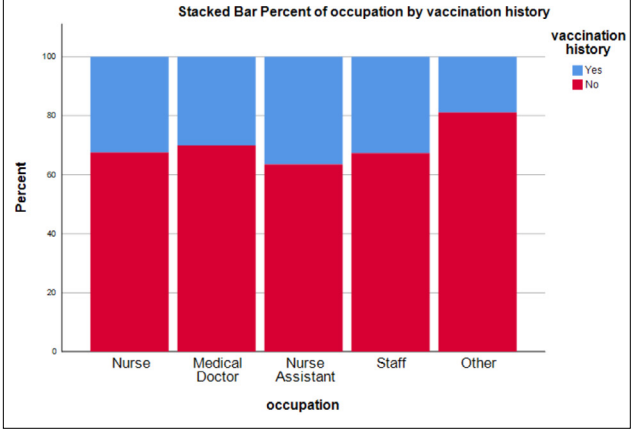
To analyze possible etiologies for not getting vaccinated, the chi-square test was used to compare questionnaire variables between vaccinated and non-vaccinated groups. The mean work experience was 11.83 and 8.92 years for vaccinated and non-vaccinated groups respectively which was statistically significant ($p < 0.05$). Besides, 33.8% of individuals in the non-vaccinated group had high self-esteem about their immune system capability which was significantly higher from 12.2% in vaccinated individuals ($p < 0.05$). Also, 75.4% of individuals who had a history of occurrence of side effects following their previous vaccination haven't participated in the new year's vaccination program, which was statistically significant ($p = 0.011$). Moreover, 14.1% of non-vaccinated individuals were heard negative feedbacks and attitudes from their colleagues, which was significantly more from 7.5% in vaccinated individuals ($p = 0.021$). Interestingly, known vaccination side effects that had been occurred in an individual's colleagues had no significant difference between vaccinated and non-vaccinated individuals ($p = 0.682$).

Lack of education and knowledge about vaccination benefits had no significant difference between vaccinated and non-vaccinated individuals in our study. In addition, vaccination was not significantly different regarding individuals' occupation, which is shown in Figure 1.

Moreover, vaccinated proportions were not significantly different across different wards and units (Fig. 2).

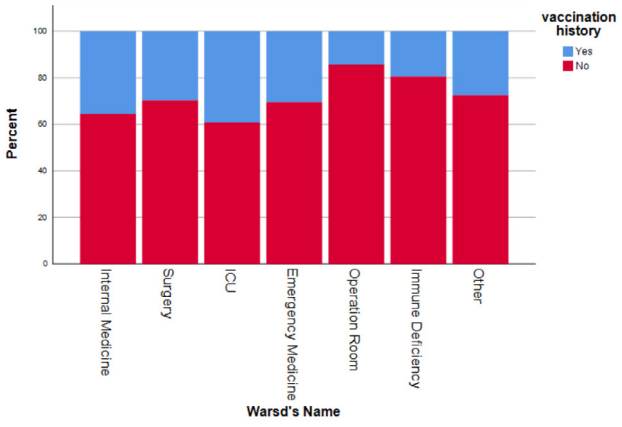
The relative frequency of different side effects following influenza vaccination from 187 vaccinated

Fig. 1. Percent of influenza vaccination by the occupation of personnel.



individuals is summarized in Figure 3. Common cold and influenza symptoms, as well as, fever were the most common side effects following the vaccination. To assess vaccination efficacy in healthcare workers, the occurrence of flu symptoms in last year were compared in vaccinated and non-vaccinated individuals. Twenty percent of vaccinated individuals experienced one or more episodes of flu-like symptoms in the past year which wasn't significantly different from 15.38% in non-vaccinated individuals; Although, vaccinated individuals had a significantly faster recovery following the onset of the symptoms ($p < 0.05$). This study about the duration of flu symptoms in vaccinated and non-vaccinated individuals suggested 69.76% of vaccinated individuals had a recovery duration of 3 days or less from their symptom onset, which is significantly more from 50% in the non-vaccinated group.

Fig. 2. Percent of influenza vaccination by hospital wards.



Discussion

Results of the current study revealed influenza vaccination coverage among healthcare centers in Iran is not satisfactory. Moreover, in this study individuals' attitude about the probability of "getting the disease" was correlated with their willingness for vaccination. Interestingly results of the current study suggest this probability is more correlated with one's self-esteem about his/her immune system capability as well as, his/her personal history of getting the flu rather than educational and knowledge of severity and prevalence of the illness. This effect of attitude in vaccination was previously shown in several studies [5, 6, 13].

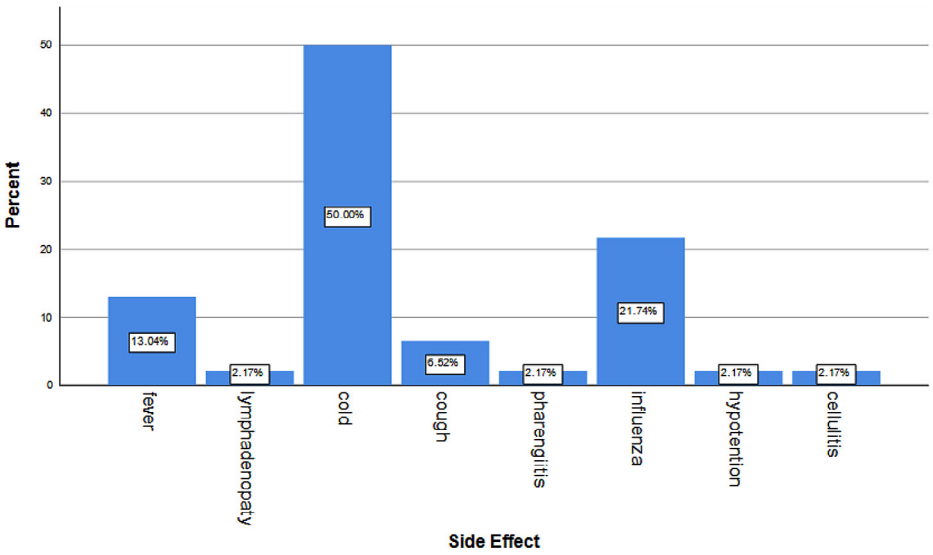
Interestingly, more working experience had a positive impact on getting the influenza vaccine. This is coherent with several studies that showed more professional experience correlation with higher vaccination rates [14-16]. Although, in contrast to the study performed by Barbodoro which stated good awareness of influenza and influenza vaccination is positively correlated with more vaccination rates [14], here such a correlation was not present.

Findings of the present study suggested although influenza vaccination can have limited to no effects in the prevention of the flue, it significantly accelerates the recovery process and reduces the severity and shortens the course of the illness. These findings are in line with the study by Nishi et al. [17] except in our study vaccination didn't decrease yearly flu episodes in HCWs.

The results from the current study suggested a relatively low prevalence of mostly mild side effects following the influenza vaccination. Hashemi et al. has reported similar results in a study performed in Shiraz [7].

Current years however are quite unique because the

Fig. 3. Relative frequency of side effects following influenza vaccination.



symptoms of patients may not necessarily be due to influenza but also due to the COVID-19. In addition, because of standing the receptors for both influenza and COVID-19 on human host cells one may get infected with either or both infection. Hence the scientists encourage everyone to take the vaccine and avoid this complex scenario [4]. Besides, in a conclusion by Debisarun et al, influenza vaccine can also induce trained immunity responses and may also create a relative protection against COVID-19. These data, coupled with similar reports, discuss a beneficial effect of influenza vaccination in the influenza season against both infections [18, 19].

Conclusions

Considering international recommendations on influenza vaccination for HCWs, the results of the current study revealed that influenza vaccination coverage among HCWs is not satisfactory in Iran. Hospital authorities and infection control units should plan to remove the factors correlated with not getting vaccinated in healthcare workers. Influenza vaccination is an effective way to prevent or reduce the severity of seasonal flu in healthcare workers with few and mostly mild side effects.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

HM: senior supervisor of the study; HNG: primary analysis and preparation of manuscript draft; MM, RP, HM, GA, AA and VYB: data collecting in Sina hospital, Shariati hospital, Amir Alam hospital, Imam Khomeini hospital, Cancer Institute and Valiasr hospital respectively; ASH, ME, HA and A-AA: study supervision and confirming the data in Shariati hospital, Imam Khomeini hospital Complex, Sina hospital and Amir Alam hospital respectively; SA: designing the study, final analysis and revising the paper. MH and NGHcontributed equally to this work. All authors reviewed the results and approved the final version of the manuscript.

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Review

Emerging fungal infections: focus on *Saksenaea Erythrospora*

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Keywords

Fungi • Emerging infections • Review

Summary

Introduction. *In recent times, improved diagnostic techniques have revealed an alarming number of cases of mucormycosis in immunocompetent individuals. The Saksenaea species, is a rare cause of mucormycosis, and is often associated with skin and subcutaneous infection due to trauma in both immunocompromised and immunocompetent subjects. The purpose of this study was therefore, through a review of the literature, to investigate the problem of infections caused by Saksenaea Erythrospora, evaluating the clinical manifestations of the infection, the triggering factors, the therapies and patients' outcomes, implementing and updating what already reported in literature.*
Methods. *A research of peer-reviewed literature in the electronic databases MEDLINE (PubMed) and Scopus was conducted in the period June 2020-January 2021 using the key word "Saksenaea erythrospora". Studies in Italian, English, French, Spanish focused on cases of Saksenaea erythrospora were included, without time restrictions. Studies that provided ambiguous or insufficient data were excluded.*
Results. *Bibliographic research yielded 23 publications; 7 were included in the review. The studies were published between 2011 and 2015 and involved a total of 11 patients of average age 37.9 years (SD 17.23) hospitalized in several hospitals in: USA, India, Argentina, Colombia, Thailand. 6 patients were women, 5 men. All patients had an almost normal immune status. The causes of the infection were: injections, traumas, surgery. Two patients, despite surgical and medical therapy, died.*
Conclusions. *Our review partially updated what already published, because only one new study was found. Serious necrotizing infections from Saksenaea erythrospora have been observed in recent years and a early identification and timely management are essential to reduce morbidity and mortality. A greater awareness and education about the risks deriving from carrying out surgical procedures abroad, especially in precarious hygiene situations, could be additional effective weapons to reduce the incidence of these infections.*

Introduction

Immunotherapies have revolutionized the treatment of cancers and autoimmune diseases and invasive fungal infections have become major complications of some of these new immunomodulators. The emergence of mucormycosis, a fungal infection caused by Mucorales, has been attracting the spotlight in recent years [1].
The significant increase in cases, high mortality rates (even up to 90%) in widespread infections, and the lack of effective antifungal treatments raised the alarm for this emerging disease. In the past, it was considered a rare and limited infection in immunocompromised patients suffering from AIDS, diabetes, organ transplants or other conditions associated with immunosuppression. In fact, in patients undergoing allogeneic bone marrow transplantation, the prevalence of mucormycosis could be up to 2-3%. However, iatrogenic outbreaks have also been described in the context of medications or use of contaminated medical instruments [2].
Soft tissue infections usually occur in patients with altered skin barriers, either as a result of traumatic impact with the soil, maceration of the skin caused by a wet surface or in nosocomial environments by direct access through intravenous catheters or subcutaneous injections. Contaminated surgical dressings have also been implicated in skin mucormycosis. In one case, skin mucormycosis occurred due to a contaminated tape used to secure an endotracheal tube in a ventilated patient [2]. However, the current improvement in diagnostic techniques has revealed an alarming number of cases of mucormycosis in immunocompetent individuals.
The *Saksenaea* species is a rare cause of mucormycosis, and is often associated with skin and subcutaneous infection as the result of trauma in both immunocompromised and immunocompetent subjects [3].
In order to deepen this argument we conducted a brief review of the literature with a focus on *Saksenaea Erythrospora*, a species identified only in recent years, evaluating the clinical manifestations of the infection, the triggering factors, the therapies and patients' outcomes, with the aim of implementing and updating what reported in 2019 by Putthirangsiwong et al. [4] and Chander et al. in 2017 [5].

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Tab. I. Main characteristics of the studies included in our review (LAMB = liposomal formulation of amphotericin B, MRI = magnetic resonance imaging, CT = computerized tomography, *= all cases are included in a unique article).

#	Author, year	Gender	Age (years)	Country	Clinical presentation	Immune status	Cause of Infection	Undergone Procedures	Laboratory Diagnosis	Pharmacological Treatment	Outcome
1	Hospenthal, 2011	M	26	USA	Proptosis of the left eye	Normal	Combat Trauma	CT + enucleation of the left eyes	Incubation on potato flake agar (PFA), subculturing on Czapek Dox agar and multilocus molecular study	Not reported	Death
2	Relloso, 2014	M	55	Argentina	Abscess on the thigh	Normal	Sailing accident with deep skin and soft tissue injuries, with muscular avulsion	MRI + debridement	Microscopic examination using Giemsa stains. Culture on malt extract agar, potato dextrose agar and agar block with sterile distilled water and salt water (0.85% NaCl) + PCR	LAMB + hyperbaric oxygen therapy + posaconazole + interferon gamma	Resolution
3	Tendolkar, 2015	F	44	India	Right-sided orbital cellulitis	Normal	History of recurrent sinusitis. No history of trauma, nasal blockage, epistaxis or dental caries	CT + MRI + Endoscopic endonasal debridement + right orbital exenteration	Incubation on Sabouraud dextrose agar; then a slide culture on water agar + PCR	Amphotericin B	Resolution
4	Rodriguez, 2016	F	29	Colombia	Fever and chills, pain and erythema in the surgical wound. Then skin necrosis.	Normal	Breast Augmentation Surgery	Radical right mastectomy and surgical debridement	Incubation on Potato dextrose agar, malt extract agar, Sabouraud glucose agar + PCR	Amphotericin B + caspofungin	Resolution
5	Chander, 2017*	F	31	India	Large ulcerative lesion on left gluteal region	Normal	Injection	Extensive surgical debridement	Incubation on Czapek Dox agar and molecular sequencing	LAMB	Resolution
5	Chander, 2017*	M	37	India	Necrotizing area on left shoulder	Normal	Unknown	Extensive surgical debridement	Incubation on Czapek Dox agar and molecular sequencing	LAMB	Resolution
5	Chander, 2017*	F	40	India	Large necrotic area on right gluteal region	Normal	Injection	Extensive surgical debridement	Incubation on Czapek Dox agar and molecular sequencing	LAMB	Resolution
5	Chander, 2017*	M	60	India	Large necrotic area on right gluteal region	Normal	Injection	Extensive surgical debridement	Incubation on Czapek Dox agar and molecular sequencing	LAMB	Death
5	Chander, 2017*	F	55	India	Large necrotic area on right gluteal region	Normal	Injection	Extensive surgical debridement	Incubation on Czapek Dox agar and molecular sequencing	LAMB	Resolution
6	Putthirangsiwong, 2019	M	16 months	Thailand	Progressive painful mass at the right medial canthus and upper cheek	Normal	Unknown	MRI + Anterior orbitotomy with biopsy + multiple surgical debridements	Incubation in Sabouraud dextrose agar and DNA extraction, amplification and sequencing analysis	LAMB + itraconazole repeated because of a recurrent right lower eyelid swelling and redness	Resolution
7	Mukherjee, 2018	F	2	India	Rapidly progressive swelling in the medial canthal region of her right eyes	Normal	Unknown. No history of trauma, nasal blockage, epistaxis or weight loss	MRI + incisional biopsy	Histopathological examination + PCR	Amphotericin B + posaconazole	Resolution

Methods

The narrative review was conducted in June 2020-January 2021 in the electronic databases MEDLINE (PubMed) and Scopus using the keyword "*Saksenaea erythrospora*". We considered eligible articles that met the following inclusion criteria:

- language: Italian, English, French, Spanish;
- publishing time: no time restrictions;
- available information: gender and age of the case (due to *Saksenaea erythrospora*), clinical presentation, undergone diagnostic and therapeutic procedures, pharmacological treatment, outcomes.

Studies that provided ambiguous or insufficient data were excluded.

Results

Bibliographic research yielded 23 publications. After the analysis of the titles and abstracts, 13 studies were excluded: 9 as duplicates, 2 as reviews, 3 because they reported data not in line with the present study. The full text of the 9 remaining articles was analyzed: 2 articles were excluded because they focused on elements not in line with the study. The overall analysis was therefore conducted on 7 studies [4-10] (Tab. I).

The studies were published between 2011 and 2015 and involved a total of 11 patients of average age 37.9 years (SD 17.23) hospitalized in several hospitals in: USA, India, Argentina, Colombia, Thailand. Six (54.5%) patients were female, 5 (45.5%) male. All patients had an immune status that could be considered normal.

In 4 cases the trigger factor was an injection [5], in 1 case a combat trauma [6], in 1 an accident injury [8], in 1 case cosmetic surgery undergone in another country [9], in 4 cases the trigger was not identified.

In most cases (90.9%) the treatment was based on amphotericin B in various formulations; in 4 (36.3%), at least one other antifungal (posaconazole, caspofungin, itraconazole) was also associated. Surgical debridement was necessary in 100% of cases: in 3 cases also extensive demolition operations were necessary (eye removal or breast removal) [4, 6, 9].

Healing occurred in 9 patients. Two patients, instead, died (one had developed the infection after a combat trauma; the other a necrotizing infection after an injection) [5, 6].

Discussion

Our review tried to update what already reported by Putthirangsiwong et al. in 2019 [4] and Chander et al. in 2017 [5], but was limited by the exiguous number of new studies (only one) that we found. This is the major limit of the study. However, we collected the information contained in the previously published studies and organized them in order to have a more complete a unique overview of this topic. Another limit is represented by authors' choice to focus only on *Saksenaea Erythrospora*, excluding the other species of Saksenaea.

Results confirmed that most *S. erythrospora* infections occur in immunocompetent subjects. The ability of the *Mucorales* to invade the arteries is responsible for thrombosis and the gradual generation of large necrotic areas: this promotes the progression and invasion of deep tissues [8].

As Pelroth et al. recommended, for the eradication of mucormycosis (including *Saksenaea Erythrospora* infections) four factors are fundamental: rapidity of diagnosis, correction of predisposing factors (if possible), adequate surgical debridement of the infected tissue and appropriate antifungal therapy.

Early diagnosis is important because small focal lesions can often be surgically removed before they progress. Unfortunately, there are no serological or PCR-based tests for a rapid diagnosis. In many cases, unfortunately, cases of mucormycosis are diagnosed post mortem [2].

The use of molecular methods based on PCR amplification and sequencing should be used in cases of atypical unresolved skin and soft tissue infections [11].

The most of cases has been associated with traumas; some with injections (that could be considered as slight traumas): correcting or controlling predisposing conditions is essential to improve the treatment outcome.

Mucormycosis is often rapidly progressive and antifungal therapy alone is often inadequate to control the infection. In addition, the angioinvasion, thrombosis and distinctive tissue necrosis of this disease result in poor penetration of anti-infectious agents into the infection site. Therefore, even if the causative organism is susceptible to the antifungal agent in vitro, the antifungal may be ineffective in vivo. Surgical debridement of infected and necrotic tissue must be done urgently [2].

The case described in 2016 by Rodriguez et al. is certainly interesting [9]: it is the first case of mucormycosis following breast augmentation performed in a context of "medical tourism".

Although many of the institutions involved in medical tourism work very well and are organized with high quality standards, many procedures can be unconventionally performed or performed in institutions that do not meet the appropriate infection control standards. Therefore, patients should be informed of the risks associated with the medical tourism procedures, including the risk of infection; moreover, doctors must be vigilant and must know the local epidemiological characteristics of the places where medical tourism procedures have been performed [12, 13].

Conclusions

Concluding, invasive fungal infections are increasingly frequent nosocomial problems [14, 15] and episodes of infections from new and rare species of fungi have been increasingly frequent. The analysis of these phenomena is a unique opportunity to learn how to quickly identify the cases, implement adequate control measures (even

when published data are lacking) and strengthen community awareness of this new risk.
Especially during severe necrotizing *Saksenaea erythrospora* infections, early identification and timely management are essential to reduce morbidity and mortality in these patients.
A greater awareness and education about the risks deriving from carrying out surgical procedures abroad, especially in precarious hygiene situations, could be further effective strategies for the reduction of these infections [16].

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

GT had the idea of the study, collected data and wrote the article. NN helped to conceptualize the ideas and to write the article.

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Review

Should men be exempted from vaccination against human papillomavirus? Health disparities regarding HPV: the example of sexual minorities in Poland

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Keywords

HPV • LGBTQ+ • Health disparities • HPV vaccines • Underserved populations

Summary

Introduction. *Social campaigns concerning vaccinations against human papillomavirus (HPV) in Poland are mainly addressed to women. In addition to cervical cancer, anal, penile, and oropharyngeal cancers can be caused by the virus, which clearly affects men as well. HPV vaccinations are voluntary and mostly not refunded in Poland.*
Methods. *A survey was published on social media's group gathering males and contained questions concerning epidemiological data, knowledge about HPV, and opinions of HPV vaccination. A questionnaire was enriched with educational note regarding HPV-dependent cancers and available vaccines against HPV in Poland.*
Results. *Because of age limitations, 169 males (115 heterosexuals, 48 homosexuals) aged 14-39 were chosen for the study. Seventyfive percent of straight and 88% of gay men were aware of HPV, but less than 4 and 17% (respectively) were vaccinated against the virus. Main sources of knowledge about HPV were the Internet (61%), media (28%) and relatives (27%). HPV infection was linked with the development of anal and oropharyngeal cancers by 28, and 37% of heterosexual males, compared with 56.3 and 43.8% of homosexual males. The majority of respondents (88%) indicated that all genders should be vaccinated, although only 57% were aware of HPV vaccination availability in Poland.*
Conclusions. *The men are at risk of HPV-related cancers and the danger is poorly understood amongst Polish men. Despite awareness of HPV vaccines, the vaccination rate is low. Consequently, there is a serious need to broaden educational campaignes with a special attention to LGBTQ+ communities.*

Introduction

The incidence of sexually transmitted infections (STIs) in Poland is increasing, with human papillomavirus (HPV) the most common cause [1, 2]. HPV is a dsDNA virus, comprising more than 170 distinguishable types [3]. Almost every sexually active person is exposed to HPV during their lifetime and both women and men are at risk of infection. Approximately 90% of HPV infections are asymptomatic and resolve spontaneously [4]. However, in some cases infection results in palmar/plantar warts, laryngeal papillomatosis, precancerous lesions, and increased risk of developing cancer [2]. More than 99% of cervical cancer is associated with HPV infection (70% caused by HPV 16 and 18), constituting the sixth most common malignant neoplasm of reproductive organs among women and the seventh highest cause of cancer related death in Poland [3, 5]. Moreover, 70% of oropharyngeal, 63% of penile, and 91% of anal cancers are associated with HPV infection [5-7]. In some minority groups, such as gay men, the risk of HPV-dependent cancers is higher [8].
HPV can be transmitted through sexual intercourse, direct skin-to-skin contact, via contaminated surfaces, as well as during labour and the perinatal period (vertically) [2, 9]. The role of blood transfusions in the process of transmission remains uncertain [10]. Early sexual activity, multiple sexual partners or impaired immune function (*e.g.* immunosuppression) are the leading risk factors for HPV infection [4]. The Centres for Disease Control and Prevention (CDC) recommends mutually monogamous sexual relationships, barrier contraceptives, and vaccines as preventive masseurs [4, 11, 12]. The World Health Organization (WHO) states that vaccination against HPV is most effective prior to the onset of sexual activity [13]. In Poland HPV vaccinations are targeted at children aged 11-12, are voluntary and mostly not refunded [14]. Whilst the risk of developing HPV-dependant cancer applies to both men and women, social campaigns regarding vaccination against papillomavirus in Poland are aimed mainly at women.
Due to a lack of sexual education in Polish schools, knowledge about STIs is usually obtained from the Internet, media, and social campaigns [15]. An absence of educational programs considering the health needs of LGBTQ+ communities in medical school curricula affects sexual minorities and results in health disparities [16, 17]. Studies regarding knowledge about HPV and vaccination rate among males in Poland are limited and to the best of our knowledge, there are no studies referring to sexual minorities in Poland.

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Therefore, we set out to explore the knowledge of Polish men about HPV infection and HPV-related cancers, and to identify any inequalities between heterosexual and homosexual men.

Methods

Institutional Review Board (IRB) approval was obtained from the Wroclaw Medical University. A survey comprising open-ended, close-ended, and nominal, multiple-choice questions with predefined answers was prepared in Google™ Form. For nominal questions an additional, optional space was provided for respondents to implement answers not included by authors. A non-probabilistic method of self-selection sampling was used for this study. Participation invitations were posted at selected groups on social media platforms such as Facebook™, Reddit™, and Wykop™.

Target groups were found with the combinations of search terms: 'men', 'boy', 'lad', 'Poland', 'polish', 'lgbt', 'lgbtqia', and 'lgbt+'. The inclusion criteria for group consisted of polish language, number of group's male members above 25, number of posts above 20 while exclusion criteria included presence of homophobic content or hate speech and last post older than 2 weeks. Finally, survey was published on 32 groups.

The questionnaire consisted of 20 questions divided into three parts. The first one concerned epidemiological profile of respondents: age, place of residence (metropolitan, non-metropolitan, rural), educational status (primary, secondary, professional, higher), medical education (medical/non-medical), and sexual orientation (straight, gay, other or I prefer not to say). The second part tested their knowledge about human papillomavirus, HPV-related diseases with distant implications of infection, possible routes of transmission, and prevention methods. The last part referred to vaccines as a protective tool against infection and opinions about HPV vaccines in Poland. Respondents were also asked to declare their vaccination status. At the end of the survey, the information note was projected on respondent's screen with basic information about HPV related cancers and available vaccines in Poland. Moreover, a link to the educational page of the National Institute of Public Health concerning vaccinations against HPV was provided.

Chi-square (χ^2) independence test with Yates correction when necessary and Fisher exact test were used to assess the relationship between the studied variables in the nominal and ordinal scales. Shapiro-Wilk test was used to assess the normality of variable distribution. Mann-Whitney test was used to assess differences between heterosexual and homosexual males. Statistical analysis was performed using Statistica™ v.13.5 (StatSoft™).

Results

Six hundred seventy-one men were asked to participate in the study, 247 responded. Fifty-three participants were excluded due to incorrectly completed survey. In order to keep age distribution normal, age limit was established and outliers (25 respondents) were removed. Finally, 169 males (aged 14-39) were chosen for the study. The mean age of respondents is 22.7 (+/- 5 years). Most respondents were straight (68.05%), lived in large cities (35.50%), were educated to a secondary school level (53.85), were not medically trained (74.65%), and were not vaccinated against HPV (92.09%) (Tab. I).

The majority (78.7%) of participants were aware (e.g. had heard of the virus) of HPV. Sexually active males were more aware than those who were not sexually active (75.18 *vs* 24.82%, $p < 0.05$). Unsurprisingly, all participants with a medical education were aware of HPV. Participants living in cities with more than 100,000 habitants were more aware of HPV than those living in areas with less than 100,000 habitants (85.7 *vs* 69%, $p < 0.05$). However, population density is not correlated with greater general knowledge about the virus ($p > 0.05$).

Whereas, place of residence influences on whether the concept of the virus is known, the percent of correct answers does not vary significantly between respondents from cities above 100,000 habitants and respondents from towns with less than 100,000 habitants and villages. The mean result in the first group is 61.6% of correct answers and 56.2% in second group ($p > 0.05$). The educational level is not associated with better outcomes either. The mean result of men with higher education level constitutes 61.7% of correct answers in comparison with men without higher education whose mean result is 58% ($p > 0.05$).

Respondents reported that information about HPV was obtained most often from the Internet (60.94%), broadcast media (28.4%), and literature [newspapers, magazines, popular science books, and school manuals (24.26%)]. Other sources of knowledge included family/friends (23.67%), social campaigns (22.49%), physicians (21.89%), universities (8.18%), and schools (5.33%). Statistically better results (defined as more than 50% of correct answers) was observed in respondents whose reported the Internet, media, family/friends, physicians, literature, and universities as their sources of information about HPV ($p < 0.05$).

Two-thirds of participants (62.72%) identified HPV infection as being associated with cervical cancer and 36.69% associated HPV with anal cancer. Vaginal and vulvar cancers were also considered a HPV-related diseases by 49.7% of participants, as was oropharyngeal cancer (38.46%), and plantar, and genital warts (43.2%). Most participants (81.07%) identified both sex intercourse, 42.6% identified labour and the perinatal period, 31.36% indicated skin-to-skin contacts, and 26.63% indicated contaminated surfaces. Two-thirds (62.13%) pointed out infected human blood and 14.79% considered droplets as a route of transmission. A small proportion thought that HPV can spread through contaminated food (9.74%) and insect bites (8.28%).

Participants considered vaccination (81.66%), avoidance of sexual encounters (65.09%), and use of condoms (62.72%)

Tab. I. Characteristic of the study group.

Variable		Heterosexual males	Homosexual males	Total
Median age- yr.		22.5	23.1	22.7
Place of living – no. of citizens (%)	City > 500.000	39 (33.91%)	19 (39.58%)	60 (35.50%)
	City < 500.000	25 (21.74%)	11 (22.92%)	38 (22.49%)
	City < 100.000	20 (17.39%)	10 (20.83%)	32 (18.93%)
	City < 10.000	4 (3.48%)	4 (8.33%)	8 (4.73%)
	Village	27 (23.48%)	4 (8.33%)	31 (18.34%)
Education level - no. (%)	Primary	9 (7.83)	8 (16.67%)	19 (11.24%)
	Secondary	68 (59.13%)	21 (43.75%)	91 (53.85%)
	Higher	35 (30.43%)	16 (33.33%)	53 (31.36%)
	Professional	3 (2.61%)	3 (6.25%)	6 (3.55%)
Medical education – no. (%)		33(28.70%)	9 (18.75%)	43 (25.44%)
Vaccinated individual against HPV – no. (%)		4 (3.48%)	8 (16.67%)	12 (7.10%)

Tab. II. HPV-related diseases in opinion of respondents.

Variable		Heterosexual males	Homosexual males	P-value
Diseases - no. of respondents (%)	Cervical cancer	70 (60.87%)	32 (66.67%)	0.49
	Anal cancer	32 (27.83%)	27 (56.25%)	< 0.001
	Testicular cancer	28 (24.35%)	16 (33.33%)	0.93
	Vaginal and vulvar cancers	55 (47.83%)	26 (54.17%)	0.46
	Breast cancer	8 (6.96%)	5 (10.42%)	0.37
	Colon cancer	12 (10.43%)	10 (20.83%)	0.77
	Oropharyngeal cancer	42 (36.52%)	21 (43.75%)	0.39
	Pancreatic cancer	5 (4.35%)	4 (8.33%)	0.45
	Lung cancer	4 (3.48%)	2 (4.17%)	0.97
	Plantar and palmar warts	50 (43.48%)	22 (45.83%)	0.78

as protective measure against HPV infection. Almost half (46.75%) indicated risk of HPV infection can be minimized by mutually monogamous relationships, while 44.37% indicated sexual abstinence. A healthy lifestyle (17.75%), the use of lubricant, and spermicides (42.6%), avoidance of crowded places (11.83%), prophylactic use of antibiotics/ antiretroviral therapy (6.51%), elimination of contaminated food/water (5.36%), and use of repellents/insecticides (3.55%) were all proposed as means through which risk of HPV infection could be minimised.

The vast majority of respondents (88.17%) know that both sexes should be vaccinated and 84.02% believe that vaccination should be compulsory in Poland. Conversely, 5.33% opposed mandatory immunization. More than half were aware of vaccine availability in Poland (56.80%), although 67.46% do not know whether vaccination is refunded. Most participants (73.37%) correctly identified that vaccination should occur before the commencement of sexual activity. Less than one-in-ten (7.1%) of participants were vaccinated against HPV. There are no statistically significant differences in vaccination rate between groups declaring medical education and non-medical education (9.30% versus 6.35%). Similarly, no links were demonstrated between residence and education level and uptake of vaccination among participants.

No significant difference existed with regards to awareness of HPV between straight and gay participants (75.65 *vs* 87.5%). Homosexual participants indicated HPV infections increased the risk of anal cancer more frequently than heterosexual participants (43.75 *vs* 27.83%, $p < 0.05$). (Tab. II). Gay people were more frequently vaccinated against HPV than straight ones (16.67 *vs* 3.48%, $p < 0.05$).

Discussion

There are currently three vaccines available against HPV – bivalent, quadrivalent and nonavalent. Countries with national programs of vaccination (at least 10 years long) have noted a 90% reduction in HPV 6, 11, 16, 18 infections, 90% depletion in genital warts and 85% decrease in high grade squamous intraepithelial lesion (HSIL) of the uterine cervix [18]. A combined analysis of vaccination with bivalent vaccine unveiled that the vaccine was effective at preventing oral, anal, and cervical infections in the cohort of HPV naive women in 83.5% [19]. Data of vaccination effectiveness in occurrence of anal, penile, and oropharyngeal cancers is limited due to their low prevalence [20]. However, evidence is emerging that vaccination for males is warranted. In a study evaluating efficiency of quadrivalent HPV vaccine in men and boys, there was an overall 85.6% reduction in persistent infection of HPV 6, 11, 16, and 18, constituting preventive measure against anogenital cancer, intraepithelial neoplasia, recurrent respiratory papillomatosis and cancer of oropharynx [21].

Most programs target girls exclusively, with only a handful of countries (e.g. Australia, Austria, Canada) vaccinating both sexes [22]. A systematic review and meta-analysis of predictions from transmission-dynamic models funded by Canadian Institutes of Health Research suggest that elimination of HPV 6, 11, 16, and 18 is possible when 80% coverage in girls and boys is reached and a high vaccine efficacy is maintained over time [22]. In 2007, Australia introduced a national HPV vaccination program, which was broadened in 2013 by vaccination of both sexes. In 2017 Australia achieved vaccination levels of 80.2% in girls and 75.9% in boys at the age of 15. It is estimated that the age-standardised annual incidence of cervical cancer will decrease to less than 4 new cases per 100,000 women by 2028 [23].

There are no specific analyses concerning the coverage vaccination level against HPV in Poland. According to estimates of Major Statistical Department, the vaccination level in Poland fluctuates around 7.5-10% [24]. However, it is estimated that vaccination for boys is much lower. In Poland, the vaccine is not mandatory, but recommended by the Ministry of Health [14]. The total cost of vaccination (regardless of type) for one child in Poland is 246 USD [25]. In 2018 the average expenditure per capita in Polish household was 286,65 USD [26]. Consequently, the cost of vaccination in Poland for one person is almost the equivalent of one month's maintenance. Currently in Poland, numerous reimbursement programs for vaccination are being implemented by local governments and are located in the southern/western parts of the country. Only 12 municipalities organize vaccinations for girls and boys [27]. This situation varies from year to year, depending on how the funds are allocated. This is likely to account for the variability in responses in regarding vaccinations reimbursement among the participants.

Current WHO recommendations target primary HPV vaccination to the population of girls aged 9-14, prior to becoming sexually active, with at least 2-dose schedule. WHO suggests that achieving > 80% vaccination coverage in girls also reduces the risk of HPV infection for boys due to herd protection. Vaccination regardless of gender and age should be considered with other elements, such as competing health priorities, disease burden, programmatic implications, cost-effectiveness, and affordability [28]. The Advisory Committee on Immunization Practices (ACIP) endorses vaccination of all boys and girls under age of 11 or 12 [12]. Catch-up vaccines are recommended for males through age 21 and 26 for females. Furthermore, the CDC advocates vaccination for homosexual men and for both men and women with compromised immune systems, by the age of 26 if they were not fully vaccinated previously [12]. Thus, the need for vaccination among boys and adult men, especially those from higher risk groups cannot be omitted [29].

Limitations

As the self-selection sampling option was chosen for, there is no random sample. Consequently, the study group may not be representative of the entire population. Taking under consideration the low number of participants (169 males), the study group should be extended in further research. Any identification verification tool was used in the study, thus one person can submit multiple responses. What is more, the fact that gay men could identify themselves as straight in the survey cannot be forgotten.

Conclusions

The men are at risk of HPV-related cancers and the danger is poorly understood amongst Polish men. Whilst the WHO suggests that vaccination rates of 80% of girls will protect men through heard immunity, gay men remain at risk. As such, HPV vaccination programs need to be extended to include boys and made more affordable to increase uptake for both sexes.

Our study has demonstrated that knowledge about HPV is no correlated with place of residence and level of education. Educational campaigns have demonstrated minimal effectiveness, suggesting that funds should be transferred to improving their influence or expanding training programs within schools and universities. Further, surcharging of HPV vaccines should be introduced. The introduction of compulsory, refunded vaccines is likely the most effective means through which to increase the percentage of vaccinated people, thus decreasing the number of HPV-related cancers in Poland.

Few respondents indicated doctors as a potential source of information about HPV. This situation requires greater engagement of physicians in programs referring to education and prophylaxis. We urge medical schools to broaden the knowledge of Polish medical students and healthcare professionals about health needs of LGBTQ+ communities, preventing from health disparities in the future.

Availability of data and material

The data reported in this manuscript have not been previously published and/or were not collected as part of a larger data collection (at one or more points in time). Findings from the data collection have not been reported in separate manuscripts. All data and materials support published claims and comply with field standards.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript. Sentence should be ended with one dot. Material preparation was performed by Konrad Reszka, data collection and analysis were performed by Agata Remiorz, Agata Walas, Łukasz Moskal and Konrad Reszka. The first draft of the manuscript was written by Konrad Reszka, Łukasz Moskal, Agata Remiorz and Agata Walas and all authors commented on previous versions of the manuscript. Drs Urszula Staszek-Szewczyk and Krzysztof Szewczyk critically revised the manuscript and supervised writting process.

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Research paper

Water, Sanitation, and Hygiene (WaSH) practices and morbidity status in a rural community: findings from a cross-sectional study in Odisha, India

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Keywords

WaSH practice • Rural area • Acute illness • Chronic illness • Infection

Summary

Introduction. *Global evidence indicates an association between poor WaSH practice and inferior health outcomes. In rural areas, this practice is predominantly compromised with limited access to safe drinking water, knowledge gaps, and unhealthy socio-behavioural practices. Suboptimal WaSH practice leads to increased vulnerability of various infections, thereby posing a challenge to the primary health care system.*
Methods. *A community based cross-sectional study was conducted among 879 participants of two villages in Tigiria block, Cuttack district, Odisha, India. Information pertaining to socio-demography, WaSH practices and self-reported morbidities were captured and analysed. Bi-variate analysis was done to assess the association between WaSH practices and any acute illnesses. Differences were considered statistically significant if p-value was less than 0.05.*
Results. *Tube well was the main source of drinking water (49.3%) followed by dug well (46.6%). Only 7.1% of participants reported to purify drinking water and around 40% were still practicing open defecation. The prevalence of acute and chronic illnesses was 9.2% and 19.1% respectively. Major acute illnesses were respiratory diseases, diarrhoeal disorders, and musculoskeletal problems, while major chronic illnesses were gastrointestinal problems, musculoskeletal problems, and hypertension. After adjusting for age, gender, and education, a significant odds ratio of 3.79 [CI = (1.23-11.70)] was observed between drinking water source (surface water Vs tube well water) for acute illnesses.*
Conclusions. *Poor WaSH practices among rural people make them vulnerable to acute and chronic morbidities. Health awareness and socio behavioural changes pertaining to WaSH practices need utmost priority to ensure better health for rural people of Odisha.*

Introduction

Sustainable Development Goal 6 (SDG-6) emphasizes on access to safe water and improving sanitation and hygiene to ensure better health and wellbeing. Global evidence indicates an association between improper WaSH practices and infections like diarrhoea and pneumonia, trachoma, infestations with soil transmitted helminths, respiratory tract infection (RTI), and pulmonary tuberculosis (PTB), causing poor health outcomes [1-3]. While it is critical to have good WaSH practices for better health, there are existing gaps in relation to awareness, behavioural practices, accessibility, and availability to safe water and essential hygienic commodities. Study in India shows that 80% of mothers practice hand washing before preparing and serving food and 50% of the school children are unaware of the timing of hand-washing practice [4]. Another study from India has found that many people from rural communities use ash/soil to wash their hand(s) after faecal contact [5]. Compared to urban settings, WaSH coverage in rural areas is significantly poor [6]. A study among adolescent girls from eastern India has shown that 82% of the adolescent girls practicing open defecation [7]. It is imperative to have health education interventions to bring positive behavioural change among community people for good WaSH practices [8]. Access to safe drinking water is still a major challenge for rural people. Poor knowledge of proper WaSH practices and high risk behaviour with regard to WaSH, make them more vulnerable to acquire infectious diseases. According to a qualitative study from India, rural people believe that their communities as less healthy, less physically active and have poorer access to nutritious food [9]. Research study has also shown that in rural communities, fever, respiratory tract diseases, gastrointestinal diseases are the major acute illnesses and heart diseases, diabetes mellitus, and respiratory diseases are the common chronic diseases [10]. India, witnessing an epidemiological transition with the dual burden of disease (both communicable and non-communicable), its rural community is becoming more vulnerable because of the change in living conditions and socio-behavioural practices [11-13]. Unsafe and unhygienic practices among rural people further add to their likelihood of various diseases, thereby posing a challenge to the health system. With this backdrop, it is critical to understand the WaSH practices and prevalent

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disease morbidities among rural people for having appropriate context-specific preventive strategies.

Methods

Study settings and design

A cross-sectional community based study was carried out in two villages of Tigiria block, Cuttack district, Odisha, India over a period of six months. Odisha is one of the states in Eastern India with a vast coast separating the Bay of Bengal. Tigiria is one of the rural dominant blocks of the Cuttack district with 89.2% of its people residing in rural villages [14]. A model rural health research unit (MRHRU) has been established in this block to carry out health research. Out of 47 total villages of the study block, two villages (Baliput and Bhejia) were randomly selected for our study.

Sampling method

Assuming a prevalence of improved sanitation facilities in 23% of rural households in Odisha [15], and considering 15% relative precision, 95% confidence level and with a design effect of 1.5, a sample size of 857 was estimated using Open-Epi sample size calculator. A total of 893 eligible participants were approached and 879 study participants (aged more than 10 years) were enrolled for the study, with a drop out of 14 (1.6%) participants.

Data collection tool and method

A structured data collection tool was developed focusing on household level socio-demographic and WaSH practices and individual level disease profile (both acute and chronic). The tool was pilot tested in another village before data collection and all necessary corrections were made prior to data collection from study villages. The data were collected by qualified and trained field investigators of MRHRU. The data were entered in epi-info software ensuring double data entry and more than 10% of collected data were range checked by the supervisor to avoid any data error.

Data analysis

Data were statistically described in terms of mean ± standard deviation (SD) or Median (IQR) for continuous data and frequency (percentage) for categorical data. The bi-variate analysis was done to assess the association between WaSH practices and any acute illnesses such as diarrhoeal disorder, skin problems, and acute respiratory tract infections. Statistical analysis was performed using IBM SPSS software version 25.0 and p-value less than 0.05 was considered as statistically significant.

Ethical consideration

Ethical approval from the institutional review board of ICMR-Regional Medical Research Centre, Bhubaneswar was obtained for this study. The study participants were informed about the objectives of this study along with the risks and benefits of their participation. Participation was completely voluntary and written informed consent and assents were obtained from all the study participants. In case of minors (10-18 years), in addition to their assent, consent was also obtained from their parents.

Results

Among total 879 study participants, 465 (53%) were male and 414 (47%) were female and their mean age was 36.7 ± 17.9 years. Majority of the participants (54.6%) belonged to other backward caste or socially and economically backward caste (OBC/SEBC), followed by the scheduled tribe (19.8%) and general category (19.7%). While about one fourth (25.6%) of study participants had no formal education, 53.6% had studied secondary or more. Among the participants, 81 (9.2%) had suffered from some acute illness during the past one month, and 168 (19.1%) had some chronic illness. The descriptive statistics of socio-demographic characteristics are detailed in Table I.

WaSH practices

Among the participants, 49.3% used to drink tube well water followed by dug well water (46.6%). Only 7.1% of participants mentioned that they adopt some method to purify their drinking water. Among the participants, 39.4% were still practicing open defecation. The descriptive details about the WaSH practices are presented in Table I.

The odds ratio (non-adjusted and adjusted) of different WaSH practices for acute infection are presented in the forest plot below (Figs. 1A and 1B respectively). Washing hands before taking food by using soap/ detergent had an odds ratio of 1.70 [95% CI (1.003-2.89)] compared to hand washing using plain water and the same was 1.24 [95% CI (0.68-2.27)] upon adjustment. After adjusting, a significant odds ratio of 3.79 [95% CI (1.23-11.70)] was observed with drinking surface water compared to tube well water.

Morbidity status (Acute and Chronic illnesses)

Acute illnesses

Among the 84 participants having some acute illness in the last one month, the majority had suffered from acute respiratory illness followed by diarrhoea. The prevalence of different acute illness is presented in Figure 2. The "others" category included diseases like anemia, malaria, and Jaundice that were less prevalent.

Chronic illnesses

Among 168 participants suffering from chronic illnesses, majority had gastrointestinal (GI) related problems followed by musculoskeletal problems and hypertension. The prevalence of the ten most common

Tab. I. Frequency distribution of socio-demographic characteristics and WaSH practices (n = 879).

Characteristics	Total (n = 879)	Acute Illness n (%)	Chronic illness n (%)
Age			
10-20	208 (23.7)	22 (10.6)	14 (6.7)
21-30	174 (19.8)	11 (6.3)	7 (4.0)
31-40	157 (17.9)	16 (10.2)	25 (15.9)
41-50	134 (15.2)	11 (8.2)	35 (26.1)
51-60	114 (12.9)	14 (12.3)	50 (43.8)
Above 60	92 (10.5)	7 (7.6)	37 (40.2)
Gender			
Male	465 (52.9)	41 (8.8)	89 (19.1)
Female	414 (47.1)	40 (9.7)	79 (19.1)
Caste			
General	173 (19.7)	12 (6.9)	30 (17.3)
OBC/SEBC	480 (54.6)	52 (10.8)	104 (21.7)
Scheduled caste	52 (5.9)	04 (7.7)	06 (11.5)
Scheduled tribe	174 (19.8)	13 (7.5)	28 (16.1)
Education			
No education	225 (25.6)	18 (8.0)	66 (29.3)
Primary	183 (20.8)	16 (8.7)	36 (19.7)
Secondary	355 (40.4)	33 (9.3)	55 (15.5)
Higher	116 (13.2)	14 (12.1)	11 (9.5)
Marital status			
Never married	269 (30.6)	28 (10.4)	22 (8.2)
Currently married	585 (66.6)	53 (9.1)	138 (23.6)
Widow/widower	25 (2.8)	0	08 (32.0)
Usual source of drinking water			
Tap water	18 (2.0)	0	02 (11.1)
Tube well	433 (49.3)	36 (8.3)	80 (18.5)
Dug well	410 (46.6)	42 (10.2)	84 (20.5)
Surface water	18 (2.0)	03 (16.7)	02 (11.1)
Any treatment method to purify drinking water			
No	817 (92.9)	76 (9.3)	154 (18.8)
Yes	62 (7.1)	05 (8.1)	14 (22.6)
Where do you go for defecation			
Toilet (own)	444 (50.5)	51 (11.5)	86 (19.4)
Open space/field	435 (49.5)	30 (6.9)	82 (18.8)
Hand washing before taking food			
With water only	722 (82.1)	60 (8.3)	139 (19.2)
With soap/detergent/hand wash	157 (17.9)	21 (13.4)	29 (18.5)
Hand washing after defecation			
With water only	86 (9.8)	08 (9.3)	15 (17.4)
With soap/detergent/hand wash	531 (60.4)	55 (10.4)	110 (20.7)
Ash/Soil	262 (29.8)	18 (6.9)	43 (16.4)

chronic illnesses is presented in Figure 3. The "other" category included less prevalent conditions such as benign tumours, deafness, thyroid, and menstrual problems. Among the participants having chronic illnesses, while 131 (78.0%) had a single health illness, 25 (14.9%) had two and 12 (7.1%) had three or more health illnesses.

The bi-variate analysis between different acute illnesses and WaSH practices showed that the odds of drinking surface and dug well water was high for ARI, diarrhoeal disorder, and skin problem.

For ARI, the odds of surface water was significantly high compared to tube well water for drinking [OR = 4.4, 95% CI (1.16-16.35), p = 0.03]. The use of toilets had an OR of 2.25 [95% CI (1.18-4.30), p = 0.01] compared to open defecation. People washing their hands before taking food by using plain water had an OR = 0.27 [CI (0.15-0.50), p < 0.001] when compared to washing hands by using soap/detergent.

For diarrhoeal illness, drinking dug well water had an OR = 3.48 [95% CI (1.26-9.58), p = 0.016] compared to drinking tube well water. Similarly, using ash/soil for hand washing after defecation had an OR = 0.098 [95% CI (0.01-0.73), p = 0.02] compared to using soap/detergent.

For skin problems, hand washing after defecation using plain water had an OR = 12.62 [95% CI (1.13-140.71), p = 0.04] when compared with using soap/detergent. The detailed bi-variate analysis of different WaSH practices and having acute illnesses are depicted in Table II.

Fig. 1. A) association of WaSH practices with any acute illness among study participants (unadjusted OR); **B)** association of WaSH practices with any acute illness among study participants (adjusted OR).

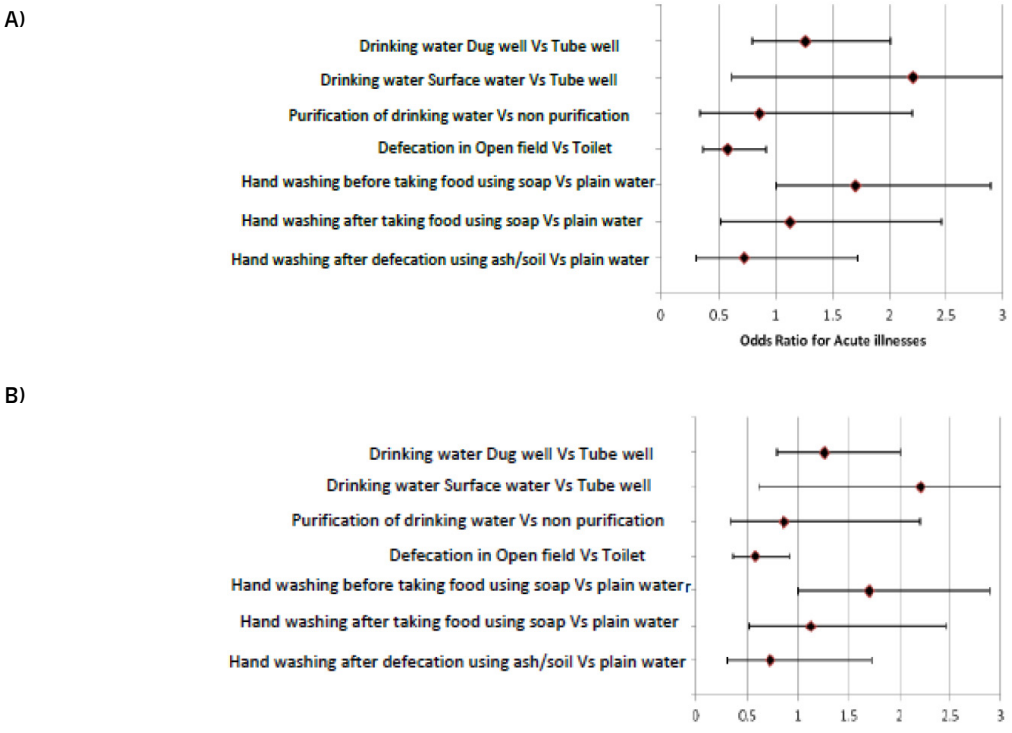


Fig. 2. Prevalence of different Acute Illnesses (N=879).

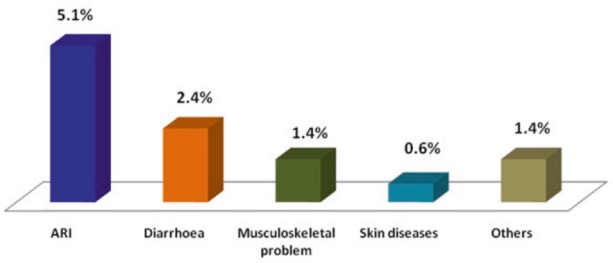
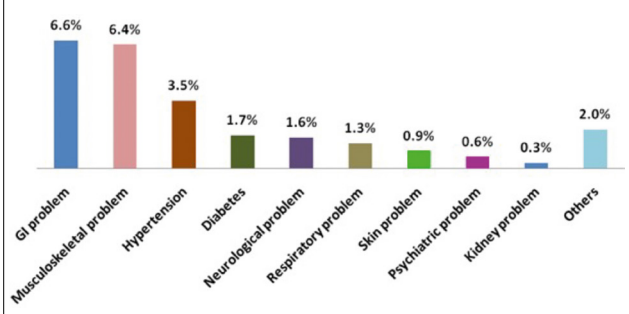


Fig. 3. Prevalence of Top 10 Chronic Illnesses (N=879).



Discussion

Clean water, toilet facilities, healthy food, and good hygiene practices are important to ensure better health. We observed the prevalence of acute infection was 8.8% among male and 9.7% among female participants respectively. According to a study among rural Indians, women face greater challenges in accessing water, sanitation, and hygiene (WaSH) resources leading to unsafe practices that increase the risk of infections [16]. Tube well was the prime source of drinking water (49.3%) followed by dug well (46.6%). A study from rural Bangladesh [17] had found 96% of people using tube well water for drinking, while another study from rural South India had shown 37% of people using tube well water for drinking [18]. National Family Health Survey-4 shows 87.5% of households in Odisha have improved access to drinking water sources in rural areas [15]. We observed a greater possibility of suffering from acute illnesses among people drinking surface and dug well water compared to those drinking tube well and tap water. The reason could be due to the greater possibility of contamination of surface and dug well water because of the high risk practices such as bathing and washing nearby the water source. In contrast to a study from India that has shown that 15.3% of people don't purify their drinking water [19], in our study only 6.6% of participants told that they purify the drinking water in their households. This implies low awareness among rural people on the importance of safe drinking water.

Tab. II. Bi-variate analysis of different acute illnesses and WaSH practices.

		ARI		Diarrhoeal disorder		Skin problem	
	N = 879	Yes (= 45)	OR	Yes (= 21)	OR	Yes (= 5)	OR
		n (%)		n (%)		n (%)	
Source of drinking water							
Tube well	433	19 (4.4)	1	05 (1.1)	1	02 (0.5)	1
Dug well	410	23 (5.6)	1.3	16 (3.9)	3.5*	03 (0.7)	1.6
Surface water	18	3 (16.7)	4.4*	0	2.1	0	4.7
Purify water for drinking							
Yes	62	03 (4.8)	1	01 (1.6)	1	01 (1.6)	1
No	817	42 (5.1)	1.1	20 (2.4)	1.5	04 (0.5)	0.3
Use toilet for defecation							
Yes	444	31 (7.0)	1	12 (2.7)	1	1 (0.2)	1
No	435	14 (3.2)	0.4*	09 (2.1)	0.8	04 (0.9)	4.1
Hand wash before taking food							
Soap/detergent/liquid hand wash	157	19 (12.1)	1	01 (0.6)	1	1 (0.6)	1
Only plain water	722	26 (3.6)	0.3*	20 (2.8)	4.4	4 (0.6)	0.9
Hand wash after defecation							
Soap/detergent/liquid hand wash	531	27 (5.1)	1	20 (3.8)	1	1 (0.2)	1
Ash/soil	262	13 (5.0)	0.9	01 (0.4)	0.1*	2 (0.8)	4.1
Only plain water only	86	05 (5.8)	1.1	0	0.1	2 (2.3)	12.6*

* Statistically significant with p-value < 0.05.

The main barriers to practice good hand hygiene have been resource limitation, lack of technical information dissemination, and not given priority [20]. The initiation of the Swacch Bharat Mission in India, has shown a great effect on improving rural sanitation and about 85.7% of people have found this program to be useful for their community [21]. According to a study on the Swacch Bharat Abhiyan, the number of acute diarrhoeal disease outbreaks have drastically come down during 2017 and 2018 after its introduction [22]. However, our study shows that around half of the participants still practice open field defecation, which is very high compared to another study that has found one-third of their rural study population practicing open defecation [19]. National Family Health Survey 4 (NFHS-4) conducted during 2016 in Odisha has found that less than one-fourth of rural households had improved sanitation facilities in the state [15]. This warrants for more awareness activities in rural communities under the Swacch Bharat Mission to bring positive change in the behaviour and practice of people. According to a study in the tribal community of Andhra Pradesh, India, open defecation was reported among 84.8% of the total population [23]. A study in rural areas of Odisha had found that most of the Government subsidized latrines were still unfinished and suggested for provisioning nearby water sources to toilets to improve its use [8].

A cluster randomized intervention trial has shown that through hand washing using soap and water, there was a 6.7% reduction of infection episodes [24]. In our study, only 17.9% of people wash their hands using soap/detergent while 82.1% of people wash their hands using plain water only, before taking food. Similarly after defecation, while 60.4% wash their hands using soap/detergent, 9.8% do it using plain water only and 29.8% wash their hands by using ash/soil. Another study had similarly found that 34% of people do not use soap/detergent to wash hands after defecation [19]. A study done from a semi-urban setting from India had found that about 43.5% of study population living with poor sanitation facilities, poor water handling practices, and having higher diarrheal incidences [25]. Other studies have also found that households not using soap/detergent to wash hands are more likely to suffer from diarrhoea [26] and pneumonia [1].

We found that practicing drinking water purification prevents 15% chances of having acute illnesses. A case study from Zambia had demonstrated that household water treatment (HWT) can improve drinking water quality and prevent diseases [27]. A study in the tribal community of Andhra Pradesh, India has found that 69% of households do nothing at home to make the water safe for drinking [23].

We observed that washing hands after defecation with ash/soil lowers the chance of suffering from acute diseases by 28% compared to using plain water only. A study from Bangladesh had shown that their study people mainly use ash and soil for hand washing after faecal contact [5]. The present study has shown that washing hands before taking food by using soap/detergent increases the chance of acute illness by about 70% compared to hand washing using plain water. This is in contrast to the conventional understanding and a trial on the effectiveness of different hand wash methods had demonstrated that hand washing using soap is better than plain water in removing the pathogens [28]. The reverse finding in our study could be due to the use of the same piece of soap by multiple members and multiple times, exposing it to get contaminated and become a source of infection. On further analysis, we found that hand washing before taking food by using soap/detergent had an odds of 3.7 times compared to plain water for ARI [OR = 3.68, CI (1.98-6.84), $p < 0.001$]. A previous study also indicates a significant increase in bacterial load on

the right hands after toilet use even after using soap for hand washing and the researchers had concluded that the paradox could be due to faulty technique of hand washing or washing for a short duration or touching contaminated surfaces after hand washing [29]. Further study on this aspect will improve our understanding on this finding. For skin related problems, the odds ratio of hand washing with plain water was 12.6 compared to hand washing with soap/detergent after defecation [OR = 12.62, CI (1.13-140.7), $p < 0.05$].

Taking the past one months' history, the prevalence of acute illnesses was found to be 9.6%. The major acute illnesses were ARI, diarrhoea, and musculoskeletal problems. The overall prevalence of chronic illnesses was found to be 19.1%. The most common chronic illnesses were GI disorders, musculoskeletal problems, and hypertension. An earlier study had shown that hypertension, cataract, and arthritis were the most prevalent co-morbid conditions [30]. Similar to our study findings, a study from middle-income countries had also observed that the burden of non-communicable disease (NCDs) has increased rapidly and is associated with higher levels of healthcare utilisation and greater financial burden for individuals [31].

Limitation of the study

The present study is from a rural setting of one block only and children aged up to 10 years were excluded. Information regarding hand washing was subjectively assessed and no information was collected about its technique and duration. The results need to be interpreted accordingly.

Conclusions

WaSH practices among the rural population are a matter of concern. Poor WaSH practices make them vulnerable to various acute and chronic morbidities. A systemic approach towards improving health awareness, socio behavioral change in WaSH practices, and adherence to appropriate techniques of hand washing including sanitization needs to be taken up on priority, for these populations through grounded interventions.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

SKP: Designing the study, obtaining ethical approval, Data collection tools, Data analysis, Manuscript writing, review and revision of the manuscript.
SK: Data analysis, Manuscript writing, review and revision, Advocacy.
MS: Data collection tool development, Data collection, Manuscript writing.
SP: Data collection, Data analysis, Manuscript writing.
DS: Data collection, Advocacy, Manuscript writing.
SP: Study planning, Ethical approval, Tool finalization, Manuscript review, Advocacy.

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Research paper

Maternal risk factors for low birth weight infants: A nested case-control study of rural areas in Kurdistan (western of Iran)

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Keywords

Low birth weight • Nested case control • Risk factors • Iran

Summary

Infant mortality is among the most important indicators of health and development in global communities. One of the causes of neonatal mortality is low birth weight. This study aims at evaluating the risk factors for LBW in infants. This study was carried out using a nested case-control study in rural areas of Kurdistan province in Western Iran in 2015. The selection of case and control groups was based on the nesting using the risk set sampling approach. In total, 182 and 364 subjects were selected for the case group and the control group respectively. Data analysis was performed using the Stata-12 software with the point and spatial estimation of OR using the conditional logistic regression method. The multivariate logistic regression analysis performed shows that the maternal gestational age, the mother's health history during pregnancy, any medication abuses by the mother, any mental stress during pregnancy, are LBW risk factors ($P < 0.05$). Prevention of LBW is possible by identifying effective factors and performing appropriate interventions in infants with low birth weight.

Introduction

Birth weight is one of the most important factors in the development, survival, and future of the baby; it is one of the main determinants of future physical and brain development of the child and also a valid sign of intrauterine growth [1, 2]. Low birth weight (LBW) is defined by the World Health Organization (WHO) as any weight less than 2,500 g regardless of the age of the baby [3]. Every year around 20 million newborns (17% of live births) weigh less than 2,500 g and more than 90% of them are born in developing countries [2, 4, 5].
According to WHO in 2015, the prevalence of LBW around the globe was 15%. It was 13% in developing countries, 9% in the US, 6% in East Asia and the Pacific, 13% in Sub-Saharan Africa, and 28% in South Asia [6].
LBW is closely related to infant mortality in the first days of life and even after infancy. It has been seen that the survival rate and survival chance of children who weigh less than 2,500 g after birth are much lower than other children [4, 7]. Generally, in these newborns the risk of neonatal mortality is 25-30 times more likely than those weighing more than 2,500 g, the lower the birth weight at birth, the greater the risk of neonatal mortality [5, 8]. It has been shown that LBW children who are alive with therapeutic interventions are two to three times more likely to suffer from short-term and long-term disabilities than other children [5, 9].

Many maternal and fetal factors are significantly associated with LBW [10-12]. Based on the results obtained from various studies, these factors include the mother's age, occupation, weight, number of pregnancies, history of smoking, length of pregnancy, previous births, reproductive multiplication, inappropriate nutritional status, socioeconomic inequalities, lack of attention to proper diet and consumption of supplements during pregnancy, birth season, number of pregnancy cares and anemia, and birth defects, along with pre-pregnancy conditions and the socioeconomic status of the family related to LBW [5, 11]. LBW birth outcomes are high, especially in developing countries and the third world. Those who survive with LBW have cognitive and neurologic disorders as well as increased risk of hypertension, pulmonary disease, blood cholesterol, kidney damage, acute watery diarrhea, and immune system disorders [4]. Moreover, LBW is one of the determinants of neurological disorders and evolution, including backwardness and mental disability in learning, and may cause disorders relating to chronic diseases in adulthood [13].
Since LBW causes the risk of mortality, disability, and many diseases in childhood and even in adulthood while causing immense economic costs to the healthcare system and communities, it is very important to identify the factors affecting underweight during birth and hospital release [14, 15]. Even though Iran has been

successful in reducing infant mortality over the past two decades, LBW is still recognized as one of the main causes of death and disability in this infant group. The purpose of this Study, which was conducted with a nested case-control study as a cost-effective [16] alternative to a cohort study, is to study the risk factors of LBW at present in a rural area of Iran.

Method

The nested case-control study was carried out in rural areas of Kurdistan province, Western Iran, for six months – from the beginning of December 2014 to the end of June 2015. In this study, the case and control groups were selected based on the design of the nest – i.e. with the risk set sampling approach.

Eligibility criteria

The infants who were born in the study area with the birth weight 2,500 g or more were in the control group and infants with the birth weight less than 2,500 g were in the study group. Therefore, the criterion was birth weight and there were no other restrictions for being in the case and control groups.

In this study, in order to reach appropriate sample size in the study time frame, two infants with the birth weight 2,500 and more were included in the study as controls for each case of infants with the birth weight less than 2,500.

Data collection tools comprised a researcher-made checklist, which included independent variables and risk factors including maternal age, the mother's education, maternal BMI, the number of pregnancies and previous births, newborn's sex, birth season, the history of smoking for the mother, whether the mother is a second-hand smoker, the use of pregnancy supplement pills, the history of specific diseases during pregnancy, the history of drug use during pregnancy, parental separation history, the mother's mental stress during pregnancy, baby birth rank, the number of pregnancy care, the kinship ratio of parents, the mother's blood group, and possibility of having anemia, whether it is a natural pregnancy or IVF, and Rh maternal and neonatal conditions .

The data analysis for this study was performed using the Stata-12 software with a point estimate and OR (and CI) spacing that deals with raw and adapted conditional logistic regression and an error rate of less than 5%.

Logistic regression analysis on nesting case data means that the design is not identical in data analysis. If the exposure is constant over time, the odds ratio estimates the consistency ratio.

The conditional logistic regression method makes it possible to compare the cases and controls in each pair in which the case and control groups are defined as the outcome [17, 18].

Findings

Mothers in the case and control groups had elementary education (49.8%), and about 90% of them were housewives. Most of the mothers did not have a kinship with their spouses, and more than 95% of them had no history of morbidity in their previous labors. The findings show that age, education, occupation, parents' separation history, and maternal birth history has no significant relationship with their neonates in both case and control groups ($P > 0.05$) (Tab. I).

Tab. I. Distribution of demographic variables and maternal history in case and control groups.

Variable	Case N = 182 (%)	Control N = 364 (%)	Chi²	P-value
Mother's age				
20-35 years	134 (74.1)	273 (74.16)		
< 19	15 (7.48)	29 (8.11)	0.12	**0.93**
> 35	33 (18.03)	62 (17.3)		
Maternal education				
College education	3 (1.64)	12 (3.31)		
Diploma	34 (18.58)	53 (14.6)		
Guidance	30 (15.92)	70 (19.16)	3.18	**0.52**
Elementary	88 (49.87)	180 (49.77)		
Illiterate	27 (14.75)	49 (13.50)		
Mother's occupation				
Housewife	164 (90.01)	322 (88.39)		
Employee	1 (0.55)	10 (2.75)		
Laborer	16 (8.74)	28 (7.71)	3.52	**0.31**
Other	1 (0.55)	4 (1.10)		
Parental relationship ratio				
No	164 (89.3)	334 (92.19)		
Yes	18 (10.7)	30 (7.81)	2.77	**0.56**
History of parents' separation (separation of living place)				
No	170 (93.44)	346 (95.04)	2.74	**0.43**
Yes	12 (6.56)	18 (4.96)		
History of stillbirth				
Yes	174 (95.63)	353 (96.97)	3.1	**0.54**
No	8 (4.37)	11 (3.03)		

Tab. II. Results of single-variable conditional logistic regression of newborns born in Kurdistan province (west of Iran).

Variable	Cases N = 182 (%)	Control N = 364 (%)	Unadjusted OR (95% CI)	P-value
Mother's age years				
20-35	134 (74.1)	273 (74.16)	1	
< 19	15 (7.48)	29 (8.11)	1.05 (0.54-2.05)	0.88
> 35	33 (18.03)	62 (17.3)	1.07 (0.67-1.72)	0.75
Maternal education				
College education	3 (1.64)	12 (3.31)	1	
Diploma	34 (18.58)	53 (14.6)	2.56 (0.67-9.70)	0.16
Guidance Elementary	30 (15.92)	70 (19.16)	1.68 (0.44-6.33)	0.43
Elementary education	88 (49.87)	180 (49.77)	1.93 (0.53-6.93)	0.31
Illiterate	27 (14.75)	49 (13.50)	2.17 (0.57-8.22)	0.25
Father's education				
College education	5 (2.73)	17 (4.68)	1	
Diploma	34 (19.26)	85 (23.34)	1.45 (0.48-4.3)	0.50
Guidance Elementary	46 (25.14)	93 (25.63)	1.76 (0.59-5.24)	0.30
Elementary education	86 (46.99)	147 (40.50)	2.12 (0.72-6.20)	0.16
Illiterate	11 (6.01)	22 (6.06)	1.74 (0.49-6.10)	0.38
Mother's occupation				
Housewife	164 (90.01)	322 (88.39)	1	
Employee	1 (0.55)	10 (2.75)	0.2 (0.02-1.56)	0.12
Laborer	16 (8.74)	28 (7.71)	1.06 (0.57-1.98)	0.83
Other	1 (0.55)	4 (1.10)	0.5 (0.05-4.50)	0.53
Father's occupation				
Employee	8 (4.37)	19 (5.23)	1	
Worker	51 (27.87)	111 (30.58)	1.13 (0.43-3.93)	0.79
Self-employment	94 (51.01)	190 (52.02)	1.19 (0.48-3.95)	0.70
Unemployed	6 (3.28)	9 (2.48)	1.63 (0.48-6.39)	0.49
Other	23 (13.37)	35 (9.86)	1.64 (0.58-4.63)	0.43
Sex				
Girl	94 (51.6)	192 (52.75)	1	
Boy	88 (48.35)	172 (74.25)	1.04 (0.73-1.48)	0.79
Abortion history				
No	146 (79.78)	298 (82.09)	1	
Yes	36 (20.22)	66 (17.91)	1.12 (0.7-1.8)	0.61
Gestational weeks				
≤ 37	76 (41.76)	330 (90.91)	1	
> 37	106 (58.24)	33 (9.09)	18.2 (9.39-34.59)	0.000
Distance between pregnancy				
3 ≤ years	148 (81.32)	317 (78.09)	1	
3 >years	34 (18.68)	47 (12.91)	1.64 (0.97-2.7)	0.06
Pregnancy				
Pregnancy1	72 (39.34)	143 (39.39)	1	
Pregnancy2	54 (28.96)	115 (31.96)	0.94 (0.61-1.45)	0.79
2< Pregnancy	56 (31.96)	106 (28.65)	1.05 (0.67-1.62)	0.82
Childbirth				
1 delivery	90 (49.18)	167 (46.01)	1	
2 delivery	56 (30.05)	114 (31.68)	0.91 (0.61-1.63)	0.66
2 < delivery	36 (20.77)	83 (22.31)	0.79 (0.49-1.27)	0.34
Pregnancy with IVF				
No	178 (97.80)	362 (99.45)	1	
Yes	4 (2.20)	2 (0.55)	4 (0.73-21.83)	0.10
Multiple birth				
Singleton	136 (74.73)	359 (98.63)	1	
≤ Twain	46 (25.27)	5 (1.37)	4.45 (2.47-6.43)	0.000
Abortion history				
No	146 (79.78)	298 (82.09)	1	
Yes	36 (20.22)	66 (17.91)	1.12 (0.7-1.8)	0.61
Mother's disease history				
No	48 (26.52)	250 (68.68)	1	
Yes	133 (73.84)	114 (31.32)	6.11 (3.95-9.45)	0.000
History of stillbirth				
No	174 (95.63)	353 (96.97)	1	
Yes	8 (4.37)	11 (3.03)	1.45 (0.58-3.61)	0.42

Continues

Follows

Tab. II. Results of single-variable conditional logistic regression of newborns born in Kurdistan province (west of Iran).

Variable	Cases N = 182 (%)	Control N = 364 (%)	Unadjusted OR (95% CI)	P-value
History of bleeding				
No	154 (84.62)	355 (97.53)	1	
Yes	28 (15.38)	9 (2.47)	7.59 (3.30-17.44)	0.000
Birthday rating				
First birthday	77 (42.31)	147 (40.38)	1	
Second birthday	62 (34.07)	126 (34.62)	0.94 (0.36-1.41)	0.78
≤ third birthday	43 (23.63)	91 (25)	0.9 (0.57-1.41)	0.65
Longing				
No	114 (62.64)	255 (70.05)	1	0.07
Yes	68 (37.36)	109 (29.95)	1.43 (0.96-2.13)	
blood group				
A	58 (31.87)	123 (33.79)	1	
B	52 (28.57)	80 (21.98)	1.36 (0.86-2.15)	0.18
AB	16 (8.79)	30 (8.24)	1.12 (0.58-2.19)	0.71
O	56 (30.77)	131 (35.99)	0.9 (0.57-1.40)	0.64
Smoking				
No	173 (95.05)	361 (99.18)	1	
Yes	9 (4.95)	3 (0.82)	8.29 (1.77-38.69)	0.007
The number of cares by the physician				
3 ≤ care	43 (23.62)	75 (20.6)	1	
2 care	28 (15.38)	77 (21.15)	0.93 (0.56-1.51)	0.77
1 care	111 (60.99)	212 (58.24)	0.63 (0.35-1.13)	0.12
The number of care by midwives				
10 ≤	6 (3.30)	9 (2.20)	1	
9-5 care	57 (31.32)	129 (35.54)	0.55 (0.17-1.74)	0.31
5 > care	119 (65.38)	226 (62.29)	0.72 (0.23-2.24)	0.57
The number of care by health care				
≤ 10	5 (2.75)	6 (1.38)	1	
9-5 care	81 (44.51)	256 (70.52)	0.37 (0.1-1.31)	0.79
< 5 care	96 (52.75)	102 (28.10)	1.19 (0.32-4.33)	0.12
Exposed to second smoke				
No	108 (59.34)	293 (80.49)	1	
Yes	74 (40.66)	71 (19.51)	2.95 (1.94-4.48)	0.000
Drug abuse				
No	142 (78.02)	361 (99.18)		
Yes	40 (21.98)	3 (0.82)	39.25 (9.48-162.51)	0.000
Drug use under medical supervision				
No	112 (61.54)	325 (89.29)	1	
Yes	70 (38.46)	39 (10.71)	4.99 (3.12-7.99)	0.000
Parental kinship relations				
No	164 (89.3)	334 (92.19)	1	
Yes	18 (10.7)	30 (7.81)	1.19 (0.65-2.19)	0.56
Separation of parent's place of residence				
No	170 (93.44)	364 (95.04)	1	
Yes	12 (6.55)	18 (4.96)	1.34 (0.64-2.82)	0.43
History of physical, mental, and psychological stress in pregnancy				
No	106 (58.24)	337 (92.58)	1	
Yes	76 (41.76)	27 (7.42)	8.52 (4.95-14.67)	0.000
RH				
Rh+	174 (95.6)	335 (92.03)	1	
Rh-	8 (4.40)	29 (7.97)	0.53 (0.24-1.19)	0.12
Mother's, BMI				
> 18.4	13 (7.14)	16 (4.41)	1	
24.9-18.5	69 (37.91)	133 (36.64)	0.63 (0.28-1.41)	0.27
29.9-25	64 (35.16)	141 (38.84)	0.55 (0.25-1.22)	0.14
≤ 30	36 (19.78)	74 (20.11)	0.59 (0.25-1.39)	0.23

The results of single-variable analysis indicate that the newborn's sex and the history of abortion with the placement of the infant in the case and control groups did not have the required conditions for being in the multi-variable model (P > 0.2), while the gestational age, multiple pregnancy, maternal disease, history of

Tab. III. Results of multivariate conditional logistic regression of newborns born in Kurdistan province (west of Iran).

		Adjusted OR (95% CI)	P-value
Gestational weeks	≤ 37	1	0.0001
	> 37	6.94 (3.11-15.50)	
Distance between pregnancy	≤ 3 years	1	0.54
	> 3 years	1.40 (0.46-4.22)	
Pregnancy with IVF	No	1	0.12
	Yes	15.35 (0.45-512.7)	
Multiple birth	Singleton	1	0.0001
	≤ twain	85.81 (5.74-128.08)	
Mother's disease history	No	1	0.002
	Yes	3.66 (1.79-7.46)	
History of bleeding	No	1	0.1
	Yes	2.81 (0.80-9.75)	
Longing	No	1	0.82
	Yes	0.91 (0.39-2.08)	
Smoking	No	1	0.27
	Yes	5.32 (0.13-205.80)	
Exposed to second smoke	No	1	0.2
	Yes	1.69 (0.74-3.83)	
Drug abuse	No	1	0.006
	Yes	2.23 (17.31-134.16)	
Drug use under medical supervision	No	1	0.39
	Yes	1.48 (0.59-3.68)	
History of physical, mental, and psychological stress in pregnancy	No	1	0.0001
	Yes	6.59 (2.52-17.18)	

hemorrhage, obsession, smoking, secondhand smoking, drug abuse, drug use under the supervision of the doctor, mental stress, and placement of the baby are required to be included in a multivariate model ($P < 0.2$) (Tab. II).

In the multivariate regression analysis, the variables that had been significant in the single-variable analysis stage were included in the multivariate model. At this stage, the variables with a significant level of 0.2 and less were introduced to the model. The results of this model analysis show that there is a significant relationship between maternal gestational age, history of illness, medication abuse during pregnancy, mental stress during pregnancy, and multiple birth with LBW in the case and control groups ($P < 0.05$) (Tab. III).

Discussion

The prevalence of LBW is one of the most important health indicators and an indicator of the survival of the baby at the moment of birth. By recognizing the risk factors associated with LBW, it is possible to prevent LBW very significantly in newborns [1]. The results of this study show that there is a statistically significant relationship between LBW and maternal gestational age, mother's disease history, medication abuse during pregnancy, psychological stress during pregnancy, and multiple pregnancies in the case and control groups ($P < 0.05$).

In Iran, the birth of LBW infants is a major cause of neonatal mortality (IMR). LBW has a direct relation with the duration of pregnancy: When the number of weeks of pregnancy is less than normal, the birth weight of the baby will be less than the normal weight due to insufficient growth of the foetus [15]

According to our study, premature infants (less than 37 weeks) had lower birth weight. The results of this study are consistent with the studies of Feresu et al. [19], Badshah et al. [20], and Muchemi et al.[21].

The results of various studies show that prematurity in developed countries and Iran is a common cause of LBW [15]. It is possible to detect different causes associated with underweight newborns – such as maternal diseases, genetic problems, and midwifery problems – to prevent the birth of a LBW baby. Moreover, the prevention measures also include teaching health promotion behaviors, pregnancy care, vaccination of pregnant women, proper education of health behaviors in fertility, improving economic, cultural, and social conditions, avoiding risky behaviors like smoking; in fact, with these measures, infants could be born with ideal weight [22]. In developing countries, this is one of the most important risk factors for birth weight and thus it is necessary to adopt methods to lessen this risk factor. Prenatal diseases and repeated infections in pregnancy are among the most effective factors relating to LBW [23, 24].

The results of this study show that mothers with a history of illness are three times more likely to have babies with LBW compared those who do not have a history of illness.

Rubari et al. in their stud represented that the prevalence of underweight in infants of mothers with a history of

disease is higher than that of mothers without a history of disease [25].
Also, findings of Batist et al. study reported that mothers with a history of disease are more likely to have infants with low birth weight. These results were consistent with the results of our study [26].
However,, these results are not consistent with the research of Sharma et al. in Nepal [27] as well as the studies of Feresu et al. [19] and Badshah et al.[20] which declare that there is no significant relationship between the history of mothers and the birth of children with LBW in the case and control groups. The need to pay attention to pregnant mothers with other illnesses should be taken more into consideration.
Pregnancy bleeding can be caused by pregnancy diseases including vaginal infections, chlamydia, gonorrhea, and swelling and inflammation of the uterus. In the second and third trimesters of pregnancy, bleeding or spotting can indicate a dangerous condition, such as sudden detachment of the foetus from the uterus, that is likely to cause abortion or preterm delivery leading to premature infants [28, 29]. Which might be a reason for their LBW. The results of this study show that the history of bleeding points to the chance of having an underweight baby more than two times, which is statistically significant. These results are consistent with the results of Moradi et al. [2] and Eshraghian et al. [30] in Iran which found the relationship between bleeding during pregnancy and LBW risk in the case and control groups to be statistically significant. This risk factor in mothers should be taken into consideration in developing countries and the intervention design to reduce this risk factor.
Drugs used during pregnancy can affect the foetus. In fact, they may affect maternal and fetal health in the coming years or cause trichoderma to the foetus. The placenta allows the passage of many medications and dietary items. Pregnant women should be trained in other non-pharmacological methods to cope with stress, pain, and discomfort as well as other illnesses, and drug must be used only when it is necessary [22, 31, 32].
According to the results of the present study, arbitrary drug use increases the probability of giving birth to an underweight infant.
This relationship is in line with the results of Huang et al. [32]. Public health and maternity care programs should pay close attention to this risk factor.
Violence during pregnancy affects the birth weight of newborns. Since it can physically and mentally affect pregnant women, widespread planning is essential to reduce violence, especially physical violence, and convince the families about its subsequent consequences [19, 33]. Violence and mental stress during pregnancy can affect the birth weight of newborns. According to the results of our study, mental stress is strongly associated with LBW infants and increases the chance of having a LBW about six times this relationship is statistically significant. The results of this study are consistent with the results of Ansari et al. [29, 34].
The studies of Johnson et al. in Canada and Kedy et al. in Uganda to investigate the relationship between mental stress and adverse outcomes of pregnancy show that there is a significant relationship between LBW and mental stress during pregnancy. These results are consistent with the results of our study [35, 36]. The results of Leung et al. do not show a statistically significant relationship between violence during pregnancy and low risk of LBW [37]. Thus, violence is a risk factor that affects women in a way that needs to be addressed and included in care plans. Since most violence comes from husbands and takes place in neighborhoods where people of low socioeconomic status live, it seems important to arrange awareness classes at times and places suitable for husbands. To reduce this risk factor, interventions targeting pregnant women should be considered.
The restriction of intrauterine growth is three times more common in twin pregnancies than in single pregnancies, the limitation of intrauterine growth is asymmetric in multiform pregnancies. The relative immaturity in placenta and competition of twins on nutrients are the most likely causes of LBW [27]. The results of this study show that twin pregnancies increase the chance of LBW infants. These results are consistent with the results of Ansari et al. [34]. In other studies, it has been shown that a twin pregnancy is somewhat related to LBW for newborns [38, 39]. Multiple pregnancies in developing countries and in societies like Iran require more care during pregnancy and delivery.
This study was conducted in rural areas of one of the Iranian provinces and may have limitations in terms of generalizing its results in respect to the whole country. Therefore, it is suggested that given the presence of potential groups in countries like Iran, researchers would have to place the nesting control case nationally on their own agendas.

Conclusions

Birth weight in infants depends on several causes, not a single cause. Drug Abuse, the interval between pregnancies, and the history of bleeding are among the most preventable factors associated with LBW. In addition, other risk factors during pregnancy should be identified and nullified to reduce the number of LBW babies.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

This study was done by ZKH and GM participated in the design of the study. Data collection was done by ZKH and MZ. ZKH, GM and EG performed the statistical analysis. ZKH, GM and EG performed the coordination and helped with the drafting of the manuscript. The authors read and approved the final version of the manuscript.

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Research paper

Physical activity and sedentary behaviors among active college students in Kuwait relative to gender status

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Keywords

College students • Exercise • Kuwait • Physical activity • Sedentary behaviors • Sleep

Summary

Objectives. *To determine the prevalence of physical activity (PA), sedentary behaviors (SB) and sleep duration and the associations between those variables among Kuwaiti Physical Education (PE) College students.*
Methods. *A total of 418 participants (220 females) were randomly selected from the Basic Education College in the Public Authority for Applied Education and Training in Kuwait. Body weight and height were measured, and body mass index (BMI) was calculated. A validated questionnaire was used to assess lifestyle behaviors.*
Results. *Based on BMI classification, the prevalence of overweight or obesity among males (34.9%) was significantly higher than that of females (16.7%). However, the mean (SD) of body fat percentage using bioelectrical impedance analysis was 21.3 (9.0) for males and 32.3 (7.7) for females. The proportions of highly active (> 1,200 METs-min/week) males (85.9%) and females (64.3%) were significantly ($p < 0.005$) different. The participants exceeding 3 hours of screen viewing time/day and insufficient sleep duration (< 7 hours/night) were 76.8% and 65.1%, respectively, with no gender differences. Logistic regression, adjusted for confounders, showed that highly active PE students had a higher proportion of SB. However, neither sleep duration nor body fat percentage exhibited any significant difference relative to PA.*
Conclusions. *Despite having high PA, Kuwaiti PE College students had a high prevalence of SB and insufficient sleep. Gender differences were found in PA but not in screen time or sleep duration. Efforts toward reducing SB and insufficient sleep among Kuwaiti PE College students are needed to reduce unhealthy lifestyle behaviors and promote health and well-being.*

Introduction

Chronic diseases, including cardiovascular disease, type 2 diabetes mellitus, obesity, and cancer are spreading rapidly worldwide, including the State of Kuwait [1, 2]. Indeed, Kuwait ranks second in obesity worldwide and first in the Middle East for type 2 diabetes [3, 4]. Since there are many risk factors for chronic diseases, including smoking status, physical inactivity, and dietary habits [5], assessing such risk factors in different segments of Kuwaiti population, such as College students, is critical.
The prevalence of overweight and obesity in Kuwaiti young generation, aged 14-19 years, was reported to be 50.5 and 46.5%, respectively [6]. This high prevalence is attributed to both sedentary behaviors and poor eating habits [6]. Therefore, awareness about the health benefits of physical activity should be emphasized among this population. Such information should be shared in schools by physical education (PE) teachers because it is their responsibility to teach students the importance of physical activity for a healthy lifestyle and well-being [7]. Needleless to say that being physically active is well recognized as very beneficial for mental, physical and social health along the life span [8].
College age students have an important role in the Kuwaiti society, especially physical education students. However, college and university students may be especially at risk for sedentary behaviors, as much of their campus day involves sitting still in classroom lectures and doing additional homework at home using computers and internet search. Elsewhere, research have shown that College students were highly sedentary [9]. Physical inactivity was also reported to be prevalent among University students. A study assessing non-communicable disease risks among college students in the United States revealed a large percentage of them did not meet the dietary and physical activity international guidelines [10]. Another study found that the majority of university students were not meeting international recommendations on physical activity, and that the percentage of overweight was increasing in both genders and across all age groups [11].
In the State of Kuwait, there is only one large PE department. Graduates of that department are prepared to work mainly in public and private schools. If PE teachers are to educate the next generation of young Kuwait's about the importance of healthy lifestyle behaviors, it is necessary that they serve as role models,

by regularly incorporating physical activity into their daily lives and avoiding as much sedentary behaviors as possible. However, to the best of our knowledge, recent and comprehensive assessment of lifestyle behaviors of Kuwaiti college physical education students is lacking. Therefore, the main objective of the present study was to determine the prevalence of physical activity levels, sedentary behaviors, and sleep duration among Kuwaiti male and female PE Colleges students and examine the associations between physical activities, and sedentary behaviors, sleep duration and body fat content.

Methods

Study design and participants

This is a cross-sectional study comprising healthy PE College students randomly chosen from all students enrolled in a randomly selected classes in the department of Physical Education and Sports at the College of Basic Education in Kuwait, which is the only PE department in the country. The sample size calculation was based on the number of participants needed to have sample proportion with 0.05 of population proportion within a 95% confidence level [12]. Ethical approval was attained from the Public Authority for Applied Education and Training (PAAET). Informed written consent was obtained from all participants prior to participation. The research procedures and protocols were conducted in accord with the principles expressed in the Declaration of Helsinki.

Body weight and height were measured in the morning with minimal clothing and without shoes using calibrated medical scales. Weight was measured to the nearest 100 gram, while height was measured to the nearest centimeter. Body mass index (BMI) was calculated by dividing the weight in kilogram over the squared height in meters. Overweight plus obesity level was calculated based on BMI ≥ 25 kg/m^2. In addition, body fat percentage and muscle mass were determined noninvasively using Tanita Body Composition Analyzer (BC-1000 Madison, WI).

Assessments of physical activity

The Arab Teen Lifestyle Study (ATLS) questionnaire was used to assess physical activity, sedentary behaviors and sleep duration [13, 14]. The questionnaire has been widely used in recent years in youth and young adults and was previously shown to be a reliable and valid instrument for assessing physical activity and other lifestyle habits in youth [14-16]. Briefly, the physical activity section of the questionnaire was intended to collect information on the frequency, duration and intensity of light-, moderate- and vigorous-intensity physical activities during a typical week. The physical activity questionnaire covers all types of physical activity domains including transport, household, and fitness, sporting and recreational activities. A variety of physical activities were included in the questionnaire such as walking, jogging, running, swimming, cycling, weight training, martial arts, dancing for women, moderate- and vigorous-intensity sports and household physical activities. To determine the participants' levels of physical activity, we used the total physical activity duration in minutes per week. Classification of physical activity (as high or low) were based on two cut-off scores. The first criteria was based on activity energy expenditure above or below 600 METs-min/week, or equivalent of 30 minutes of moderate intensity physical activity for 5 days per week (30 minutes x 4 METs x 5 days). The second criteria was based on activity energy expenditure above or below 1,200 METs-min/week, or equivalent of 60 minutes of moderate intensity physical activity for 5 days per week (60 minutes x 4 METs x 5 days). This cut-off score was based on the recommended amount of health enhancing physical activity for adults [14].

Assessment of sedentary behaviors and sleep duration

The ATLS questionnaire includes questions designed to asses typical time in hours spent per day in sedentary activities, including television (TV) viewing, video games, and recreational use of computer, internet, and social media during weekdays and weekends. In addition, participants were asked to state their typical sleep duration in hours spent on weekday and weekend nights. Total screen viewing time cut-off value was 3 hours per day. Sufficient and insufficient sleep duration was calculated as above or below 8 hours per night, respectively [17].

Data and statistical analysis

Data were entered into a coded SPSS data entry sheet, checked, cleaned and analyzed using IBM SPSS software, version 22. Descriptive statistics were calculated and presented as means and standard deviations (SD) or proportions. Prevalence of low and high levels of physical activity, sedentary behaviors, sleep, and overweight or obesity were calculated using cross tabulation. T-tests for independent samples were used to detect differences in time spent in physical activity between males and females. Finally, we used logistic regression analysis, adjusted for age, weight and BMI, to test the differences in selected variables, including screen time, sleep duration and body fat percentage, relative to activity energy expenditure (METs-min/week) cut-off scores. Adjusted odds ratio and confidant intervals were reported. Alpha level was set at 0.05 and p-value less than alpha level was considered significant.

Results

Table I presents the descriptive characteristics of the participants. A total of 418 participants (198 males and 220 females) were randomly selected from college students in the Department of Physical Education & Sports at the Public Authority for Applied Education and Training during the 2017-2018 academic year.

Tab. I. Descriptive characteristics of the participants (means ± standard deviations or percentage).

Variable	All (n = 422)	Male (n = 198)	Female (n = 224)
Age (year)	20.8 ± 2.3	20.5± 2.3 *	21.1 ± 2.3
Weight (kg)	63.4 ± 14.7	71.3 ± 15.8 *	56.5 ± 9.2
Height (cm)	165.6 ± 8.8	172.7 ± 7.1 *	159.3 ± 4.3
BMI (kg/m²)	23.0 ± 4.0	23.8 ± 4.5 *	22.3 ± 3.4
Fat (%)	27.2 ± 10.0	21.3 ± 9.0 *	32.3 ± 7.7
Muscle mass (kg)	32.1 ± 8.5	39.3 ± 5.5 *	25.5 ± 4.2
Body mass index (BMI) (%)			
Normal weight (< 25 kg/m²)	74.8	65.1 *	83.3
Overweight or obese (25+ kg/m²)	25.2	34.9 *	16.7
Physical activity/inactivity (%) **			
High active 1 (> 600 METs-min/week)	87.9	96.0 *	80.8
Low active 1 (< 600 METs-min/week)	12.1	4.0 *	19.2
High active 2 (> 1,200 METs-min/week)	74.4	85.9 *	64.3
Low active 2 (< 1,200 METs-min/week)	25.6	14.1 *	35.7

* p < 0.005 for the difference between the male and female participants (t-test for independent samples or Chi-Square tests); ** Based on total activity energy expenditure above and below 2 specific cut-offs.

Mean (SD) age of the whole group was 20.8 (2.3) years, ranging from 17 to 33 years. Males were significantly heavier, taller and have higher mean BMI score than females. Fat percent was lower while muscle mass was higher among males compared with females. Based on BMI classification, the prevalence of overweight or obesity among male participants (34.9%) was significantly higher than that of females (16.7%). The overall prevalence of highly active students, based on activity energy expenditure above or below 600 METs-min/week, was 87.9%, with males reporting significantly greater levels of physical activity level (96%) than females (80.8%). However, the average level of highly active students dropped slightly when activity energy expenditure cut-off value was increased to equal or above 1200 METs-min/week, thus reaching 74.4%.

Table II shows the profile of physical activity and sedentary behaviors of the participating College students relative to gender. Compared with females, male participants exhibit significantly greater amounts in all types of physical activities except dance and household activity. Total physical activity (mean and standard errors) in minutes per week were 685.8 (34.3) and 455.2 (25.5) in males and females, respectively. Male participants reported a greater total amount of vigorous-intensity physical activities, whereas females reported a greater total amount of moderate-intensity physical activities. The proportion of all students exceeding

Tab. II. Means and standard errors of the times spent in different types of physical activity, screen activity and sleep by active Kuwaiti college students.

Variable	All (n = 422)	Male (n = 198)	Female (n = 224)	p value *
Walking (min/week)	109.7 (5.6)	129.9 (9.0)	91.9 (6.7)	**0.001**
Stair Stepping (min/week)	9.5 (0.22)	10.1 (0.29)	8.9 (0.33)	**0.011**
Jogging (min/week)	72.1 (5.4)	98.9 (9.8)	48.4 (4.9)	**< 0.001**
Cycling (min/week)	20.5 (3.1)	23.6 (5.7)	17.7 (3.0)	**0.349**
Swimming (min/week)	41.4 (3.2)	51.7 (5.4)	32.3 (3.5)	**0.003**
Martial art (min/week)	18.2 (3.5)	31.4 (7.2)	6.5 (1.5)	**0.001**
Resistance training (min/week)	71.1 (6.2)	119.0 (11.1)	28.6 (4.7)	**< 0.001**
Household (min/week)	54.5 (4.0)	21.3 (4.2)	66.9 (6.3)	**< 0.001**
Traditional female dance (min/week)	37.4 (3.7)	0.0	70.5 (6.2)	**< 0.001**
Moderate-intensity sports (min/week)	61.8 (5.1)	68.3 (6.9)	56.0 (7.4)	**0.227**
Vigorous-intensity sports (min/week)	76.3 (6.3)	131.6 (11.6)	27.5 (3.9)	**< 0.001**
Sum of all moderate-intensity physical activity (min/week)	245.4 (10.9)	219.5 (13.1)	285.3 (16.6)	**0.002**
Sum of all vigorous-intensity physical activity (min/week)	309.0 (15.6)	466.3 (25.8)	169.9 (12.8)	**< 0.001**
Total physical activity (min/week)	563.4 (21.7)	685.8 (34.2)	455.2 (25.5)	**< 0.001**
Average screen time (hours/day)	5.55 (0.15)	5.62 (0.22)	5.49 (0.20)	**0.662**
Proportion of screen time above 3 hours/day (%)	76.8	78.3	75.4	**0.491**
Average sleep duration (hours/night)	7.23 (0.08)	7.35 (0.10)	7.12 (0.12)	**0.141**
Proportion of insufficient sleep (< 7 hours/day) (%)	65.1	64.6	65.5	**0.859**

* T-test for independent samples for the differences between male and female.

Tab. III. Physical activity choices and reasons for being active (%) among active Kuwaiti college students.

Variable	Male	Female	P-value *
Where do you exercise?			
Sport/recreational center	59.6	36.1	< 0.001
Health club/fitness center	28.3	12.5	
At home	7.6	36.2	
At university	4.0	13.4	
Other than the above	0.5	1.8	
Total (%)	***100***	***100***	
With whom do you exercise?			
With a friends/school mates	63.6	42.9	< 0.001
With no body	26.3	30.8	
With parents or relative	8.1	15.2	
Other than the above	2.0	11.1	
Total (%)	***100***	***100***	
When do you mostly exercise?			
Evening	70.2	50.0	< 0.001
Morning	7.6	20.1	
No specific time	13.6	15.2	
Noon/afternoon	8.6	14.7	
Total (%)	***100***	***100***	
Reason for being active			
For health benefits	71.2	46.4	< 0.001
For recreation	9.6	20.1	
For weight loss	6.1	19.1	
For competition	11.6	9.8	
To meet friends (social)	1.5	4.4	
Total (%)	***100***	***100***	

* Chi square test for the differences between observed and expected frequencies.

3 hours of screen viewing time per day was 76.8%, while those students with insufficient sleep duration was 65.1%, with no significant (< 0.05) differences in these parameters relative to gender.

Table III displays the participants' responses to questions related to place and timing of exercise as well as with whom they exercise. There were significant gender differences in those responses. The majority of males engaged in physical activity at sports or recreational centers (59.6%) followed by health clubs or fitness center (28.3%), whereas female exercise most at home (36.2%) followed by recreational center (36.1%). Again, males exhibited different patterns than females in responses to whom they exercise with. More than 63% of the males exercised with friends, while females exercised mostly alone (30.8%) or with parents or relatives (15.2%). In terms of timing of physical activity, more than 70% of the males and 50% of the females exercised in the evenings. However, one fifth of females preferred to exercise in the morning. The most important reasons for being physically active by the Kuwaiti college participants are also presented in Table III. There are more males (71.2%) than females (46.4%) exercising for health reason, whereas females engage in exercise mostly for recreation (20.1%) or weight loss purpose (19.1%).

Table IV shows cross tabulation of two activity energy expenditure cut-off values with screen viewing time, sleep duration, and fat percent categories for Kuwaiti college students. At cut-offs 1 (above or below 600 METs-min/week), there was significantly different patterns for screen viewing time relative to activity levels ($p < 0.001$). Highly active participants were showing higher proportion (79.5%) of screen viewing time spent above 3 hours per day than low active students (56.9%) do, whereas the opposite is true for time spent below 3 hours in screen viewing time. No significant difference was shown in sleep duration relative to activity levels. However, categorizing body fat percentage into normal fat percent and obesity indicated a significant ($p = 0.012$) difference relative to activity cut-off score above or below 1200 METs-min/week (cut-offs 2), as active students were showing lower proportion (40.2%) of being in obesity category compared with low active students (54.2%).

Results of logistic regression analysis, adjusted for age, weight and BMI, for selected variables relative to activity energy expenditure in METs-min/week is shown in Table V. Male PE College students exhibited significantly higher activity energy expenditure than females (aOR = 2.668; CI = 1.239-5.747; p = 0.012). Also, highly active PE students showed lower proportion of time spent at less than 3 hours of screen viewing time (aOR = 0.517; CI = 0.279-0.958; p = 0.036). On the other hand, neither sleep duration nor body fat percentage exhibited any significant difference relative to activity energy expenditure levels of both cut-off criteria.

Tab. IV. Cross tabulations of two activity energy expenditure cut-off values with Screen viewing time, sleep duration, and fat percent categories for Kuwaiti college students.

Variable	Activity cut-off 1		P-value *	Activity cut-off 2		P-value *
	Low active (< 600 METs-min/week)	High active (> 600 METs-min/week)		Low active (< 1200 METs-min/week)	High active (> 1200 METs-min/week)	
Screen viewing time (hours/day)						
Low (< 3 hours)	43.1%	20.5%	**< 0.001**	26.9%	22.0%	0.300
High (3 + hours)	56.9%	79.5%		73.1%	78.0%	
Sleep duration (hours/night)						
Insufficient (< 8 hours)	66.7%	64.9%	0.800	67.3%	64.3%	0.579
Sufficient (8 + hours)	33.3%	35.1%		32.7%	35.7%	
Fat percent (%)						
Normal	46.0%	57.6%	0.122	45.8%	59.8%	**0.012**
Obesity	54.0%	42.4%		54.2%	40.2%	

* Chi-Square test for the differences in proportion.

Tab. V. Results of logistic regression analysis, adjusted for age, weight and BMI, for selected variables relative to activity energy expenditure in METs-min/week.

Variable	Activity level (Low *versus* High) *			
	aOR	(95% CI)	SEE	P-value
Age	1.109	0.988-1.246	0.059	0.080
Weight	1.028	0.976-1.083	0.026	0.292
BMI	0.893	0.756-1.054	0.085	0.182
Gender (female = ref)	1.00			
Male	2.668	1.239-5.747	0.830	**0.012**
Screen time (high = ref)	1.00			
Low	0.517	0.279-0.958	0.315	**0.036**
Sleep duration (sufficient = ref)	1.00			
Insufficient	0.862	0.522-1.423	0.256	0.561
Fat percent (obesity = ref)	1.00			
Normal fat percent	1.464	0.863-2.834	0.303	0.141

* Based on activity energy expenditure of < 1,200 or > 1,200 METs-min/week. The reference category is inactive. aOR = adjusted odds ratio for age, weight and BMI; CI = confidence interval; ref = reference category; SEE = standard error.

Discussion

The present study described the patterns and interrelationships of physical activity, sedentary behaviors and sleep duration among a randomly selected cohort of PE students at a major higher education institution in Kuwait. To our knowledge, this is the first study from the State of Kuwait to report physical activity, sedentary behaviors and sleep data for college age participants using a validated physical activity questionnaire that is widely used in the Arab countries [6, 14, 18-21]. The benefits of health-enhancing physical activity for humans are well-recognized [5]. Insufficient physical activity, on the other hand, is considered a major risk factor for NCDs and total mortality [5, 22].

The main finding of the present study indicated that the level of physical activity is fairly high among this group of College PE students. Males exhibited higher levels in most types of physical activity, however, females were more active in dance and household physical activity. In addition, despite having high levels of physical activity, overweight or obesity prevalence, based on BMI classification, was fairly high, especially among males. The findings also indicate that large proportions of those college students had high screen viewing time and insufficient sleep. A recent international study including 1.9 million participants from 358 surveys and 168 countries reported a global age-standardized prevalence of insufficient physical activity of 23.4% in males and 31.7% in females, with a mean of 27.5% [23]. Based on the cut-off criteria of 1200 METs-min/week that was used in the present study, the proportions college PE students who scored below this cut-off level were 14.1% for males and 35.7% for females.

Our findings that was showing high prevalence of overweight or obesity among male participants, based on common BMI classification, deserve some explanation. The present study is comprised of active PE students, including some athletes with high lean body mass. Therefore, BMI use among athletes is not without limitations, and does not accurately reflect the actual body composition among the participants [24, 25]. This

is evident by the lower body fat percentage and higher body mass content of males compared with females. The high BMI may simply reflect increased large muscle mass due to the popular weight training practice among Kuwaiti young males, which does not confer less favorable health.

The present study indicated that a large percentage of males engaged in physical activity at sport or recreation centers, whereas more females were exercising at home. Similarly, a study conducted on Saudi medical students living in western Saudi Arabia showed that more females than males exercised at home [26]. However, exercise opportunities for females in Kuwait are increasing nowadays. Thus, in the present study, the percentage of females who reported exercising at recreation centers was nearly equivalent to that percentage of females who exercised at home. Compared to males, female participants in the present study showed significantly different reasons for engaging in physical activity. While females exercised mostly for recreation and weight loss, Kuwaiti young males mostly engaged in exercise for health and competition. This is consistent with findings reported in many Arab countries, as the most important reasons for being physically active among adolescents and adults were health, losing or maintaining body weight or for recreation [14, 19, 21, 26-29]. Also, in the majority of the above mentioned studies, there was a gender difference in the reason for being active. The finding that health reason is an integral part for motive to be active among PE students in the current study is very important, because those student will be PE teachers in the future and will be responsible for instilling positive health behaviors in their future students.

The current study revealed different patterns for screen viewing time relative to activity levels. Compared with less active students, more active PE students were spending greater proportion of time for more than 3 hours per day on screen viewing. This means that active students seem to be more sedentary. Research showed that sedentary behaviors appeared to be linked to adverse health outcomes in a way that is somewhat different from those ascribed to the lack of physical activity [30]. In addition, it is believed that physical inactivity and sedentary behaviors, such as screen viewing, appear to be independent entities and distinctly were associated with obesity and metabolic risk [31]. Moreover, a previous work conducted on Saudi youth showed that physical activity was more linked with healthy dietary choices, while screen viewing time was associated more with unhealthy dietary habits [32]. Also, among undergraduate Chinese medical students, low screen time and vigorous physical activity were found to be independently and concurrently associated with significantly lower stress [33]. It is possible that the reason behind this finding might be due to the fact that active PE students think they were meeting the physical activity recommendations, so they can be more relaxed and kept sitting the rest of the day. In other words, the PE students may have reduced their non-exercise activity thermogenesis (NEAT), as an earlier study had shown that structured exercise program may lead to a reduction in spontaneous daily physical activity [34].

Getting good quality sleep is vital to the individual's physical and mental health [17]. Insufficient sleep and irregular sleep-wake patterns have been reported at alarming levels in the college student population [35]. In addition, vigorous physical activity and quality sleep were shown to be beneficial in helping college students to reduce stress and regulate depressive symptoms [36]. Also, among University students, physical activity and sufficient sleep duration were reported to have a positive effect on the health-related quality of life (HRQOL) of university students, whereas sedentary time was not related to HRQOL [37]. However, the present study showed that nearly two third of the PE College students had insufficient sleep and that neither physical activity nor screen viewing time significantly correlated with sleep duration. Similarly, poor quality of sleep was widely reported among undergraduate female students in eastern Saudi Arabia, and that insufficient sleep was associated with low physical activity and skipping breakfast [38]. Further comparison with our findings, a study involving Kuwaiti adolescents 15-19 year-olds revealed that more than 76% of males and above 74% of females had insufficient sleep duration of less than 7 hours per day [6].

Finally, there were several limitations to our study. We used a cross-sectional study design which does not imply causal relationship between the selected variables. Only PE students from the Physical Education Department at the College of Basic Education were recruited, thus more students from non-PE department should be recruited in future studies to examine the differences in activity levels, sedentary behaviors, sleep patterns, and body composition status. Also, future research may use a more objective method of assessing physical activity, despite the fact that in the present study a comprehensive and validated PA assessment instrument was used.

Conclusions

The findings of the present study indicated that despite having high activity levels, Kuwaiti PE College students had high prevalence of sedentary behaviors and insufficient sleep. Gender differences were found in physical activity levels but not in screen time or sleep duration. Results of logistic regression analysis, adjusted for age, weight and BMI, showed that highly active PE College students had higher proportion of sedentary behaviors. However, neither sleep duration nor body fat percentage exhibited any significant difference relative to activity energy expenditure levels. Future research should include the assessment of eating habits and nutritional intake among Kuwaiti PE students and compare the lifestyle behaviors of PE College students with those of non-PE College students. Efforts toward reducing sedentary behaviors and increasing sleep duration of Kuwaiti PE College students are needed to decrease unhealthy lifestyle behaviors and promote total health and well-being among college students.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. Any additional data are available from the corresponding author on reasonable request.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: MA, KA, AA, and HMA; data collection: MA, KA, AA, AA, SA, and KA; statistical analysis: HMA; findings interpretation: MA, KA, AA, AA, SA, KA, and HMA; drafting the paper: MA, KA, and HMA; critically revising the manuscript for intellectual content: AA, AA, SA, and KA; all authors read and approved the final version of the manuscript.

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Research paper

Osteoporosis guideline awareness among Iranian nurses: results of a knowledge and attitudes survey

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Keywords

Beliefs • Knowledge • Screening • Osteoporosis • Prevention

Summary

Introduction. *Osteoporosis is a chronic and progressive disease associated with gradual bone loss and elevated risk of fracture. Role of health care professional especially nurses in lowering burden of osteoporosis via patients and public education is critical. Current study conducted to evaluate knowledge and attitude regarding osteoporosis among the nurses in orthopedic wards and their experience with national clinical osteoporosis guideline.*
Methods. *A cross-sectional study was conducted from August to December 2016 among all nurses in orthopedic ward of hospitals affiliated to Shiraz University of Medical Sciences. The 23- item self-administered scale consisted of knowledge and attitude questions were used. Moreover, data regarding participation in osteoporosis training courses and awareness of the national osteoporosis clinical guideline were collected as a measure of nurses' experience with guideline. The gathered data were analyzed using SPSS (V. 16), student t-test was used to compare total knowledge and attitude scores between categorical demographic and professional data. Pearson test was used to calculate the correlation between total knowledge and attitude scores and years of practice. A p-value < 0.05 was considered statistically significant.*
Results. *From total of 160 nurses, 143 of them completed the questionnaire (response rate: 89.3%). The total mean ± SD knowledge and attitude scores were 11.60 ± 3.10 and 3.47 ± 0.92 respectively. Six nurses (4.2%) had participated in osteoporosis training courses after graduation, and 39 (27.3%) had been aware of the national osteoporosis clinical guideline. Knowledge and attitude scores among nurses who practice in private hospitals was higher than those practices in the teaching hospitals. These differences were statistically significant based on student t-test. According to Pearson correlation coefficient, there was positive and significant correlation between nurses' knowledge and attitude score (Correlation coefficient: 0.199, p-value = 0.037).*
Conclusion. *Our findings reveal that nurses' knowledge and attitude regarding osteoporosis was not satisfactory. Most of them were not aware of national osteoporosis clinical guideline and had not participated in osteoporosis training courses after their graduation. We need more empowered nurses to lowering burden of osteoporosis and its consequences in the future.*

Introduction

Osteoporosis, the most common metabolic bone disorder, is a chronic and progressive disease associated with gradual bone loss and increased risk of fracture [1-3]. As a major public health issue in all over the world, it is estimated that more than 15% of women aged 50 and over have osteoporosis, based on defined criteria by world health organization [4, 5]. According to Iranian reference data at 2006, the prevalence of osteoporosis in lumbar vertebrae was 44.4% in women and 13.4% in men aged 50 years or more [6].
While osteoporosis is a preventable disease with modifiable risk factors, which have been previously described very well [7-11], it is responsible for about 36,027 years lost due to premature mortality and disability, based on disability-adjusted life years (DALYs) [12-14]. Therefore, health care professionals, especially nurses, are well-positioned to reduce the cost burden of osteoporosis by increasing the knowledge of patients and community people [10, 15-17].
Lack of knowledge about osteoporosis and loss of awareness regarding national guidelines among health care professionals is evident in the previous researches [15, 18, 19]. A cross-sectional survey among public health nurses in Taiwan evaluated knowledge of nurses about six dimensions of osteoporosis using a 50-item self-report scale. Chen and et al. reported low level of knowledge regarding osteoporosis especially in symptoms/signs, diagnosis/treatment and risk factors. Moreover, only 13.0% of Taiwanese' nurses had attended osteoporosis classes as their continuing education experience [15]. Current study was conducted to evaluate the knowledge and attitude regarding osteoporosis among nurses in orthopedic wards and their experience with national clinical osteoporosis guideline.

Methods

This cross-sectional study was conducted from August to December 2016 among all nurses working in orthopedic wards of all hospitals, located in Shiraz, the largest city in southern Iran. All nurses with a bachelor's or master's

degree with more than one year of experience in orthopedic ward were eligible to participate in this study. Nurses without consent to participate or unavailable after three visits were excluded from the study.

Ethical considerations

The study protocol complied with the Helsinki Declaration and was approved by local research ethics committee of Shiraz University of Medical Sciences (95-01-56-121-89). Permission was obtained from all hospital administrators. Verbal informed consent was obtained from all participants and anonymity and data confidentiality were guaranteed.

Questionnaire

The main questionnaire was a 23-item self-administered scale designed by the authors based on a review of the relevant literature and the national osteoporosis clinical guideline released at 2014 for the diagnosis and management of osteoporosis [18, 20-23]. It consisted of knowledge questions (18 items regarding definition, risk factors, prevention, and screening) and attitude questions (5 items regarding socio-cultural attitude, importance of prevention, and self-perceived responsibility). Demographic data and professional characteristics of the participants including gender, setting of practice [non-profit (teaching hospital) or for-profit (private hospital)], years of practice, participation in osteoporosis training courses (continuing education), and awareness of the national osteoporosis clinical guideline were collected.

The questionnaire underwent face and content validation by an expert panel comprised of three community medicine specialists, two orthopedic surgeons, and one epidemiologist. A literature review and experts' opinions established the validity of the questionnaire's content. Its reliability was verified in a pilot test with 30 participants. Cronbach α coefficient was in acceptable range for knowledge and attitude questions, and it took, on average, 25-30 minutes to complete.

In knowledge section, two response options were provided: "correct" or "incorrect". One point was given for each correct response, and 0 point was given for each incorrect response. In the attitude section, a 5-point Likert scale was used to rate the extent to which the participant agreed with each statement: "strongly disagree", "disagree", "neutral", "agree" and "strongly agree". The 5-point Likert scales were re-categorized into 2 groups: "strongly agree" and "agree" were combined into the "agree" group, and the other responses were combined into the "did not agree" group to rate the extent of agreement with items. Knowledge and attitude scores were classified into three levels using Bloom's Theory [24], which categorizes by percentage based on summed scores: ≤ 60% represented poor knowledge, >60-80% moderate knowledge, and > 80% a good level of knowledge. Likewise, attitude scores were classified into poor (≤ 60%), moderate (> 60-80%) and good level of attitude (> 80%).

Statistical analysis

The collected data were entered, verified, and analyzed with SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Descriptive variables including number, percentage, mean and standard deviation (SD) were calculated for demographic and professional data and for knowledge/attitude items. Student t-test was used to compare total knowledge and attitude score between gender, practice setting (Private/ teaching), participation in training courses (yes/no) and awareness of guideline (yes/no). Pearson test was used to calculate the correlation between total knowledge and attitude score and years of practice (as a nurse, as an orthopedic nurse). A p value less than 0.05 was considered statistically significant.

Results

Among 160 orthopedic nurses, 10 were not available during the data collection and 7 refused to participate in the survey, thus the participants were 143 nurses (response rate: 89.3%). Most of participants were female (83.9%) and 98 (68.5%) of the nurses worked in the teaching university hospitals. The mean (SD) of years of practice as an orthopedic nurse was 5.17 (4.75) years. Only 6 nurses (4.2%) had participated in osteoporosis training courses after their graduation, and 39 (27.3%) had been aware of the national osteoporosis clinical guideline (Tab. I).

The overall mean (± SD) score of knowledge and attitude for all participants was 11.60 ± 3.10 (out of maximum possible score of 18) and 3.47 ± 0.92 (out of maximum possible score of 5), respectively. Based on Bloom's scale, mean total knowledge and attitude score regarding osteoporosis were in moderate level.

Table II shows frequency of nurses' responses to knowledge and attitude questions. Among 143 participants, less than 50% of them correctly responded the following questions (yes/no): "Osteoporosis is rarer in white and

Tab. I. Demographic and professional characteristics of the participants.

Variables	N (%) or mean ± SD
Gender	
Male	23 (16.1)
Female	120 (83.9)
Practice setting	
Teaching	98 (68.5)
Private	45 (31.5)
Years of practice	
As a nurse	5.17 ± 4.75
As an orthopedic nurse	7.31 ± 5.73
Participate in continuing education	
Yes	6 (4.2)
No	137 (95.8)
Awareness of national guideline	
Yes	39 (27.3%)
No	104 (72.7%)
Total	143 (100%)

Tab. II. Frequency of participants' responses to knowledge and attitude questions.

	Answers [n (%)]	
Knowledge questions	**Correct**	**Incorrect**
Definition		
1-Osteoporosis is a most common metabolic bone disease. (Yes)	106 (74.1)	37 (25.9)
2-Osteoarthritis is an another name of osteoporosis. (No)	87 (60.8)	56 (39.2)
Risk factors		
3-Osteoporosis is rarer in white and Asian. (No)	64 (44.8)	79 (55.2)
4-Genetic factors are associated with osteoporosis. (Yes)	88 (61.5)	55 (38.5)
5-The likelihood of osteoporosis in men and women is the same. (No)	120 (83.9)	23 (16.1)
6-The decline in bone density begins at age 45 and it accelerated after menopause. (Yes)	118 (82.5)	25 (17.5)
7-Physical activity decreases the risk of osteoporosis. (Yes)	108(75.5)	34 (23.8)
8-Smoking is one of the risk factors for osteoporosis. (Yes)	102 (71.3)	41 (28.7)
9-Alcohol use is not associated with osteoporosis. (No)	86 (60.1)	57 (39.9)
10-The use of corticosterone for more than three months causes a rapid decrease in bone mass. (Yes)	120 (83.9)	23 (16.1)
11-Some diseases and medications have effect on the rate of bone loss. (Yes)	87 (60.8)	56 (39.2)
12-Menarche age is associated with osteoporosis in women. (Yes)	105 (73.4)	38 (26.6)
Prevention		
13-Fracture is a most important complication of osteoporosis in the elderly. (Yes)	122 (85.3)	21 (14.7)
14-Daily need for calcium to prevent osteoporosis in different age groups ranged 1,000-1,300 milligram. (Yes)	42 (29.4)	77 (53.8)
15-Daily need for vitamin D to prevent osteoporosis in different age groups ranged 600-800 units. (Yes)	41 (28.7)	73 (51.0)
Screening		
16-All postmenopausal women should be evaluating for osteoporosis risk factors. (Yes)	131 (91.6)	12 (8.4)
17-For all women aged over 65 years measuring BMD *is necessary. (Yes)	35 (24.5)	108 (75.5)
18-Osteoporosis can be screened by plain x-ray. (No)	70 (49.0)	73 (51.0)
Attitude questions	**Agree n (%)**	**Disagree n (%)**
1-Osteoporosis is a silent disease	102 (71.4)	41 (28.7)
2-Osteoporosis is a preventable disease so screening is necessary	134 (93.8)	9 (6.3)
3-It is our culture that osteoporosis is a not- treatable disease	35 (24.5)	108 (75.5)
4-Patient education on osteoporosis prevention and screening is my responsibility	110 (76.9)	33 (23.1)
5-I am confident in giving counseling regarding osteoporosis prevention and screening to public and patients	27 (18.9)	116 (81.1)

Asian" (44.8%), "For all women aged over 65 years measuring bone mineral density (BMD) is necessary" (24.5%), "Osteoporosis can be screened by plain x-ray" (49 %), "Daily need for calcium to prevent osteoporosis in different age groups ranged 1,000-1,300 milligram" (29.4%), and "Daily need for vitamin D to prevent osteoporosis in different age groups ranged 600-800 units" (28.7%). Most of these questions with lowest correct answers were related to prevention and screening aspects of osteoporosis.

Regarding nurses' attitude towards osteoporosis; 102 participants (71.4%) agreed with "Osteoporosis is a silent disease". Screening for osteoporosis was believed to be necessary (93.8%). A majority of nurses perceived that patient education is a part of their job responsibilities (76.9%); however, only 27 (18.9%) of them confident in giving counseling to public and patients.

Table III presents the result of comparison of knowledge & attitude scores with demographic and professional variables. Mean knowledge score was 13.13 ± 2.17 among nurses who work in private setting and 11.02 ± 3.29 among those who work in government/public settings ($P = 0.01$). Mean attitude scores were 3.32 ± 0.90 and 3.80 ± 0.89 among nurses who worked in public and private settings, respectively, and this difference was statistically significant ($P = 0.04$). Nurses participated in the osteoporosis training courses and that awareness of the national guideline had higher knowledge scores; however, there were no statistically significant association between these variables. According to Pearson rank correlation coefficient, there was a significant positive correlation between mean knowledge and attitude scores ($r = 0.199$, $P < 0.037$). There was positive correlation between nurses' knowledge and attitude scores and years of practice, but these correlations were not statistically significant (Tab. IV)

Discussion

Osteoporosis will become a future public health issue especially in our country with upward trending of elderly population [25, 26]. High mortality rate after hip fracture in elderly Iranian population reported in

Tab. III. Mean of knowledge and attitude scores towards osteoporosis by categorical demographic and professional data.

Variables	Knowledge score	Attitude score
	Mean ± SD	Mean ± SD
Gender		
Men	11.05 ± 3.26	3.60 ± 0.98
Women	11.70 ± 3.07	3.45 ± 0.91
p-value	0.418	0.453
Practice setting		
Governmental/public	11.02 ± 3.29	3.32 ± 0.90
Private	13.13 ± 2.17	3.80 ±0.89
p-value	0.001	0.004
Participate in training courses		
Yes	11.75 ± 1.50	3.83 ± 0.40
No	11.59 ± 3.14	3.45 ±0.93
p-value	0.922	0.335
Awareness of national guideline		
Yes	11.71 ± 2.91	3.43 ± 0.088
No	11.56 ± 3.17	3.49 ± 0.94
p-value	0.823	0.755

previous studies [27, 28]. Therefore, role of nurses as a frontline staff, in patient education and prevention of osteoporosis is critical.

Our findings revealed that majority of nurses were not aware of most up-to-date national osteoporosis clinical guideline. Low level of guideline awareness among health care professionals had been reported in previous studies. Sixteen percent of awareness among practitioners in the Kingdom of Saudi Arabia, 25% among general practitioners in the United Kingdom, and 24% among family physicians in Iran [18, 29, 30]. Fourie et al. reported low adherence with osteoporosis published recommendations among New Zealand orthopedic nurses [11]. Directors of nursing from Duke university were aware of guidelines and strongly agreed that osteoporosis guidelines are useful and cost-beneficial; however, they have some barriers in use of these guidelines [31]. The lack of awareness in our setting may be explained by how the latest guideline are advertise or disseminate. In this regard, managers could be used of new methods of announcements such as mobile notification or tack periodic quick examinations from the last version of guideline.

In nurses' knowledge evaluation, knowledge score of our participants were not satisfactory. The correct answers in some important questions such as method of screening/risk factors of osteoporosis/daily need for vitamin D and Ca were low. Knowledge results were in line with previous findings. Zhang et al. and Vered et al. reported low or modest level of osteoporosis knowledge among hospital nurses [16, 32]. Swedish nurses stated in focus group interview that they have insufficient knowledge about diagnosis, fracture risk assessment tool such as fracture risk assessment tool (FRAX®) and bone-specific medications [19]. New Zealand nurses perceived that play a passive role in osteoporosis prevention and educating patients, because of inadequate osteoporosis knowledge [11].

Although the education of health care professionals has been improved in recent years; however, our results revealed that we need more plans to empower nurses. So use of practical/motivational training methods and some revision and possibly changes in nursing student curricula seem necessary.

In our analysis, nurses worked in the private hospitals had higher knowledge and attitude scores than those in the teaching hospitals. One reasons for this association may be more inexperienced workforce due to large influxes of graduate nurses in the teaching hospitals; however, more studies are required to further document the influence of this factor.

Regarding attitude, majority of nurses had positive attitude about necessity of osteoporosis screening. Also, more than two thirds of them perceived that patient education is a part of their job responsibilities. Majority of nurses were not confident in giving counseling to public and patients. This can be related to low level of nurses' knowledge in osteoporosis. Low level of knowledge perceived as a barrier to improve osteoporosis care among Alabama nursing directors [33]. Bandura's of self-efficacy theory [34], low level of person's knowledge can be effect on their future confidence and practice.

Limitation and strength

Our participants were recruited from orthopedic ward of hospitals affiliated to Shiraz University of Medical Sciences. This participants might not be representative of all Iranian nurses. But this was the first study in Iran to evalute awarness of nurses regarding most recent up-to-date national osteoporosi guideline.

Tab. IV. Correlation between age and work experience with participant.

Variables	Analysis	Years of practice as a nurse	Years of practice as an orthopedic nurse	Knowledge score	Attitude score
Years of practice as a nurse	Correlation coefficient	1			
	p-value	-			
Years of practice as an orthopedic nurse	Correlation coefficient	0.80	1		
	p-value	< 0.001	-		
Knowledge score	Correlation coefficient	0.15	0.11	1	
	p-value	0.106	0.251	-	
Attitude score	Correlation coefficient	0.109	0.190	0.199	1
	p-value	0.197	0.143	0.037	-

Conclusions

Nurses' knowledge and attitude regarding osteoporosis was not satisfactory and most of them were not aware of national osteoporosis clinical guideline. Although, nurses had positive attitude in screening and patient education; however, they were not confident in giving counseling to public and patients. So in order to decrease the burden of osteoporosis and its consequences, we need to empower our nurses via revision and possibly changes in educational methods with measurable and reliable criteria.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

HM and VK was contributed in study design, data gathering and writing the draft. MJE, ZK and ARV were contributed in study design, analyzed and interpreted the patient data, and critically appraise the draft of manuscript. All authors read and approved the final manuscript.

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Researc paper

Assessment of the validity and reliability of the Indonesian version of Short Form 12 (SF-12)

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Keywords

Internal consistency • Test-retest reliability • Factor analysis • Validity

Summary

Introduction. *Psychometric evaluation of the 12-item Short-Form Health Survey (SF-12), a well-used scale for measuring health-related quality of life (HrQoL), has not been done in general populations in Indonesia. This study assessed the validity and reliability of the SF-12 in middle-aged and older adults.*
Methods. *Participants self-completed the SF-12 and SF-36. Scaling assumptions, internal consistency reliability, and 1-week test-retest reliability were assessed for the SF-12. Confirmatory factor analysis was conducted to assess its construct validity. Correlations between SF-12 and SF-36 component scores were computed to assess convergent and divergent validity. Effect size differences were calculated between SF-12 and SF-36 component scores for assessing criterion validity.*
Results. *In total, 161 adults aged 46-81 years (70% female) participated in this study. Scaling assumptions were satisfactory. Internal consistency for the SF-12 Physical Component Summary (PCS-12) and the Mental Component Summary (MCS-12) were acceptable (a = 0.72 and 0.73, respectively) and test-retest reliability was excellent (ICC = 0.88 and 0.75, respectively). A moderate fit of the original two-latent structure to the data was found (root mean square error of approximation [RMSEA] = 0.08). Allowing a correlation between physical and emotional role limitation subscales improved fit (RMSEA = 0.04). Correlations between SF-12 and SF-36 component summary scores support convergent and divergent validity although a medium effect size difference between PCS-12 and PCS-36 (Cohen's d = 0.61) was found.*
Conclusions. *This study provides the first evidence that SF-12 is a reliable and valid measure of HrQoL in Indonesian middle-aged and older adults. The algorithm for computing SF-12 and its association with SF-36 in the Indonesian population warrant further investigation.*

Introduction

Indonesia's population is ageing [1]. Currently, one in four Indonesians is aged over 45 years, and by 2035, more than 100 million Indonesians are expected to be aged over 45 years with 30 million of these aged over 65 years [2]. As morbidity increases with age, there is a growing interest in instruments that measure health-related quality of life (HrQoL), a multidimensional concept that includes physical, psychological, and social domains of health [3, 4]. HrQoL is increasingly being accepted as an important patient-reported outcome measure in health care, including among middle and older adult populations [5].
Generic and disease-specific instruments are used for measuring HrQoL [4]. The Short-Form Health Survey (SF-36) is one of the most widely used generic instrument. It consists of 36 items, 35 of which are divided into eight subscales that can be summarised into two component summary scores, one for physical health (PCS-36) and the other for mental health (MCS-36) [6]. The SF-36 has been shown to have high internal consistency reliability and high convergent and discriminant validity in Indonesian middle-aged and older adults [7].
The 12-item Short-Form Health Survey (SF-12) was developed from the SF-36 as a shorter instrument that would reproduce physical and mental health component summary scores (PCS-12 and MCS-12) [8]. Having fewer items, the SF-12 can be completed by most participants in less than a third of the time needed to complete the SF-36 [8]. Thus, it can be used by researchers and practitioners wanting to reduce participant burden.
The reliability and validity of the SF-12 have been widely documented worldwide. The scale has been validated in general populations in many countries including Tunisia [9], Iran [10], China [11], Greece [12], Australia [13], Israel [14] and European countries [15]. It has been found to valid and reliable in older adults in Sweden [16], Israel [17], the US [18-20], the UK [21] and China [22, 23]. Furthermore, SF-12 component summary scores have been shown to be valid measures of HrQoL in patients with rheumatoid arthritis [24], immune deficiencies [25], mental health disorders [26], low back pain [27], retinal diseases [28], osteoarthritis [29], obesity [30], diabetes [31], stroke [32] and coronary heart disease [33]. The SF-12 has not been validated in general populations of middle-aged and older Indonesians.
In the initial development of the SF-12 and SF-36 in the US, the scales were found to be highly correlated, and scores on PCS-12 and MCS-12 each explained about 90% of the variation in the corresponding SF-

36 component summary score [8]. Findings from subsequent studies suggest that the factor structure of the SF-12 in some countries many not follow the scale's initial structure [17, 20, 27]. Thus, it is unclear whether these scales can be used interchangeably in Indonesia.

In Indonesia, the SF-12 has been used minimally, in only two studies as a patient-reported outcome measure [34, 35]. The limited use of the SF-12 is partly due to the lack of its validation in the Indonesian general population as it has only been validated in Indonesian patients with cardiovascular disease [33] and rheumatoid arthritis [36]. The validation of the SF 12 in the general population would likely increase its use more broadly to community settings throughout Indonesia. After validation, it is expected to be used to assess the burden of disease in communities and monitor progress in achieving the nation's health objectives [37]. As a short HrQoL instrument, it is also expected to be used in clinical settings to supplement objective clinical or biological measures of disease for assessing the quality of services, the need for health care, and the effectiveness of interventions, as well as for cost utility analysis [38]. Therefore, the current study aimed to examine the psychometric properties of the SF-12 in Indonesia middle-aged and older adults. We assessed scaling assumptions, internal consistency and test-retest reliabilities, and construct validity. We also assessed criterion validity with the SF-36 serving as the criterion, to justify the use of the SF-12, particularly as an alternative to the more time-consuming SF-36, in Indonesia.

Methods

Study design and study sample

This study assessed the psychometric properties of the Indonesian version of the SF-12 using guidelines from the International Quality of Life Project [15, 39]. The sample size calculation followed the recommendation of Jackson [40], who indicated a sample of at least 10 participants per item or parameter. As the SF12 contains 12 items, at least 120 participants were required for this study. To achieve this number, we invited 200 members of two organisations that offered educational and health services to middle-aged and older adults in the City of Yogyakarta through the organisations' community leaders. We expected a response rate of 60%. Members with mental or physical impairments that hindered participation were excluded. Participants provided written informed consent.

Data collection procedures and measures

All data collection took place in the community halls of the two organisations. At an initial visit and a follow-up visit 1 week later, participants self-completed a paper-based questionnaire that included the SF-12, the SF-36 and socio-demographic questions.

Tab. I. The Indonesian SF-12 factor structure and number of response options.

Component	Subscales	Item code	Number of response options
Physical component score (PCS-12)	General health	Item 1	5
	Physical health	Item 2 and 3	3
	Role-physical	Item 4 and 5	2
	Bodily pain	Item 8	5
Mental component score (MCS-12)	Role-emotional	Item 6 and 7	2
	Mental health	Item 9 and 11	6
	Vitality	Item 10	6
	Social function	Item 12	5

Four items were reversed scored: the General health item (item 1), the Bodily pain item (item 8), one Mental health item (item 9; 'Felt calm and peaceful') and the Vitality item (item 10).

Short-form 12 (SF-12)

The SF-12 consists of 12 items within eight subscales [8, 41]. As shown in Table I, six items from four subscales are used to generate a physical component summary score (PCS-12). These subscales measure general health perception (GH), physical functioning (PF), role limitation due to physical health (RP) and bodily pain (BP). Another six items from another four subscales are used to create a mental component summary score (MCS-12) [41]. These subscales measure role limitations due to emotional problems (RE), vitality (VT), mental health (MH), and social functioning (SF) [8]. Higher scores on PCS indicate better physical HrQoL, and higher scores on MCS indicate better mental HrQoL.

Raw item scores were transformed into a 0 (the worst) to 100 (the best) scale [41]. The mean score of the transformed items within a subscale was computed to obtain the subscale score. Item and subscale scores were not standardised. This summated rating method of scoring assumes that item and subscale scores can be transformed without standardisation of scores or item weighting [8, 41, 42]. To calculate PCS-12 and MCS-12 scores, a norm-based scoring algorithm empirically derived from US population data was used, as suggested by Ware [41] because no algorithm has been developed for the Indonesian population. The US algorithm has been validated in other countries where country-specific algorithms are absence [8].

Short-form 36 (SF-36)

The SF-36 [6], administered as a separate scale from the SF-12 in this study, was used to validate the SF-12. It contains 36 items, 35 of which are within the same eight subscales as in the SF-12. Likewise, two component summaries (PCS-36 and MCS-36) can be created. These were created using a summated method suggested by Hays [6]. The summary scores then were transformed into standardized T scores [6].

Socio-demographic characteristics

Participants were asked about socio-demographic characteristics, which included age, sex, marital status,

and two measures of socio-economic status: education and employment.

Statistical analysis

To assess whether the assumptions for creating subscales and the summated scoring from the items were justified, we used data collected from the initial visits with participants. Four assessments were conducted, as suggested by Leung [43]. First, we assessed whether there was equality in item variance. All subscale items should have similar standard deviations and means; otherwise, the computation of subscale scores would require standardisation. Second, we assessed the equality of item-subscale correlations. Subscale items should have similar corrected item-subscale correlations that are ≥ 0.40. Third, we assessed the floor and ceiling effects of subscales and component summaries. The percentage of participants with scores at the minimum value (floor) and maximum value (ceiling) should be < 20% to ensure scores capture the full range of responses in the population and that changes can be detected over time. Last, we assessed item discriminant validity, by determining whether the correlation between each item and its corresponding component summary score was significantly higher than its correlation with the other component summary score. Spearman correlation coefficients were computed for this analysis.
We then conducted tests of reliability. Internal consistency reliability was assessed by calculating Cronbach's alpha for each subscale and component summary. A Cronbach's alpha > 0.70 signified acceptable reliability [44]. The 1-week test-retest reliability of each component summary was assessed by calculating the intra-class correlation (ICC) of items within the component summary (1-way average model). An ICC > 0.60 was considered good, and an ICC > 0.75 was judged excellent [45].
For construct validity, we first conducted a confirmatory factor analysis (CFA) to assess whether the hypothetical factor structure, using the maximum likelihood estimation [8, 41] fit the observed data. The hypothetical structure allowed for correlations between PCS and MCS but not between subscales [8, 41]. Model modification indices were generated to guide model specification if the fit was not good. A good fit required a χ^2/df ratio of < 3.00 [46]. A root mean square error of approximation (RMSEA) value of < 0.08 indicated a good fit whereas a value between 0.08 and 0.10 indicated moderate fit [47]. Values > 0.90 for the Comparative Fit Index (CFI) and Tucker Lewis Index (TLI) and values < 0.08 for the standardised root mean square residual (SRMR) indicated an adequate fit [48]. We also assessed factor loadings of subscales onto composite summaries. As suggested by Shevlin [49], factor loadings of 0.30 to < 0.50 were considered low, 0.50 to < 0.70 as medium, and ≥ 0.70 as high.
Next, divergent validity was assessed by evaluating the correlations (i) among subscales, (ii) between a subscale and the composite summary that does not include that subscale and (iii) between PCS-12 and MCS-12. Divergent validity was demonstrated if correlations were weak (r < 0.40). Convergent validity was assessed by evaluating the correlations (i) between each subscale and the composite summary that includes that subscale and (ii) between PCS-12 and PCS-36 and between MCS-12 and MCS-36. The convergent validity was demonstrated if correlations were strong (r > 0.60). Correlations between 0.40 to 0.60 were considered moderate [10, 22]. Spearman correlation coefficients were computed for these analyses.
Last, criterion validity was assessed by calculating effect size differences between SF-12 and SF-36 component summary scores. The effect size difference was calculated by dividing the difference in scores by the pooled standard deviation. It has been suggested that an effect size of < 0.20 I very small; 0.20 to 0.49 is small; 0.50-0.79 is medium; and ≥ 0.80 is large [50]. Effect size < 0.20 demonstrated acceptable criterion validity.
Data were analysed using SPSS® version 21.0 (IBM Corp., Armonk, NY, USA), except for CFA, for which Stata 15 (Stata Corp, College Station, TX, US) was used. For all tests, statistical significance was set at $p < 0.05$.

Results

Participant characteristics

In total, 161 participants (response rate = 80.5%) completed the first data collection, above the minimal sample size required for the analysis. They were aged 46 to 81 years with a mean age of 62.7 ± 7.9 years and were predominantly female, married, with no tertiary education, and unemployed/retired. The 70 participants who returned to complete the test-retest reliability assessment (43%) did not differ significantly on any of these characteristics from the 91 participants who did not return for this assessment ($p > 0.05$) (Tab. II).

Descriptive statistics and scaling assumptions

The descriptive statistics for assessing the scaling assumptions for the SF-12 item, subscale, and component summary scores are presented in Table III. For each subscale, the means and standard deviations of the items were similar, except for the PF subscale, for which Item 2 had a higher mean than Item 3. The standard deviations of those two items, however, were similar. These results show that there was equality in item variance within subscales. The corrected item-subscale correlations were acceptable (r ≥ 0.40), except for the BP item (r = 0.39) and the first RE item (RE1; r = 0.38). The percentage of participants with subscale scores at the minimum or maximum values was > 20% for all subscales except GH and MH, showing that most subscales had floor or ceiling effects. However, no floor and ceiling effects were found for PCS-12 or MCS-12. The item discriminant validity assessment indicated that the correlation between each item and its

Tab. II. Participants' characteristics.

Characteristics	Total sample (n = 161) n (%)	Test-Retest sample (n = 70) n (%)	P-value*
Age (years)			0.14
< 65	82 (51)	31 (44)	
≥ 65	79 (49)	39 (56)	
Sex			0.81
Female	112 (70)	48 (69)	
Male	49 (30)	22 (31)	
Marital status			0.31
Married	117 (73)	48 (69)	
Not married/widowed	44 (27)	22 (31)	
Education levels			0.81
Primary/secondary	92 (57)	38 (54)	
Tertiary	69 (43)	32 (46)	
Employment status			0.84
Employed	17 (11)	7 (10)	
Unemployed/retired	144 (89)	63 (90)	

* Tested differences between participants who returned for the test-retest reliability and those who did not.

Tab. III. Summary of assessments of item, subscale and component score assumptions (n = 161).

	Mean	SD	Floor %	Ceiling %	Corrected item -subscale	Item – PCS-12	Item-MCS-12
Physical Health Component*	44.40	8.29	0.62	0.62	-	-	-
General Health (GH): health rating	44.72	19.85	1.86	3.73	0.40	**0.63**	0.31
Physical Function (PF)^	75.93	23.37	1.86	36.65	-		
Limited in moderate activities (PF1)	86.02	24.50	1.86	73.91	0.54	**0.54**	0.06
Limited in climbing several stairs (PF2)	65.84	29.80	6.83	38.51	0.51	**0.54**	0.24
Physical Role Limitation (RP)^	63.98	41.16	23.60	51.61	-		
Accomplished less due to physical health (RP1)	63.35	48.33	36.65	63.35	0.46	**0.55**	0.29
Limited in kind of work (RP2)	64.60	47.97	35.40	64.60	0.64	**0.70**	0.17
Bodily Pain (BP): Pain interferes with work	64.44	27.62	23.60	76.40	0.39&	**0.62**	0.17
Mental Health Component*	49.51	9.48	0.62	0.62	-		
Emotional Role Limitation (RE)^	72.67	37.89	16.14	61.49	-		
Accomplished less due to emotional health (RE1)	76.40	42.60	31.06	68.94	**0.38**&	0.24	**0.41**
Not work as carefully (RE2)	68.94	46.42	4.97	22.36	0.49	0.10	**0.53**
Vitality (VT): have a lot of energy (VT)	68.32	19.31	0.62	19.88	0.48	0.29	**0.58**
Mental Health (MH)^	68.01	20.03	0.62	8.69	-		
Felt calm and peaceful (MH1)	70.43	22.03	0.62	13.66	0.68	0.26	**0.74**
Felt downhearted and blue (MH2)	65.59	22.27	0.62	14.29	0.52	0.32	**0.67**
Social Function: physical/emotional interfere with social	76.24	23.68	0.62	36.65	0.47	0.18	**0.58**

*: using US algorithm to create a standardised score on a 0 to 100 scale; ^: mean of the two subscale items; all other subscales are composed of one item; Bold: highest correlation Item–PCS-12 an Item-MCS-12 are item-scale correlations (using Spearman correlation); #: floor and ceiling % was the proportion of participant with lowest and highest responses; &: A correlation < 0.40 indicates that the assumption of equality of item-subscale correlations was not supported.

corresponding composite summary was higher than the correlation between the item and the other composite summary score. Therefore, each item demonstrated item discriminant validity.

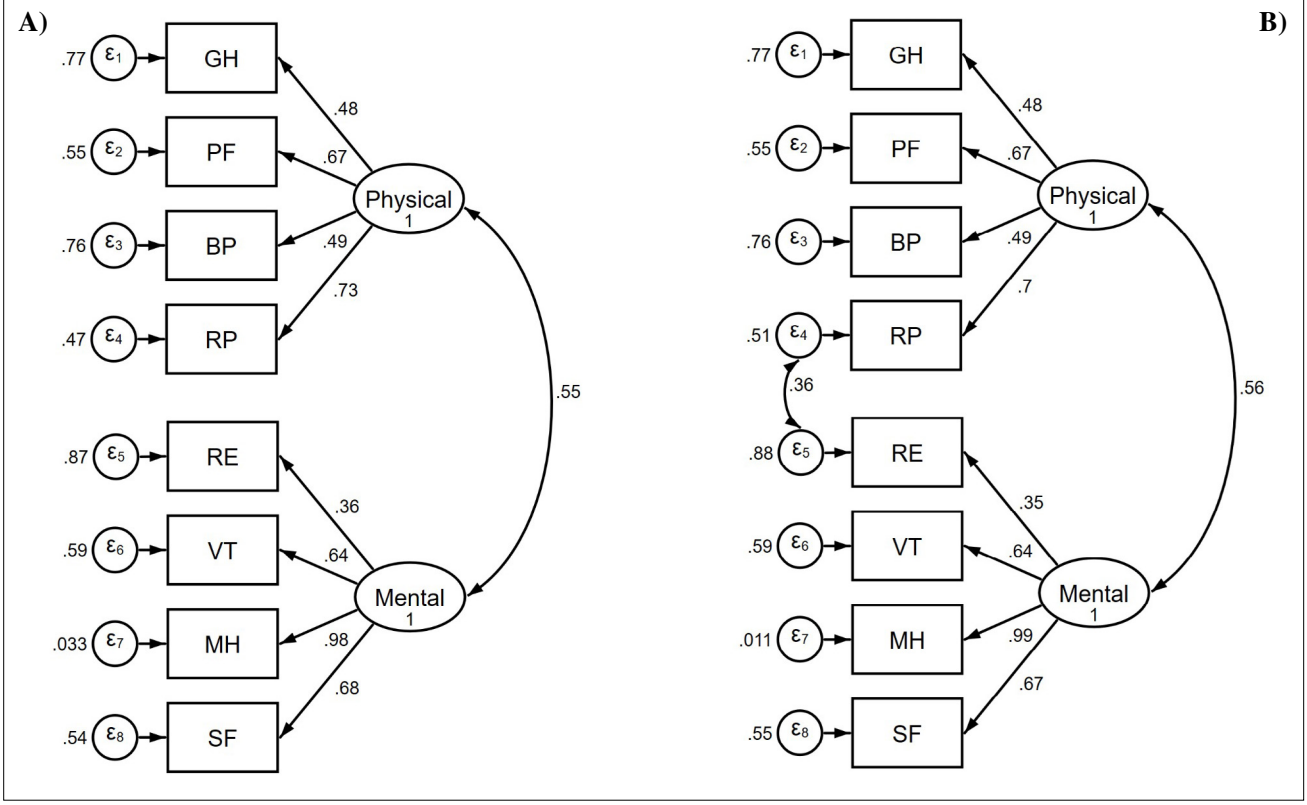
Internal consistency and test and retest reliabilities

The Cronbach alphas for PCS-12 (a = 0.72) and MCS-12 (a = 0.73) indicated acceptable internal consistency reliability. The ICC of items within PCS-12 (ICC = 0.88; 95% CI: 0.81-0.92) and within MCS-12 (0.75; 95% CI: 0.62-0.84) demonstrated excellent test-retest reliability of both composite summaries.

Confirmatory factor analysis

Figure 1 illustrates the factor loadings for both the original (Fig. 1a) and a modified factor structure (Fig. 1b), and Table IV summarises the structures' fit statistics. All fit indices except one (RMSEA = 0.08) indicated a moderate fit of the original structure to the data. The model specification suggested a correlation between RP and RE, and thus, in the modified structure, RP and RP were allowed to correlate. As a result, all fit indices indicated a good fit including RMSEA (= 0.04). In both structures, only RE, GH and BP loaded poorly into their composite summary (factor loadings < 0.50).

Fig. 1. The original structure (**1A**) and the modified structure (**1B**) of the Indonesian version of the SF-12 in a sample of middle-aged to older Indonesians. Each abbreviation is a separate subscale of the SF-12.



Tab. IV. Goodness-of-fit statistics of the original and the modified SF-12 structure (n = 161).

	Hypothesised structure	Modified structure
χ^2/df	2.04	1.26
RMSEA (90% CI)	0.08 (0.04-0.12)	0.04 (0.00-0.09)
CFI	0.94	0.99
TLI	0.92	0.98
SMSR	0.07	0.05

df: degree of freedom; RMSEA: root mean square approximation; CFI: comparative fit index; TLI: Tucker Lewis index; SMSR: standardised root mean square residual.

Convergent and divergent validity

As shown in Table V, divergent validity of the subscales was partially supported with weak inter-subscale correlations ($r < 0.40$), except for correlations between RP and PF ($r = 0.46$), RR and RE ($r = 0.43$), MH and SF ($r = 0.66$), and MH and VT ($r = 0.60$) Divergent validity was supported by weak correlations between MCS-12 and each subscale of PCS-12 and between PCS-12 and each subscale of MCS-12 ($r < 0.40$) and by a weak correlation between PCS-12 and MCS-12 ($r = 0.17$). There was support for convergent validity as there were strong correlations between subscales and their corresponding composite summary ($r > 0.60$), except for the correlations between MCS-12 and three subscales, RE ($r = 0.57$), VT ($r = 0.58$) and SF ($r = 0.58$), which were slightly below the threshold. Convergent validity was also supported by strong correlations between MCS-12 and MCS-36 and between PCS-12 and PCS-36 ($r > 0.60$).

Criterion validity

The effect size difference between PCS-12 and PCS-36 was 0.61, a medium effect size. The difference between MCS-12 and MCS-36 was 0.05, a very small effect size. Thus, criterion validity was demonstrated for MCS-12 but not for PCS-12.

Discussion

This is the first study to evaluate the psychometric properties of the SF-12 in a general Indonesian population. The overall findings provide satisfactorily evidence that the Indonesian version of SF-12 is a reliable and valid scale that can be used in monitoring and measuring HrQoL in middle-aged and older adults in Indonesia. These results thus add Indonesia and the Indonesian language to the growing list of cultures and languages for which the SF-12 is valid.

The mean scores for PCS-12 and MCS-12 in our study were 44.4 and 49.5, respectively. The lower PCS-12 score was also reported in studies of adults aged ≥ 60 years residing in community and nursing home settings in Guangzhou, China (39.9 and 49.1 for PCS-12 and MCS-12, respectively) [23], of Swedes aged ≥ 75 years (37.5 and 50.3, respectively) [16], and of community-dwelling African Americans aged ≥ 60 years (42.7 and 51.9, respectively). Similarly, community-dwelling adults aged ≥ 70 years in Israel had lower raw scores on subscales within PCS-12 than on subscales within MCS-

Tab. V. Correlations among subscales and composite summaries computed for assessing convergent and divergent validity.

	GH	PF	RP	BP	RE	VT	MH	SF	PCS-12	MCS-12	PCS-36	MCS-36
GH	1.00											
PF	0.30	1.00										
RP	0.39	0.46	1.00									
BP	0.25	0.31	0.31	1.00								
RE	0.28	0.21	0.43	0.21	1.00							
VT	0.26	0.25	0.26	0.22	0.25	1.00						
MH	0.23	0.27	0.37	0.34	0.32	0.60	1.00					
SF	0.09	0.26	0.29	0.27	0.19	0.38	0.66	1.00				
PCS-12	0.63	0.62	0.72	0.62	0.20	0.29	0.31	0.18	1.00			
MCS-12	0.31	0.18	0.27	0.17	0.57	0.58	0.79	0.58	0.17	1.00		
PCS-36	0.55	0.49	0.55	0.46	0.50	0.56	0.68	0.50	0.64	0.71	1.00	
MCS-36	0.54	0.46	0.68	0.48	0.47	0.47	0.62	0.45	0.70	0.62	0.63	1.00

GH: general health; PF: physical function; RP: role-physical; BP: bodily pain; VT: vitality; RE: role-emotional; MH: mental health; SF: social functioning; PCS: physical component summary; MCS: mental component summary; Note: Statistics in the table are Spearman correlation coefficients.

12 [17]. The lower PCS-12 than MCS-12 scores seen in our study and in these previous studies were not seen in a validation study of adults of all ages (e.g., aged ≥ 18 years) in nine European countries and the US [15]. In that study, mean scores were approximately 50.0 for both PCS-12 and MCS-12 [15]. The findings of our study and of these studies together suggest that physical HRQoL is negatively affected more than mental HRQoL as we age. We also found that the mean and standard deviation was equivalent for all SF-12 items except for Items 2 and 3. Item 2 asks about physical function in conducting moderate activities, and Item 3 asks about physical function in conducting vigorous activities. Given our population was composed of middle-aged and older adults, it was not surprising that Item 2 would have a higher mean than Item 3. This finding has been shown in other studies [17, 22]. The standard deviations, however, were comparable between these items, supporting the summation of these items into a subscale.

Although most subscales showed floor or ceiling effects, no floor or ceiling effects were observed for the SF-12 composite summaries, indicating the ability of PCS-12 and MCS-12 to capture a full range of health states in our study population. Our findings were similar to the findings in a general population in Iran [10]. In that study the percentage of participants who scored at the lowest level (i.e., floor effect) and highest level (i.e. ceiling effect) was less than 1% for PCS-12 and for MCS- 12. Our findings do not, however, support findings from two Israeli studies, one of a general adult population [14] and the other of an older adult population [17]. Those studies showed minimal floor and ceiling effects in items with more than three response options. We found acceptable corrected item-scale correlations for all but two items for which correlations were slightly below the threshold for acceptable. Consistently high correlations between items and their corresponding component summary score were also found in two previous studies of older adults in China [22, 23]. Although we found acceptable items' equivalency and discriminant validity as well minimal floor and ceiling effects for PCS-12 and MCS-12, the considerable ceiling or floor effects were found for most subscales, thus, the assumptions for creating subscales for summated scoring the items in our study population warrant further investigation.

Internal consistency reliability of the component summaries was supported. Internal consistency values were similar to those reported previously for a sample of Indonesian patients with cardiovascular disease (PCS-12: a = 0.79; MCS-12: a = 0.77) [33] and from a sample of adults from the Iranian general population (PCS-12: a = 0.73; MCS-12 a = 0.72) [10]. However, higher values have been reported for other populations including for older adults in Israel (PCS-12: a = 0.86; MCS-12: a = 0.71 [17]) and for a general population in Sweden (PCS-12: a = 0.85; MCS-12: a = 0.76) [16], and for a general population in China (PCS-12: a = 0.81; MCS-12: a = 0.83) [23]. Nonetheless, all these findings support the internal consistency reliability of SF-12 across different populations including in our study population.

Our study showed that the component summaries have good 1-week test-retest reliability (PCS-12: ICC = 0.88; MCS-12: ICC = 0.75) in middle-aged and older Indonesians. Other studies have shown acceptable test-retest reliability of the SF-12 in different populations, such as in a general population in Israel (PCS-12: ICC = 0.92; MCS-12: ICC = 0.85) [14] and in a general US population (PCS-12: ICC = 0.89; MCS-12: ICC = 0.76 [8]. Our findings thus support those of previous studies.

We showed that the original two-factor structure of the SF-12 moderately fitted our data (RMSEA = 0.08). The fit of data to this structure has varied across studies. A study from Iran [10] showed a moderate fit (RMSEA = 0.09), as we did. In contrast, in samples of older adults in China [23] the structure fit the data fit well (RMSEA < 0.08) whereas in a general Danish population [51] the fit was poor (RMSEA = 0.12). Our findings along with these previous findings suggest that the algorithms used for creating component summary scores may need to be modified for different populations. Furthermore, we found a low factor loading for the RE subscale. The modification indices suggested that RE and RP be correlated. The wordings and response options of these subscales were almost identical. They only differed in whether limitations were caused by physical or emotional problems; thus, adding a correlation

between these subscales appears to be plausible. Adding the correlation improved model fit (RMSEA = 0.04). This evidence further suggests that specific scoring algorithms for specific populations may be required.

As expected, the correlations between the subscales that compose PCS-12 (PF, RP, BP and GH) and PCS-12 were stronger than the correlations between these subscales and MCS-12. Likewise, the correlations between the subscales that compose MCS-12 (VT, SF, RE and MH) and MCS-12 were stronger than the correlations between these subscales and PCS-12. These findings support the convergent and divergent validity of the subscales, as shown in previous studies of older adults in China [22].

We also found moderate correlations between PCS-12 and PCS-36 (r = 0.64) and between MCS-12 and MCS-36 (r = 0.62), findings that support the component summaries' convergent validity. Moderate correlations were also found in the study of older adults in China [22]. Our estimates, however, were lower than those reported in the initial validation study of the US general population [8], in a study of the Australia general population (r ≥ 0.95) [13], and in a study in the general Hong Kong population (r ≥ 0.94). One explanation for the difference in findings between our study and findings of these previous studies was the difference in the administration of the SF-12. The researchers in the earlier studies administered the SF-36 only and then selected out the items used in the SF-12 for validating the SF-12. We administered the SF-12 separately from the administration of the SF-36, which could have resulted in lower correlations between SF-12 and SF-36 component summaries. Our lower correlations consequently decreased the total variance of the SF-36 that could be explained by the SF-12. Additional studies are required to explore further whether the SF-12 adequately replicates the SF-36 in the Indonesian context. As the previous studies' estimates were derived from general populations with wider age spans and with relatively large sample sizes [8, 13], exploration of the convergent validity in Indonesia likewise may require a more heterogenous and larger sample.

Last, we found a considerable effect size difference between PCS-36 and PCS-12 (*Cohen's d* = 0.60) although a negligible effect size difference between MCS-36 and MCS-12 (*Cohen's d* = 0.05). The responses to SF-12 items were weighted using a US-standard algorithm, and so our findings raise a question about the appropriate algorithms used for weighing items within PCS-12 in our population. Therefore, further investigation into appropriate regression weights for the Indonesian version of PCS-12 is needed. Finally, although the component summary scores of the SF-12 may not fully capture those in the SF-36, the overall evidence suggests that the Indonesian version of the SF-12 possesses adequate reliability and validity for use in populations of healthy, community-dwelling middle-aged and older adults in Indonesia.

Strengths and limitation

A major strength of our study was that we thoroughly investigated the psychometric properties of the Indonesian SF-12 using well-used guidelines [15, 39]. Another strength was that we gave participants the SF-12 and SF-36 as separate surveys. In most other validation studies of the SF-12 the SF-36 was administered, and the 12 relevant items were selected from the SF-36 to create the SF-12. Our approach better replicates what would be expected when the SF-12 is used as an alternative to the SF-36. Another strength was that we used the US norm-based scoring algorithms commonly used in studies worldwide for calculating PCS-12 and MCS-12 [41]; therefore, our results can be used for cross-cultural HrQoL comparisons with other studies that use the same algorithms. However, caution is warranted in making comparisons to studies that use version 2 of SF-12 (we used version 1), that recruit participants with dissimilar characteristic to our participants (ours were generally healthy, community-dwelling adults), or that administer the SF-12 using other modes (in this study the SF-12 was self-administered and was separately measured from the SF-36).

Limitations of the study also need to be acknowledged. First, although the packet of surveys was self-administered, staff supervised the process and asked participants to complete the surveys. Our findings might not be replicated if surveys were self-administered without supervision. Second, the ratio of participants to number of items/parameters in this study was above 10:1, an acceptable sample size for CFA analysis, as suggested by Jackson [40]; however, the ratio was below the sample size for CFA of at least 200 participants that is recommended by Myers [52]. Third, the study was conducted in a community-dwelling setting, thereby limiting the generalizability to other populations including adults in residential care and younger adults.

Conclusions

This study provides the first evidence that the SF-12 is a reliable and valid measure of HrQoL in Indonesian middle-aged and older adults. The study also provides preliminary evidence that the MCS-12 can be used instead of the MCS-36, the gold standard measure of mental HRQoL, but that a more appropriate algorithm for computing PCS-12 scores for the Indonesian middle-aged and older populations is warranted. To further establish the validity of the Indonesian version of the SF-12, psychometric testing of the scale in younger populations is warranted, to assess whether our findings apply to younger age groups. In addition, studies of responsiveness to change over time are warranted, to determine whether the scale is sensitive to time-related changes in health status, critical for use in health care settings.

Ethical approval

The study protocol was approved by the Human Ethics Committee of Gadjah Mada University (approval No. KE/0142/02/2019).

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: NIA. Data curation: NIA. Formal analysis: NIA, KCH. Funding acquisition: NIA. Methodology: NIA, KCH. Project administration: NIA. Visualization: NIA: Writing - original draft: NIA, KCH. Writing - review & editing: NIA, KCH.

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Pesearch paper

Tobacco consumption in Chilean university students and associations with anthropometry, eating habits and sleep quality multicentric study

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Keywords

Tobacco • University students • Food • Breakfast • Health

Summary

Tobacco Consumption (TC) is one of the main causes of the deterioration of health; however, there are few studies linking its consumption with diet and nutrition among university students. The objective of this study is to test the association of smoking with anthropometry, diet and sleep quality among Chilean university students. Cross-sectional study. University students (n = 1454) from the North, South and Central parts of Chile were evaluated. A self-assessment survey was used to evaluate healthy and unhealthy eating habits. Nutritional status was evaluated by Body Mass Index (BMI). Two surveys were used to assess sleep quality: the Questionnaire of Insomnia and the Epworth Scale. Finally, participants were consulted about Tobacco Consumption: 30% of the students consume tobacco and have a higher score in unhealthy food consumption, less frequent weekly breakfast consumption (< 0.01), lower daily fruit (< 0.01) and vegetables (< 0.05) consumption, higher alcohol consumption (< 0.05) and daily junk food consumption (< 0.05) compared to non-consuming students. Men who consume tobacco present greater insomnia (< 0.001), sleep latency (< 0.001) and daytime sleepiness (< 0.05) compared to non-consumers; and women who consume tobacco have a higher weight (< 0.001) and BMI (< 0.01). When performing logistic regression, tobacco consumption is positively associated with major alcohol consumption (< 0.001), whereas fish (< 0.05) and vegetable (< 0.05) consumption was negatively associated. In conclusion, students of both sexes who smoke have more unfavorable health factors and a poorer quality of life.

Introduction

Between 1960 and 2000, Chile has experienced economic, social and health changes that have influenced lifestyles related to eating habits, sedentary lifestyles, and consumption of tobacco, alcohol and other drugs [1]. Many of these changes have gone hand in hand with the deterioration of the quality of life. In the last two decades an increase in malnutrition due to excess has been reported, affecting 64.5% of the population over 18 years of age [2]. Chile is now among the top countries in the Americas, surpassed only by the United States and Mexico, on the World Health Organization's list of countries with the highest prevalence of obesity [3].

University years are a period of transition to early adulthood where lifestyles associated with risk behaviors are established and the risk of developing obesity and chronic diseases increases [4]. Lifestyle characteristics of university students include factors related to the later development of disease: low economic capital, poor eating habits, frequent skipping of meals, high fast food consumption [6], sedentary lifestyle, smoking, and stress [5-8].

Tobacco consumption is one of the main causes of health deterioration, associated with several chronic diseases and is positively correlated with a decrease in physical activity [9]. Chile has the highest prevalence of tobacco consumption in Latin America, both among youth and adult population; the 2016-2017 National Health Survey indicates that 33.3% of the population currently smokes, with rates greater in men than in women (37.8 *vs* 29.1%) [2]. The average age of the first cigarette is 15 (a prevalence rate that has been increasing in recent years), but the habit is established at college age. On the other hand, sleep problems have been shown to be associated with the pathophysiology of severe disorders related to smoking [10]. The university population is especially prone to develop sleep disorders due to external factors (social and environmental) and lifestyle habits that can deteriorate their quality of life.

Several recent studies have tried to relate tobacco consumption with Body Mass Index (BMI), eating habits and sleep quality; however, there are few studies, especially in Latin America, relating these 3 variables.

The objective of this study was to test the association of smoking with anthropometry, diet and sleep quality among Chilean university students.

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Method

We conducted a descriptive study with 1455 students from 6 universities: University of Antofagasta (located in Northern Chile), University San Sebastian (in Central and Southern Chile), University Autónoma de Chile (in Central and Southern Chile), University Bernardo O Higgins (Central Chile), University Playa Ancha (Central Chile), and the University Católica de Temuco (Southern Chile). The sample was selected using non-probabilistic criteria. All students present at the time of the evaluations were included. Participants provided informed consent. Reasons for non-participation included: unavailability due to internships, illness, or failure to sign the informed consent. The study was developed following the Declaration of Helsinki and was approved by the Ethics Committee of the Universidad Católica de Temuco.

Questionnaires

Eating habits survey

The Food Habits Survey created by Durán et al. [11] was used. The survey is self-administered and measures healthy and unhealthy eating habits. The frequency of health habits, such as the consumption of food groups recommended in the Chilean dietary guidelines is assessed with nine items with a minimum score of 1 (does not consume) and a maximum of 5 (suggested portion per day or week). Responses are added up together to obtain a total value between 9 to 45 points; a higher value indicates healthier eating habits. Unhealthy eating habits are assessed with six items: consumption of sugary drinks, alcohol, fried foods, fast food, snacks, and adding salt to meals without tasting them first. Available responses range from 1 (does not consume) to 5 (> 3 portions per day/week) or from 1 to 3 for the question about salt. Response values are added up and the total ranges from 6 to 28 points, with higher values indicating poorer eating habits.

Insomnia Questionnaire or Insomnia Severity Index (ISI)

The ISI is a self-report questionnaire to assess the nature, severity and impact of insomnia [12,13]. A score between 0 and 7 indicates absence of clinical insomnia, 8-14 subclinical insomnia, 15-21 moderate clinical insomnia and 22-28 clinical insomnia (severe).

Epworth Sleepiness Scale (ESE)

The ESE evaluates the propensity to fall asleep in eight different sedentary situations. This scale is self-administered and response options for each item range between 0-3. At the end, cumulative scores between 0 and 24 are obtained, where higher scores represent a greater degree of drowsiness [14].

Information on the amount of sleep and sleep latency was also asked.

Weight and height were measured. Participants were weighed in light clothing using a mechanical scale (SECA) with a maximum capacity of 220 kg and 50 g precision. Height was measured with a height rod that is incorporated in the scale. Body mass index (BMI) was calculated to categorize the nutritional status according to WHO criteria [15].

Finally, participants were asked about tobacco consumption. Participants who reported having smoked in the last week were labeled smokers.

Statistical analysis

The results are presented as mean ± standard deviations and as percentages according to the type of variable. Kolmogorov-Smirnov normality test was used to determine the normality of the variables. Participants were analyzed by groups, according to their nutritional status. For categorical variables, the Chi-square test was used. For non-categorical variables the T-Test used. Logistic regression was used to assess associations with tobacco consumption. The level of significance used was $\alpha = 0.05$ in all cases. STATA 12.1 was used for analyses.

Results

Out of the 1455 students surveyed, 1439 had complete data. Figure 1 shows a high overall prevalence of tobacco consumption (30.1%), with prevalence starting high in the first year of study and decreasing in the second year, before increasing again in subsequent years. However, no significant differences were observed (0.073).

Among participants who exercised, 32 smoked and 29% of those who did not exercise, smoked ($p > 0.05$).

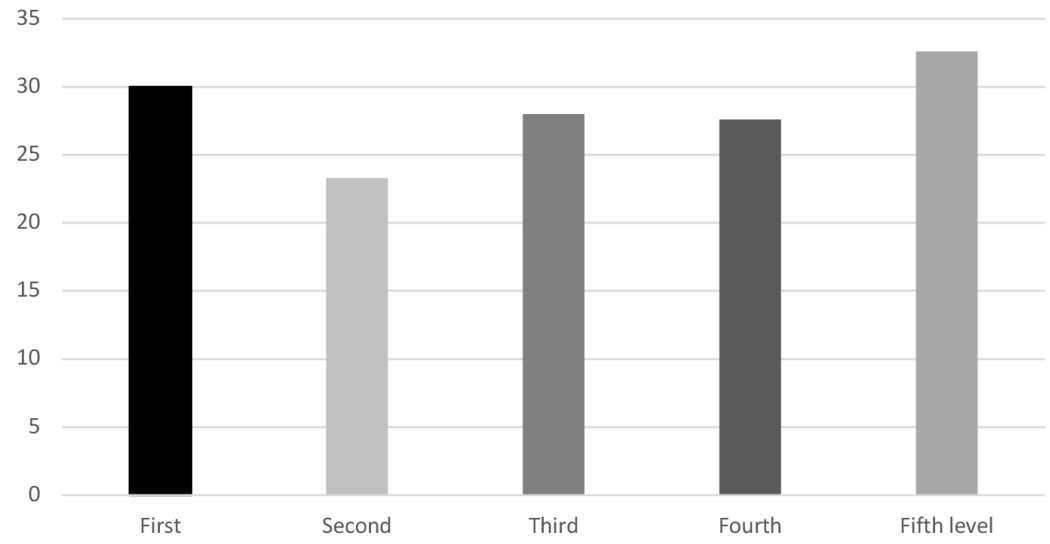
Table I shows that students who smoke, regardless of sex, have significant differences in BMI, height, score for unhealthy foods, greater daytime sleepiness, insomnia, sleep latency and greater sleep hours, compared to those who did not smoke.

Table II shows that male smokers have a less favorable sleep quality compared to non-smokers, reflecting greater daytime sleepiness, insomnia, sleep latency and also had higher unhealthy food scores. In contrast, female smokers weighed significantly more, had a higher BMI and unhealthy food score compared to non-smoking women, with no differences observed for sleep variables.

Figures 2, 3, 4 and 5 show a dependent and significant relationship between smoking and an unfavorable diet, reflected in lower frequency of breakfast during the week, lower daily fruit consumption, higher daily consumption of junk food (pizzas, hotdogs, hamburgers, fries or *sopaipillas*) and higher consumption of alcoholic beverages compared to non-smoking students ($p < 0.05$). However, as shown in Figure 6, we observed that smokers reported greater daily consumption of vegetables compared to non-smokers.

Table III shows when performing logistic regression, that the consumption of tobacco is positively associated with the consumption of alcohol, while is negatively associated with the consumption of fish and vegetables.

Fig. 1. Tobacco consumption by year of university study (Chi Square = 0.073).



Tab. I. Comparison of anthropometry, food survey score, insomnia and daytime sleepiness by smoking status [1].

	Non-smokers (n = 1015)	Smokers (n = 424)	P-value[2]
Weight (kg)	61.6 ± 10.5	64.1 ± 11.7	0.059
Height (m)	1.62 ± 0.07	1.63 ± 0.08	0.025
BMI (k/m^2)	23.2 ± 3.1	23.8 ± 3.4	0.001
Healthy foods score	55.1 ± 7.3	54.7 ± 7.2	0.375
Unhealthy foods score	12.7 ± 3.3	14.3 ± 3.7	0.011
Epworth	7.3 ± 4.9	8.0 ± 5.0	0.033
Insomnia score	10.2 ± 4.8	10.9 ± 4.9	0.015
Sleep latency (min)	26.3 ± 30.3	31.4 ± 31.4	0.007
Sleep duration (h)	7.6 ± 1.5	7.8 ± 1.6	0.028

[*] Values are mean ± SD. [2] Student T test.

Tab. II. Comparison of anthropometry, food survey score, insomnia and daytime sleepiness by smoking status, stratified by sex [1].

Men	Non-smokers (n = 231)	Smokers (n = 111)	P-value[2]
Weight (kg)	72.3± 10.9	73.7 ± 13.1	0.342
Height (m)	1.72 ± 0.06	1.72 ± 0.07	0.656
BMI (k/m^2)	24.3 ± 3.2	24.5 ± 3.4	0.480
Healthy foods score	55.1 ± 7.3	54.7 ± 7.2	0.061
Unhealthy foods score	12.7 ± 3.3	14.3 ± 3.7	0.001
Epworth	7.3 ± 4.9	8.0 ± 5.0	0.030
Insomnia score	10.2 ± 4.8	10.9 ± 4.9	0.001
Sleep latency (min)	26.3 ± 30.3	31.4 ± 31.4	0.001
Sleep duration (h)	7.6 ± 1.5	7.8 ± 1.6	0.199
Women	**Non-smokers (n = 784)**	**Smokers (n = 313)**	**P-value[2]**
Weight (kg)	58.7 ± 8.4	60,9 ± 9.3	0.001
Height (m)	1.59 ± 0.05	1.60 ± 0.05	0.137
BMI (k/m^2)	22.9 ± 3.0	23.6 ± 3.3	0.002
Healthy foods score	55.1 ± 7.2	55.2 ± 7.5	0.877
Unhealthy foods score	12.5 ± 3.2	14.0 ± 3.5	0.002
Epworth	5.1 ± 4.5	6.3 ± 4.9	0.072
Insomnia score	8.0 ± 4.8	8.6 ± 4.9	0.184
Sleep latency (min)	26.5 ± 31.7	29.0 ± 30.2	0.249
Sleep duration (h)	7.6 ± 1.4	7.7± 1.5	0.106

[1] Values are mean ± SD. [2] Student T test.

Fig. 2. Breakfast consumption by smoking status (Chi Square = 0.004).

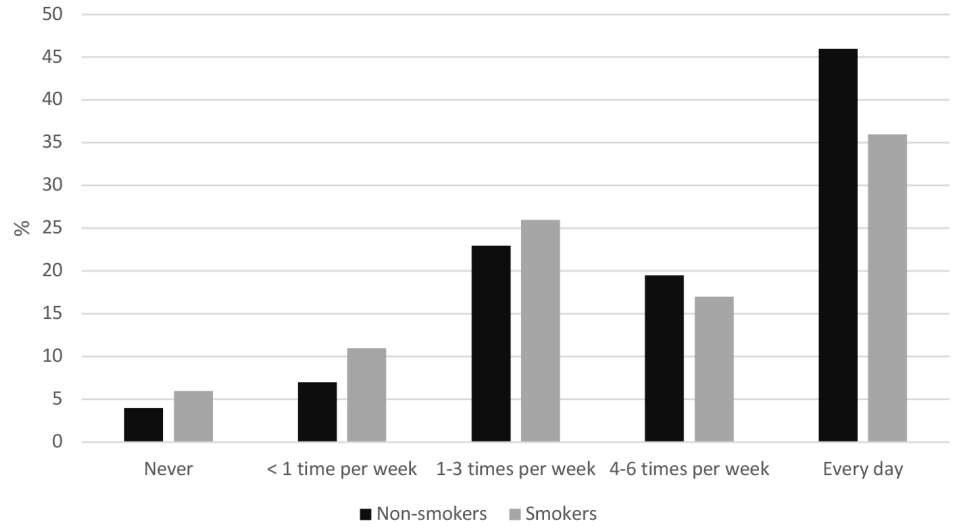


Fig. 3. Daily fruit consumption by smoking status (Chi Square = 0.002).

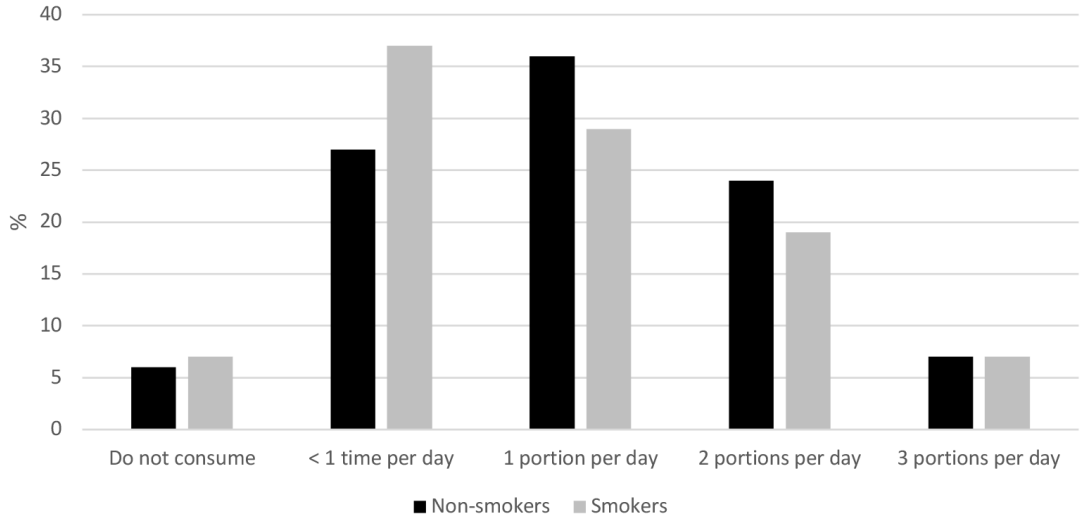


Fig. 4. Daily alcohol consumption by smoking status (Chi Square = 0.001).

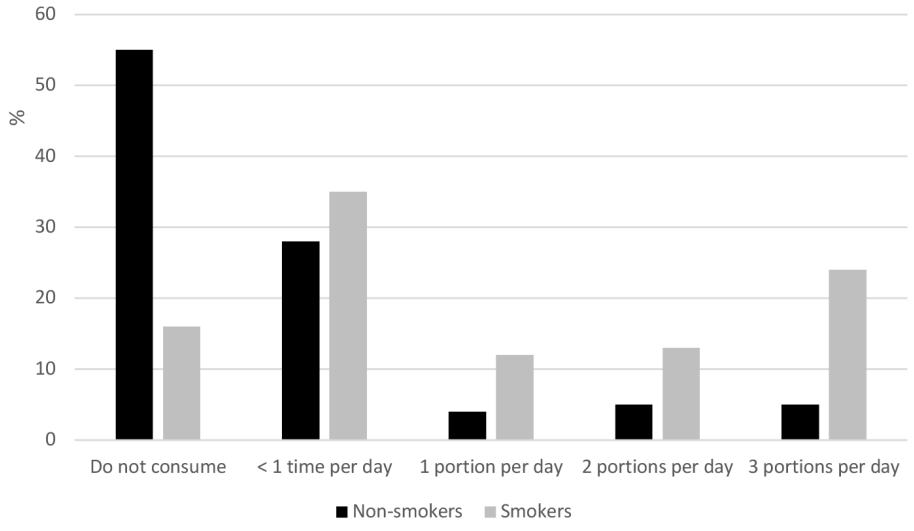


Fig. 5. Daily junk food consumption by smoking status (Chi Square = 0.02).

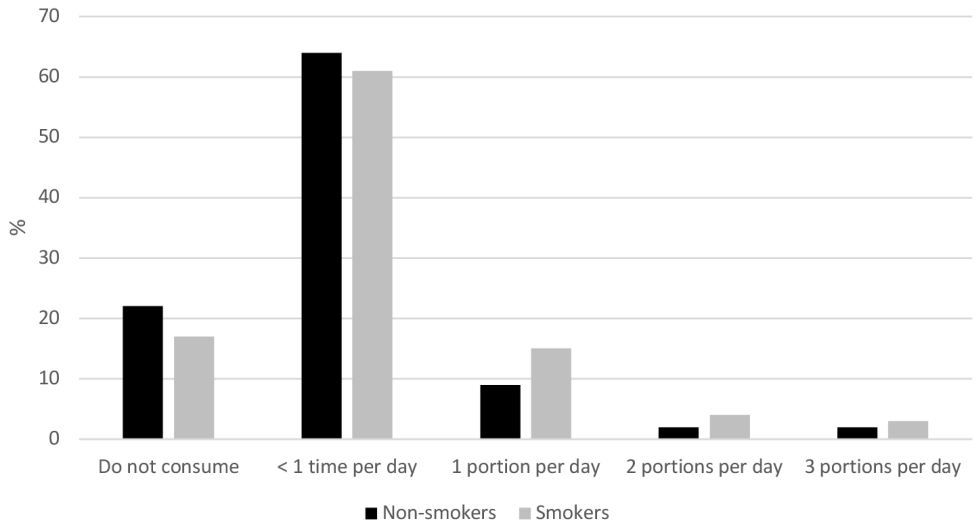
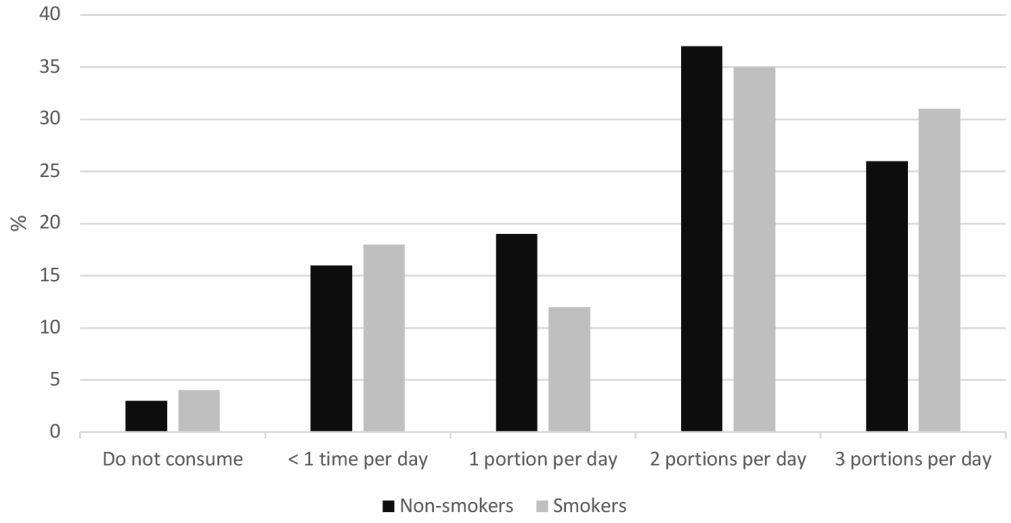


Fig. 6. Daily vegetable consumption by smoking status (Chi Square = 0.03).



Discussion

The main result of this study is that university students of both sexes who smoke have higher unfavorable health factors and a poorer quality of life: they present a higher unhealthy food consumption score, lower frequency of weekly breakfast consumption, lower daily fruit consumption, and higher daily consumption of alcohol and junk food compared to non-smoking students. Male smokers had greater insomnia, sleep latency and daytime sleepiness compared to non-smokers; and female smokers had higher weight and BMI.

Smoking is a chronic and addictive disease, considered by the WHO as the main cause of avoidable death in the world. It is one of the most important risk factors for disease and death in Chile and is related to chronic obstructive pulmonary disease, pulmonary emphysema, lung cancer, laryngeal cancer, and heart and cerebrovascular diseases [16]. It causes premature death (shortens life by 5-10 years) in more than 50% of smokers, affecting the respiratory and cardiovascular systems, and can cause various neoplasms in the body [17]. According to recent studies that evaluated the age at which the smoking begins, 1 in 3 smokers starts in adolescence or between 18 and 25 years old. We also note that the prevalence of smoking among female has approached that of men in recent years [18-20].

The university population modify their lifestyle to be accepted by their peers. Some studies define university students as a vulnerable group, since many of the healthy habits for adult life can be acquired and modified during this stage [1]. One of the main results obtained in this study is that smoking was associated with unhealthy eating habits. Among men, there

Tab. III. Factors associated with tobacco consumption.

	Estimate	Std. Error	T value	P-value
(Intercept)	-0.084	0.175	-0.484	0.628
Age	0.003	0.005	0.618	0.536
Sex	0.052	0.035	1.461	0.144
nutritional status	0.023	0.052	0.442	0.658
Breakfast	0.045	0.028	1.617	0.106
Dairy products	0.010	0.049	0.208	0.835
Fruits	-0.083	0.077	-1.088	0.276
Vegetables	-0.068	0.032	-2.073	0.038
Fish	-0.096	0.038	-2.518	0.011
Legumes	-0.034	0.031	-1.092	0.275
Bread	-0.007	0.033	-0.219	0.826
Lunch	0.011	0.027	0.404	0.686
Dinner	0.033	0.044	0.752	0.452
Health food habits	-0.015	0.032	-0.464	0.642
Soft drik	0.001	0.034	0.045	0.964
Alcohol	0.307	0.028	10.68	< 0.001
Fries food	0.034	0.054	0.64	0.522
Salt	0.027	0.027	1.016	0.309
Pizza/hog-dog	-0.007	0.037	-0.201	0.840
Cookies	-0.048	0.033	-1.445	0.147
Unhealthy eating habits	0.017	0.042	0.406	0.684
Epworth	0.031	0.031	1.012	0.311
insomnia	0.002	0.029	0.079	0.936
Sleep duration	-0.001	0.001	-0.672	0.501
Sleep Latency	0.016	0.032	0.517	0.605
Physical activity	-0.001	0.001	-0.852	0.394

was a tendency towards a lower score for healthy eating in non-smokers, versus smokers, although the difference was not statistically significant. An attempt has been made to evaluate the relationship between healthy eating and smoking. In a cross-sectional study, young people who consumed fruit ≥ 2 times a day were 53% less likely (RR = 0.47, $p < 0.05$) than those who did not normally consume fruit to be more heavy smokers. Longitudinally, the association of fruit and tobacco consumption was not significant (RR = 0.61, p = 0.28). There were no significant associations between the consumption of vegetables and smoking. The consumption of fruits, but not the consumption of vegetables, was inversely associated with the frequency of smoking cross-sectionally, but not longitudinally [21]. Another study conducted in a Japanese population, compared the consumption of food and nutrients between persons who consumed tobacco and non-tobacco users, showing that there was a lower intake of vegetables and fruits rich in antioxidants, preventive factors for many diseases, in those who consumed tobacco. In men, smoking was positively related to the consumption of rice, three alcoholic beverages (sake, beer and whiskey), carbohydrates and other eight foods/nutrients ($p < 0.05$) and negatively associated with consumption of animal protein, fat, fatty acids, dietary fiber, isoflavones and 36 other foods/nutrients ($p < 0.05$ for all foods). In contrast, in women, smoking was positively associated with the intake of 13 foods/nutrients, while being negatively associated with the consumption of rice, energy, dietary fiber and other 14 foods/nutrients ($p < 0.05$ for all food) [22]. These studies support the results obtained in our work, which shows that smokers have a lower nutritional value compared to non-smokers, with less frequent breakfast consumption during the week, less daily fruit consumption, and higher frequency of junk food and alcoholic beverages consumption, compared to non-smokers ($p < 0.05$). However, it was observed that smokers consumed more daily portions of vegetables compared to non-smokers. Attempts have been made to postulate mechanisms that explain the choice of unhealthy foods in smokers, and the explanation could be at the level of the brain. Jastreboff et al. compared responses in different regions of the brain between smokers and non-smokers during an exposure to their favorite food. Those who consumed tobacco exhibited decreased activation in the caudate, putamen, insula and thalamus [23].

In our study, smoking was associated with greater sleep latency, insomnia and daytime sleepiness. These results are in agreement with other studies [24-28]. Sleep disorders that result in insufficient sleep have been linked with negative physical, cognitive and public health outcomes. Tobacco consumption has been shown to be a predictive variable of sleep disturbances [23]. This interaction was also observed

in individuals with chronic rheumatic diseases, who were more likely to report an average < 6 h of sleep per night and frequent insomnia compared to individuals with a chronic rheumatic condition that did not consume tobacco [25]. A study in US individuals also showed that smokers reported significantly less total sleep time, greater sleep latency, greater difficulty in falling asleep, maintaining sleep and waking earlier than desired compared to those who did not consume tobacco, a result similar to our study. Individuals who were former tobacco users reported alterations similar to non-smokers and smokers experienced lower quality sleep than non-smokers, compared with those who had never used tobacco, smokers had a significantly higher probability of self-reported snoring (OR = 2.0, 95% CI = 1.56-2.56) and short sleep (OR = 1.68, CI 95% = 1.35-2.10; OR = 1.38, 95% CI = 1.09-1.74). A dose-response relationship was observed between amount smoked and sleep symptoms [26]. In multivariate analysis, no significant interaction was observed between sex and smoking for snoring, short sleep or poor sleep. In a study conducted among US adults, current TC was independently associated with greater odds of snoring and sleeping poorly [27]. Sleeping is considered a healthy behavior. Within the relationships that have been described in the literature, persons with a better diet also have better sleep quality and smokers are more likely to report insomnia and insufficient sleep [28].

Although tobacco consumption has been associated with relatively thinner body mass and smoking cessation with weight gain [29], the brain mechanisms underlying these relationships are not well understood and the results have been contradictory in studies that have tried to understand these variables. Compared to non-smokers, smokers have diminished nervous system responses to non-gratifying tobacco stimuli, however, brain response to favorite foods in relation to smoking status have not been investigated. During the exposure to their favorite food, smokers exhibited decreased activations in the caudate, putamen, insula and thalamus, compared to non-smokers. Neuronal responses during stress and neutral relaxation conditions were similar between the groups that smoke versus those who do not and subjective indices of food cravings were similar between groups. Relatively diminished neural responses to favorite food signals in smokers can contribute to lower BMI [23].

Among the main metabolites associated with tobacco consumption, are nicotine, cotinine, thiocyanate, o-cresol sulfate, and hydroxycotinine, among others. Studies have postulated that nicotine could be the cause of weight gain, however it has been shown to stimulate the basal metabolic rate of smokers [30]. TC and nicotine directly affect the metabolism of glucose and body weight as a result of changes in metabolism, activating lipoprotein lipases that break triglycerides to form free fatty acids, which activates the sympathetic nervous system. These are among other changes that result in greater energy consumption and weight loss. Weight loss is associated with the direct stimulation of the melanocortin 4 receptor (MC4-R), which leads lower food consumption and lower leptin levels. It also stimulates the sympathetic nervous system, which increases adrenaline levels and noradrenaline, lipolysis among other processes [31]. Another study showed an inverse correlation between leptin concentrations and nicotine dependence in people who used tobacco [32]. In contrast, our study shows that smokers weighed more and had a higher BMI, especially in women. It is possible that these results are explained by the fact that non-smokers had healthier eating habits, which is protective for weight gain.

The weaknesses of this study include that the number of cigarettes per day was not quantified. In addition, this was a cross-sectional study, thus causality cannot be inferred. The study had several strengths. We were able to evaluate specific relationships between foods consumed, eating habits and tobacco consumption. We considered several variables – diet, physical activity, anthropometry, and sleep quality – which are not usually evaluated together.

Conclusions

University students who smoked were significantly different from non-smokers in factors related to deteriorating health: higher BMI, greater daytime sleepiness, insomnia and sleep difficulties, lower frequency of weekly breakfast consumption, lower fruit consumption, higher consumption of junk food and alcoholic beverages and a higher unhealthy food score. However, tobacco consumption was associated on a differentiated manner according to sex. In men, tobacco consumption had a negative effect on daytime sleepiness, insomnia and sleep difficulties and in women, it was associated with higher weight and BMI.

Abbreviations

Body Mass Index (BMI); Insomnia Severity Index (ISI); Epworth Sleepiness Scale (ESE); World Health Organization (WHO); melanocortin 4 receptor (MC4-R); Unites States (US).

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

SDA, VV; Conceptualization. Methodology, formal analysis, investigation, data curation, writing, original draft, writing, review and editing. Conceptualization. Methodology, formal analysis, investigation, data curation, writing, original draft, writing, review, editing and Project administration, GO, MF, MV, MC, VE, FM: Methodology, Investigation, Writing – Review & Editing.

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Pesearch paper

Utilization pattern of antenatal care and determining factors among reproductive-age women in Borama, Somaliland

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Keywords

Antenatal Care • Maternal Health Service • Utilization • Pregnancy • Somaliland

Summary

Background. *Antenatal care is essential care given during pregnancy, to diagnose and treat complications that could endanger both the lives of mother and child. The risk of dying from pregnancy-related issues is often associated with a lack of access to antenatal care services. This issue is a prominent matter in developing countries such as Somaliland which has one of the highest maternal mortality rates in the world.*
Objective. *The objective of this study is to determine the frequency and timing of antenatal care utilization and factors influencing it among reproductive-age women.*
Methods. *A population-based cross-sectional survey is conducted among 330 randomly selected mothers who gave birth in the past two years in Borama, Somaliland.*
Result. *Although a significant number of women utilized antenatal care in their pregnancy only 31.1% initiated the first visit within the first trimester and 48.3% received less than the recommended four visits. Fewer antenatal care visits are significantly associated with age (OR = 3.018; CI = 1.264-7.207), gravida (OR = 3.295; CI = 1.200-9.045), and gestation age (OR = 1.737; CI = 1.013-2.979). Early marriage (OR=0.495; CI = 0.252-0.973), and large family size (OR = 3.952; CI = 1.330-11.742) are associated with delay in the commencement of the first antenatal care visit.*
Conclusion. *Young women, women with multiple pregnancies, women married at a young age, and women with a large family size have a higher probability of delaying prenatal care and having fewer visits. Based on the findings, uplifting the socioeconomic status and literacy level of women through community-based education and developing strategies that would take the determining factors into account may contribute to improved and adequate utilization of antenatal care.*

Introduction

Despite the decrease in global maternal mortality, the number of deaths remains unacceptably high, especially in low-income countries. Complications during pregnancy and childbirth are the major cause of death and disability in reproductive-aged women [1]. Most of these pregnancy-related deaths can be prevented by simple cost-effective maternal care services including antenatal care (ANC), skilled birth attendants, and postnatal care [2, 3]. ANC reduces the maternal mortality rate (MMR) by screening high-risk mothers for complications and facilitating a rapid diagnosis and management of life-threatening obstetric conditions [4]. ANC is the care provided for pregnant women by qualified healthcare professionals to ensure a better pregnancy outcome [5]. World Health Organization (WHO) recommended a minimum of four visits for an uncomplicated pregnancy, initiating the first visit prior to 14 weeks of gestation [3]. However, in 2016, the ANC guidelines provided by the WHO increased from four to at least eight ANC visits, due to an increased fetal mortality risk associated with a reduced number of ANC visits [5].
While the utilization of ANC in developing countries has considerably improved, a limited number of pregnant women attend a total of four ANC visits with 72% initiating the first visit after 12 weeks of gestation [6]. For example, in a study conducted in Kenya 58% of women had at least four ANC visits [7], while in Somalia, the utilization rate is even lower with 33% of pregnant women initiating the first visit during the 4th month of the gestation period [8]. Thus, the WHO underlines the vital need to put the focus on mothers who commence fewer visits and initiate the ANC late [9].
Numerous studies on the determinants of ANC utilization have found an association between the socio-demographic, reproductive, and obstetric variables of the mother with the utilization of ANC [10-12]. However, few studies investigated the determinants of frequent use and timing of ANC visits [13]. Delay in the timing of the first visit increases the risk of the development of complications for both mother and child [14]. Thus, knowing only the proportion of pregnant women attending ANC is insufficient, it is also important to know when attendees commence such visits and whether they pay an adequate number of visits. Moreover, addressing the factors and socioeconomic barriers is imperative for increasing women's overall utilization of health services. To the best of our knowledge, no study attempted to investigate the timing and number of visits in ANC utilization and elucidating the various factors

influencing the use of this service in the Borama district of Somaliland. Therefore, this paper aims to contribute to this end.

Methodology

Study design and setting

This study is a community-based cross-sectional study that is conducted in the urban part of Borama District, Awdal region of Somaliland from February to August 2017. As of 2014, the estimated population of the district is around 398,609 [15]. There are twelve maternal and child health centers (MCH), eleven health posts, and two governmental hospitals at different locations within the district.

Study population and sampling

The study population are women of the reproductive age group (15-49 years) that gave birth within 2 years preceding this survey irrespective of the outcome of the delivery and are permanent residents (or at least a 2 years resident) in the study area. Women who are unable to communicate are excluded.

The sample size is determined using a single population proportion formula $n = (z\sigma/2.pq)/w^2$ by considering a 95% level of confidence, 5% marginal error with an estimated proportion of 32% from Multiple Indicator Cluster Survey (MICS) [16]. The minimum required sample size is determined to be 334 participants.

To assign a representative sample, the population within the region is clustered into four zones, and two zones are randomly selected. A total of 7244 households are located in the selected zones. Using the probability proportional to size (PPS) technique, the sample size is equally allocated to each zone. Furthermore, after acquiring a list of household numbers from the government statistics department; eligible respondents are selected using a systematic sampling technique. The first study subject is randomly selected, next; respondents in every tenth household are interviewed.

Variables and measurement

The analysis is based on two ANC-related outcomes: (a) the number of ANC visits attended during the most recent pregnancy, (b) the gestational age at which the first visit is initiated. The predictor variables are classified as socio-demographic characteristics of respondents, obstetric history, and ANC practices.

Data collection

A structured interviewer-administered questionnaire adopted from published literature and subsequently translated into the local language (Somali) is used for data collection. To check the internal validity, the questionnaire is back-translated to English and pretested on 20 women. The questionnaire consists of three sections. The first section collects information on the socio-demographic characteristics of the respondents (age, marital status, educational status, average monthly income, family size), the second section collects information on the obstetrical history of the mother (age of marriage, gravity, parity, history of abortion, stillbirth, and child mortality), and the last section collects information on the practice and level of ANC service utilization (awareness of the pregnancy risks, perception of mothers on the advantage of the ANC, timing, and frequency of ANC visits, husband's attitude toward ANC and received services). Data collectors are trained on subject matters such as the purpose of the study, the rights of the study subject, and the content of the questionnaire prior to the actual data collection. In this study, an ANC visit is defined as the care provided by a skilled healthcare professional to pregnant women without illness being the reason for the visit. Adequate utilization of ANC is defined as early attendance (initiating the first ANC visit during the first trimester) and frequent visits (at least four ANC visits). If one of these indicators is not met, the women have not utilized ANC adequately.

Data analysis

The collected data is entered and analyzed using the Statistical Package for Social Sciences (SPSS) version 23. Descriptive analysis is conducted on respondent's background characteristics and reported in frequencies and percentages. Bivariate analysis using the chi-square test is performed to examine the association between timing and frequency of ANC visits and the explanatory variables. The criterion for inclusion of factors in the multivariate analysis is to offer all variables with a p-value of < 0.05. All variables that met these criteria are used for building the final model. Furthermore, multivariable logistic regression analysis is used to determine the odds ratios (with the corresponding 95%CI) of attending less than four ANC visits and delayed initiation of the visits.

Ethical consideration

The study obtained an ethical review approval from the Ethical Review Committee of Horn International University. Study subjects are informed of the purpose of the study and their voluntary participation is obtained through oral consent. Also, the anonymity of the respondents is assured in the study tool.

Result

Socio-demographic characteristics

The sociodemographic characteristics of the respondents given in (Tab. I) show that a total of 330 women participated in this study giving a 98% response rate. More than half (53.3%) of the respondents fall within the age range of 25–35 years old and the mean age is 29.83 ± 6.35 years. On the educational status of respondents over three quarters (78.2%) of women never attended formal education. Marital status and family size show that the majority (94.5%) are currently married and about 51.2% have a family size of 5-10. A vast majority

of the study subjects (90.9%) are unemployed and 31.5% of the respondents have a family income below 100$. As shown in (Tab. II), 37% of the respondents married under the age of 18. The majority (90.6%) of the women gave birth 2 times or more and, a total of 19.7%, 11.8%, and 19.1% have a history of abortion, stillbirth, and child death respectively.

Distribution of ANC knowledge and utilization

As shown in (Tab. III), the majority of the participants (91.5%) attended ANC during their last pregnancy, and out of these subjects, 85.1% went for regular checkups. About 51.7% of the women attended the recommended 4 visits whereby the majority (62.3%) initiated their first

Tab. I. Sociodemographic characteristics of respondents (n = 330).

Variables	Categories	Frequency (N)	Percentage (%)
Age of mother	15-25 years	97	29.4
	25-35 years	176	53.3
	35-45 years	57	17.3
Marital status	Married	312	94.5
	Divorced	18	5.5
Educational status of mothers	Unable to read/write	207	62.7
	Able to read/write	51	15.5
	Formal education	72	21.8
Educational Status of husband	Unable to read/write	104	31.5
	Able to read/write	69	20.9
	Formal education	157	47.6
Occupational status	Employed	30	9.1
	Unemployed	300	90.9
Income	< 100 $	104	31.5
	100-200 $	132	40.0
	> 200 $	94	28.5
Nearest healthcare facility (walking)	< 20 min	113	34.2
	20-40 min	133	40.3
	> 40 min	84	25.5
Family size	< 5	140	42.4
	5-10	169	51.2
	10-15	21	6.4

Tab. II. Obstetric history of the study participants (n = 330).

Variables	Categories	Frequency (N)	Percentage (%)
Age of marriage (year)	< 18	122	37.0
	18-30	203	61.5
	> 30	5	1.5
Gravida	Primigravida	49	14.8
	Multigravida	281	85.2
Parity	Primipara	31	9.4
	Multipara	299	90.6
History of abortion	Yes	65	19.7
	No	265	80.3
Number of abortion	1	50	15.2
	> 1	15	4.5
History of stillbirth	Yes	39	11.8
	No	291	88.2
Number of stillbirth	1	31	9.4
	> 1	8	2.4
History of any child mortality	Yes	63	19.1
	No	267	80.9
Number of child mortality	1	41	12.4
	>1	22	6.7

Tab. III. Antenatal care utilization pattern among reproductive age group (n = 330).

Variables	Categories	Frequency (N)	Percentage (%)
Husband attitude	Positive	318	96.4
	Negative	12	3.6
Awareness of the pregnancy risk	Aware	66	20.0
	Non-aware	264	80.0
Attend ANC in the last pregnancy	Yes	302	91.5
	No	28	8.5
Reasons of visit	Health problem	45	14.9
	Regular checkups	257	85.1
Where did you hear about the sources of ANC?	Health institute	51	16.9
	Radio/TV	28	9.3
	Relatives	53	17.5
	Woman's group	170	56.3
Benefits of ANC	Maternal health	13	4.3
	Both maternal and child health	289	95.7
Knowledge of the required number of ANC visit	< 4 visits	140	46.4
	≥ 4 visits	162	53.6
Timing of ANC	1st trimester	94	31.1
	2nd trimester	188	62.3
	3rd trimester	20	6.6
Total number of visits	Once	13	4.3
	Twice	55	18.2
	Three	78	25.8
	Four or more	156	51.7
Health institute utilized	Hospital	18	6.0
	MCH	284	94.0
Why this particular health institute?	Nearness	252	83.4
	Little or no expenses	20	6.6
	High quality of service	30	9.9
Did you receive a Tetanus injection	Yes	282	93.4
	No	20	6.6
Number of injections	Once	85	30.1
	Twice or more	197	69.9
Prophylaxis for anemia or multivitamin	Yes	280	92.7
	No	22	7.3
Deworming	No	302	100
Health education about pregnancy and childbirth	Yes	253	83.8
	No	49	16.2
Did you ever pay for ANC	Yes	45	14.9
	No	257	85.1
How do you feel about payment	Unaffordable	15	31.8
	Fair	30	68.2
Waiting time	Long hours	92	30.5
	Short hours	210	69.5
If you didn't attend ANC, why not?	Non-requirement	19	67.9
	Poor services	5	17.9
	Busy	4	14.3

visit in the second trimester. Furthermore, a majority of the women's partners (96.4%) have a positive attitude towards ANC. However, only 20% knew the risk of pregnancy-related complications.

The percent of participants that are required to pay for utilizing ANC's services is 14.9%, out of which 31.8% reported the payment as unaffordable. Furthermore, 30.5% of women reported long waiting hours. Women who did not utilize ANC during their last pregnancy listed the most common reason for not attending as, a non-requirement (67.9%), followed by poor services (17.9%), and being too busy to attend ANC (14.3%).

Factors associated with the number and timing of ANC visits

Bivariate analyses show significant differences in number of visits for, age of the mother ($p = 0.025$), family size ($p = 0.015$), gravida ($p = 0.018$), gestation age ($p = 0.009$), and knowledge of the required visits ($p < 0.001$).

Tab. IV. Bivariate model evaluating the significant association between independent variables and number and timely use of antenatal care (n = 302).

Predictor Variables	Categories	Number of ANC visits			initiation of the first ANC visit		
		< 4 visits	≥ 4 visits	P-value [a]	< 3 month	> 3 month	P-value [a]
Age of mother	15-25 years	44 (30.1)	45 (28.8)	0.025*	37 (39.4)	52 (25.0)	0.011*
	25-35 years	74 (50.7)	88 (56.4)		48 (51.1)	114 (54.8)	
	35-45 years	28 (19.2)	23 (14.7)		9 (9.6)	42 (20.2)	
Educational status of mothers	Unable to read/write	91 (62.3)	96 (61.5)	0.323	48 (51.1)	139 (66.8)	0.033*
	Able to read/write	19 (13.0)	29 (18.6)		19 (20.2)	29 (13.9)	
	Formal education	36 (24.7)	31 (19.9)		27 (28.7)	40 (19.2)	
Family size	< 5	55 (37.7)	73 (46.8)	0.015*	50 (53.2)	78 (37.5)	0.009*
	5-10	86 (58.9)	69 (44.2)		36 (38.3)	119 (57.2)	
	10-15	5 (3.4)	14 (9.0)		8 (8.5)	11 (5.3)	
Gravida	Primi	14 (9.6)	30 (19.2)	0.018*	21 (22.3)	23 (11.1)	0.010*
	Multi	132 (90.4)	126 (80.8)		73 (77.7)	185 (88.9)	
Parity	Primi-para	11 (7.5)	16 (10.3)	0.407	13 (13.8)	14 (6.7)	0.045*
	Multipara	135 (92.5)	140 (89.7)		81 (86.2)	194 (93.3)	
Age of marriage	< 18	55 (37.7)	54 (34.6)	0.528	34 (36.2)	75 (36.1)	0.030*
	18-30	43 (29.5)	41 (26.3)		31 (33.0)	53 (25.2)	
	> 30	48 (32.9)	61 (39.1)		29 (30.9)	80 (38.5)	
Knowledge of required number of ANC visit	<4 visits	114 (78.1)	32 (21.9)	<0.001*	55 (58.5)	107 (51.4)	0.254
	≥4 visits	26 (16.7)	130 (83.3)		39 (41.5)	101 (48.6)	
Waiting time	Long hours	49 (33.6)	43 (27.6)	0.258	18 (19.1)	74 (35.6)	0.004*
	Short hours	97 (66.4)	113 (72.4)		76 (80.9)	134 (64.4)	
Gestational age	< 3 months	35 (24.0)	59 (37.8)	0.009*			
	> 3 months	111 (76.0)	97 (62.2)				

[a] chi-square test; *Significant at p < 0.05.

Regarding the initiation of the first ANC visit, a relationship with multigravida (p < 0.010), age (p = 0.011), educational status (p = 0.033), parity (p = 0.045) and waiting hours (p = 0.004) are observed. Inaddition, the analyses shows significant differences in women with large families (p = 0.009), and women that married at a young age (p = 0.030) as shown in (Tab. IV). The multivariate analysis in (Tab. V) shows the significant factors affecting the initiation of ANC within the first trimester and the required number of visits. The following characteristics are independently associated with the number of ANC visits received: Age, gravida, knowledge of required ANC visits, and gestational age. In terms of gravida, the primigravida mothers had more ANC visits compared to multigravida (OR = 3.295; CI = 1.200-9.045). Women aged 25 or older (OR = 3.018; CI = 1.264-7.207) and those who knew the required number of visitation (OR = 0.045; CI = 0.024-0.085) completed the required ANC visits. Furthermore, women who commenced ANC early (before 12 weeks) had a higher number of visits (OR = 1.737; CI = 1.013-2.979). Regarding the initiation of the first ANC visit, mothers who got married at the age of 18 and above are more likely (OR = 0.495; CI = 0.252-0.973) to initiate the visits early. While the odds of delay in ANC visits are higher with large family size (3.9 times higher odds) and long waiting hours in previous pregnancies (OR = 2.609; CI = 1.409-4.832).

Discussion

In accordance with the WHO's focused antenatal care module (FANC), the recommended minimum is 4 ANC visits with early commencement of the first visit occurring within the first 12 weeks of the gestational period [17]. The study revealed that even though most of the mothers did receive ANC visits, almost half (48.3%) did not receive the minimum recommended four visits. The research attempts to investigate the reasons for the failure to acquire the minimum recommended ANC visits. Several factors ascertained this limitation, in particular, the study illustrates that younger females are not motivated to acquire ANC. This concurs with other studies in India [18] and Nigeria [19] which demonstrated a higher commencement of ANC in older women. It may be that younger women are unaware of or fail to recognize the early signs of pregnancy. Moreover contradicting result has been reported in Bangladesh and Benin [20, 21]. Nonetheless, B. Simkhada et al. suggests that parity has a confounding effect on the utilization of ANC for both teenage mothers and women that are no longer expecting other pregnancies [22]. This view presents to be more satisfactory. Multigravida is also found to be an important factor in determining decreased visits. This could be attributed to women's confidence from experiences of previous pregnancy and thus are deemed in need of less support. This coincides with findings in other literatures [21, 23, 24]. Moreover, the

Tab. V. Factors associated with delayed and fewer antenatal care visits using Logistic Regression Model (n = 302).

Predictor Variables	Categories	Number of ANC visits ≥4			Delayed initiation of ANC visit		
		Odd ratio	95%CI	P-value	Odd ratio	95%CI	P-value
Age of mother	15-25 years	1.558	0.568-4.274	0.389	0.370	0.132-1.040	0.060
	25-35 years	**3.018**	**1.264-7.207**	**.013**	0.515	0.210-1.263	0.147
	35-45 years	1.0			1.0		
Educational status of mothers	Unable to read/ write				1.451	0.755-2.789	0.264
	Able to read/ write				0.913	0.399-2.093	0.830
	Formal education				1.0		
Family size	< 5	0.576	0.148-2.233	0.425	2.144	0.703-6.542	0.180
	5-10	0.378	0.104-1.370	0.139	**3.952**	**1.330-11.742**	**0.013***
	10-15	1.0			1.0		
Gravida	Primi	**3.295**	**1.200-9.045**	**0.021***	0.641	0.218-1.886	0.419
	Multi	1.0			1.0		
Parity	Primi-para				1.043	0.295-3.692	0.948
	Multipara				1.0		
Age of marriage	< 18				0.783	0.399-1.538	0.478
	18-30				**0.495**	**0.252-0.973**	**0.041***
	> 30 (Ref)				1.0		
Knowledge of required number of ANC visit	< 4 visits	**0.045**	**0.024-0.085**	**< 0.001***			
	≥ 4 visits	1.0					
Waiting time	Long hours				**2.609**	**1.409-4.832**	**0.002***
	Short hours				1.0		
Gestational age	< 3 months	**1.737**	**1.013-2.979**	**0.045***			
	> 3 months	1.0					

women's perception of the required number of visits is also found to be a positive contributor indicating that prior awareness is of significance [25].

The early commencement of ANC visits is of significance because it prevents obstetric complications, facilitates the detection and care of various conditions posed by pregnant women, and contributes to a sufficient number of visitation for mothers [26-28]. However, in this study, the overall magnitude of early attendance of ANC is 31.3%, this value is far below the required threshold indicating that they are likely at risk of pregnancy-related complications. Age of marriage played a significant factor in delayed utilization of ANC, the acquired result in this work suggests women that married at a younger age (< 18 years) failed to commence early ANC visits. This further highlights the detrimental impact of child marriage on maternal healthcare utilization and seeking behavior [29, 30]. In addition, the mother's timely use of ANC is hindered in larger households. This could be due to the preoccupation of women with children's care and household activities. This was also reported in previous works [31, 32].

The results obtained in this work suggest that acquiring the recommended number of ANC visitation depends on the early commencement of ANC. Thus, the provision of ANC from the early stages of pregnancy is imperative in prenatal care.

The husband's attitude and perception of maternal healthcare services impact women's access to such services [33] However, in this work, despite attaining a high positive attitude of the husband a correlation that is in favor of ANC utilization or its hindrance couldn't be established.

Maternal health services are free and subsidized by the government, however, some participants reported out-of-pocket payments for the service. This may have implications for the utilization of ANC.

In malaria-endemic countries, the infection is primarily asymptomatic and contributes to fetal morbidity and mortality [34] to prevent that, malaria chemoprophylaxis is included in ANC essential interventions. However, one of the limitations of this study is the coverage of malaria chemoprophylaxis is not examined. Further limitation includes the gestational age measurement is based on the women's last menstrual cycle report, which may have resulted in some inaccuracies. Moreover, the study did not investigate the respondent's reasoning behind the inadequacy of ANC utilization, and the quality of care

received which may influence the reproductive service utilization, thus, further research focusing on this aspect is warranted in the future.

Conclusions

The initiation of ANC within the early stages of pregnancy as well as the completion of an optimum number of visits required throughout the pregnancy is crucial in preventing pregnancy-related complications and reduces maternal mortality. Thus, in this study the levels of ANC utilization in Borama, Somaliland is researched. The findings in this work indicate an inadequate level of ANC utilization and a high prevalence of delayed timing and less ANC attendance during pregnancy. Moreover, several socio-demographic and maternal factors that are related to the frequency and timing of ANC visits are highlighted. Mother's age, multiple pregnancies, perception of the required number of visits, child marriage, high fertility rate, and large family size were drivers for the inadequate utilization of the ANC services. Hence, this study possesses the potential to improve policymakers' awareness of the determinants of ANC utilization and provide a framework to increase the use of the service in the country as a potential intervention.

The study concludes that in order to improve the quality and utilization of ANC, female education should be prioritized. Health programs that address pregnancy-related issues and emphasize the importance of early initiation and the frequent utilization of maternal health services should be developed to increase awareness and enhance the health-seeking behavior of women. Additionally, laws against child marriage should be implemented to protect underage girls from pregnancy-related and often life-threatening health complications.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

HM: study design, data collection, and analysis; NM: critically reviewed, edited, and approved the manuscript

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Research paper

Short-term insomnia symptoms are associated with level and not type of physical activity in a sample of Indian college students

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Keywords

Exercise • Insomnia • Behaviour • Sleep • Physical activity

Summary

Objective. *There is diverse results on the association between physical activity and sleep. So this study investigated association of level and type of physical activity with short term insomnia among college students.*

Methods. *A cross sectional study was conducted among college students in India. The sample was 662 students with 359 males and 303 females. The predictor variables were type and level of physical activity and predicted variables were sleep complaints. Physical activity components were aseesesed through international physical activity questionnaire and sleep complaints using Pitsburg sleep questionnaire. The binary logistic regression models were used for data analysis. Level of significance was set at $p \leq 0.05$ for all the analysis.*

Results. *The age (mean ± SD) of the participants were 23.2 ± 3.5 years. The self reported symptoms of short trem insomnia such as global sleep quality (adjusted odds ratio(AOR) = 15.58), subjective sleep quality (AOR = 6.01), sleep latency (AOR = 5.09), sleep duration (AOR = 0.13), sleep disturbances (AOR = 4.88), day time sleep dysfunction (AOR = 5.59) had shown association with level of physical activity. There was no association of type of physical activity with any other predicted variables.*

Conclusions. *The findings of the present study supports that level of physical activity is a key predictor of short term insomnia symptoms among college students. There should be Interventions to maintain and improve the level of physical activity among students.*

Introduction

Sleep problems are a significant public health burden, with an impact both at individual as well as on the community level [1, 2]. The international classification of sleep disorders (ICSD3) identified short-term insomnia disorder as short-term trouble in initiating or maintaining sleep resulting in overall sleep dissatisfaction. The accompanying daytime symptoms with sleep disturbances happen in people with a conducive situation and opportunity at night for getting normal sleep. The reported one-year prevalence of short-term insomnia disorder is around 15 to 20% in the adult population [3]. There is scarcity of data available for prevelance of short term insomnia in university students. However a systematic review has shown insomnia prevelance of 18.5% in the university students, and its 7.4% higher than in the general population. Its being reported that 60% of college students have issues with sleep quality [4]. Sleep problems are the second leading cause affecting academic performance among this group [5]. Physical activity is vital for the maintenance of health. It confers numerous physical and psychological health advantages. It was observed that majority of the students at the university level are not sufficiently active [6]. Quality of life, work habits, and different facets of academic activities are associated with physical activity among college-going individuals [7-9].

Short-term insomnia is generally identified based on self-reported subjective symptoms [3]. Different questionnaires are available to quantify the magnitude of subjective sleep problems. The level of physical activity can also be quantified with the help of self-assessment questionnaires. The Pittsburg sleep quality index (PSQI) is one of the widely used questionnaires to evaluate sleep quality and insomnia. The scale assesses and measures symptoms, which are part of short-term insomnia disorder [10, 11]. The international physical activity questionnaire (IPAQ) is a reliable and valid tool to calculate the level of physical activity [12].

The relationship between physical activity and sleep can be bidirectional. Interventions to improve physical activity have resulted in improved sleep, but not the other way around [13]. The levels of physical activity

have shown mixed effects on various sleep parameters among collegiate students.A systematic review with meta analysis have found that modereate physical activity have shown better sleep quality in college students but its suggested that more studies are required in this area [14]. Differences in the methodology used in various studies made it difficult to compare the results.
It was reported by Štefan et al., that poor sleep quality and its domains leads to reduced levels of physical activity levels in young adults [15]. There are limited studies reporting the sleep problems among college students, in south Asian countries [16, 17]. The symptoms related to short-term insomnia can affect both mental and physical function capacity. There is lacunae in information regarding the association of physical activity level with subjective symptoms of short-term insomnia in collegiate students.Hence the study was done to find whether there is any association between short term insomnia symtoms and physical activity in collegiate students. We hypothesized that there is a significant association between different physical activity levels and self-reported symptoms of short term insomnia symptoms in college students.

Methods

Study design, setting and sample selection

The study was a cross sectional observation study. The participants were recruited from Jamia Millia Islamia (JMI), New Delhi, India. It is a federal government-funded university. The participants age ranged from 18-30 years, with a mean age of 23.2 ± 3.5 years, including both males (359; 54.2%) and females (303; 45.8%) (Tab. I). The inclusion criteria were those students who can follow and understand the English language. Students with any physical or mental disorder that may affect sensory, motor, or cognitive functions and those with history or presently having a primary sleep disorder, such as sleep apnea, primary insomnia, were excluded. The inclusion and exclusion criteria were ascertained from the health records and by self-reporting of the participants.
The prospective participants of the study were contacted through emails with details of the study. They were informed about the aims, objectives, and significance of this study. Those who were willing to participate were personally met by the investigators for further part of the study. Data collection was done by the first author himself; he was available throughout the data collection procedure, in case the respondents needed any assistance. Seven hundred university students were screened for the study. The participants were provided with a list of health conditions that they had to self-report for screening. Twenty- two students were excluded as they did not meet the inclusion criteria. The PSQI and IPAQ-SF were distributed among 678 participants, and they were informed to answer the questionnaire. The demographic details of the participants collected were age, gender, height, weight, academic level, years at university, type of residence, and smoking habit. Six hundred sixty-

Tab. I. Participants characteristics & descriptive statistics of the variables.

Participants characteristics/variables	Mean ± S.D/ frequency (%)
Age (years)	23.2 ± 3.5
Gender	
Male	359 (54.2%)
Female	303 (45.8%)
Body Mass Index (kg/m²)	22.3 ± 3.6
Underweight	90 (14%)
Healthy weight	424 (64%)
Overweight	124 (19%)
Obese	24 (4%)
Level of study	
Under-graduation	363 (54.8%)
Post-graduation	171 (25.8%)
Research scholar	128 (19.3%)
Years at university	
Junior level (< 1 year)	227 (34%)
Senior level (> 1 year)	435 (66%)
Residence	
Hostel in university	285 (43%)
Rented accommodation outside university	224 (34%)
Home (with family)	153 (23%)
Tobacco smokers	198 (30%)
PSQI global (total) score: global sleep quality	5.2 ± 2.4
Healthy sleep quality - total score < 6	321 (48.5%)
Poor sleep quality - total score ≥ 6	341 (51.5%)
PSQI: subjective sleep quality	
Code 0 (0 - very good & 1 - fairly good)	566 (85%)
Code 1 (2 - fairly bad & 3 -very bad)	96 (15%)
PSQI: sleep latency+	
Code 0 (0 - < 15 minutes & 1- 16-30 minutes,)	413 (62%)
Code 1 (2 - 31-60 minutes & 3 - > 60 minutes)	249 (18%)
PSQI: sleep duration	
Code 0 (0 - > 7 hours & 1 - 6-7 hours)	627 (95%)
Code 1 (2 - 5-6 hours & 3 - < 5 hours)	35 (5%)
PSQI: sleep efficiency	
Code 0 (0 - > 85% & 1 - 75-84%)	611 (92%)
Code 1 (2 - 65-74% & 3 - < 65%)	51 (8%)
PSQI: sleep disturbance++	
Code 0 (0 - not during past month &1- less than once a week)	506 (76%)
Code 1 (2 - once or twice a week & 3- three or more times a week 3)	156 (42%)
PSQI: daytime dysfunction	
Code 0 (0 - no problem at all & 1- only a very slight problem)	484 (73%)
Code 1 (2 - somewhat of a problem & 3 - a very big problem)	178 (27%)
IPAQ: level of activity	
Vigorous	73 (11.0%)
Moderate	252 (38.1%)
Low	337 (50.9%)
IPAQ: type of activity	
Vigorous	95 (14%)
Moderate	125 (19%)
Walking	442 (67%)

PSQI: Pittsburgh sleep quality index; IPAQ: International physical activity of questionnaire.

two participants were included in the study; data of 16 participants were excluded due to improper filling up of the questionnaires. The complete procedure for filling the consent form and the questionnaires took approximately 15-20 minutes.

The participants were required to fill up a consent form attesting to their status as volunteers and understanding their rights. The details of the participants were kept confidential by assigning a number. The study was approved by the institutional ethics committee of the Jamia Millia Islamia, New Delhi, India.

Variables

Predictor variables

The predictor variable level and type of physical activity were measured with the international physical activity questionnaire, short-form (IPAQ-SF). It is a self-report questionnaire primarily designed for assessing physical activity among adults (age range of 15-69 years) [11]. The IPAQ-SF consists of 7 items and classifies physical activity at four intensity levels. The IPAQ-SF asks participants to report activities performed for at least 10 minutes during the last seven days. Respondents were asked to report time spent in a physical activity performed across leisure time, work, domestic activities, and transport at each of the three intensities: walking, moderate, and vigorous. Using the instrument's scoring protocol, the level of total weekly physical activity was estimated by weighing time spent in each activity intensity with its estimated metabolic equivalent (MET) energy expenditure. The IPAQ-SF scoring protocol assigns the following MET values to "light intensity" activities, such as walking, and to "moderate", and "vigorous" intensity activities as 3.3 METs, 4.0 METs, and 8.0 METs, respectively [12]. The original authors recommended the "last 7-day recall" version of the IPAQ-SF for physical activity surveillance studies, in part because the accurate recollection beyond seven days is limited [18].

Predicted variable (outcome variable)

The Pittsburgh Sleep Quality Index (PSQI) questionnaire was used to assesses the predicted variable short term insomnia symptoms. The PSQI is a self-reported questionnaire that quantitatively assesses the respondent's quality of sleep for the past month [19]. The PSQI, which was evaluated in different populations, was designed for both clinical and research applications [20]. The PSQI includes 19 questions, which are separated into seven groups that account for the global sleep quality score. The aggregate global score is made up of sleep characteristics, which include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, and daytime dysfunction. These characteristics are evaluated based on subjective self-reporting or inferred from the basic information such as the respondent's usual wake time, number of actual hours slept, and amount of time to fall asleep" [21, 22].

The questionnaire's self-reported item is scored on a scale ranging from 0 to 3. The scores are then cumulated using sub-totals from each of the seven categories, giving a final score between 0 to 21. The lower scores indicating healthy and higher scores indicating poor global sleep quality [17]. We used the reported cut-off score of > 6 global score in Indian students to classify participants as poor and healthy sleepers [23].

Data analysis

The Statistical Package for the Social Sciences 21.0 (SPSS Inc., Chicago, Illinois) was used for data analysis. Descriptive statistics were used for the presentation of participant characteristics. PSQI individual component scores of 0-1 and 2-3 were coded as 0 and 1, respectively [24, 25]. The logistic regression analysis was done for symptoms of short-term insomnia and with the level and type of physical activity and socio-demographic characteristics. The variable which had shown a association with a $p < 0.25$ were included for the final model of multiple logistic regression. The significance level of $p \leq w\ 0.05$ was set for the final model.

Results

Demographic variables, insomnia symtoms and physical activity: age, body mass index (kg/m^2), the PSQI, the frequency distribution of sex (male/female), level of education, years at university, type of residence, component scores of the PSQI, and the level and type of physical activity are presented in Table I.

Global sleep quality and subjective sleep quality: the level of physical activity had a significant association with global sleep quality (after controlling for age, BMI, type of residence, type of physical activity, education level, and academic year. Those who were doing lower physical activity were 15 more times likely to have poor sleep quality. Similarly, the level of physical activity has a significant association with subjective sleep quality. Those who were doing lower physical activity were six times more likely to report poor sleep quality than a high level of physical activity achievers (Tab. II).

Sleep latency and sleep duration: The level of physical activity had a significant association with sleep latency after controlling for the type of physical activity. Those who were engaged in lower physical activity were five times more likely to have higher sleep latency than a high level of physical activity achievers. The level of physical activity has a significant association with sleep duration after controlling for age, residence, and type of physical activity of the participants. Those who were engaged in lower physical activity were less likely to have a short sleep duration than a high level of physical activity achievers (Tab. III).

Habitual Sleep Efficiency: gender had a significant association with habitual sleep efficiency after controlling for age, academic year, level of education, and type and level of physical activity of the participants. Males were less likely to have lower habitual sleep efficiency (74% or less) than females (Tab. IV).

Sleep disturbances and daytime dysfunction: the level of

Tab. II. Association of level of physical activity with global sleep quality and subjective sleep quality.

Predicted variable	Predictor variable	COR (95% CI)	AOR (95% CI)
Global sleep quality	**PA level**		
	Low	10.896 (5.855-20.280)**	15.585 (6.438-37.733)***
	Moderate	1.625 (0.865-3.054)	1.772 (0.865-3.632)
	High	Reference	-
	PA type		
	Vigorous	0.217 (0.132-0.357)	1.574 (0.861-2.879)
	Moderate	0.286 (0.186-0.439)	1.478 (0.715-3.058)
	Walking	Reference	-
	Age (+ 1 year)+	0.958 (0.917-1.002)	1.038 (0.934-1.155)
	BMI+		
	Underweight	1.166 (0.471-2.891)	1.082 (0.370-3.164)
	Healthy weight	0.892 (0.391-2.038)	0.873 (0.335-2.275)
	Overweight	0.674 (0.279-0.1.631)	0.710 (0.259-1.952)
	Obese	Reference	-
	Level of education+		
	Under-graduate	1.523 (1.008-2.301)	1.266 (0.545-2.943)
	Post-graduate	1.020 (0.635-1.639)	0.680 (0.358-1.291)
	PhD scholar	Reference	-
	Type of residence+		
	Hostel in college	0.744 (0.498-1.112)	0.853 (0.532-1.365)
	Rent outside the college	1.110 (0.728-1.693)	1.116 (0.687-1.814)
	Home (with family)	Reference	-
Subjective sleep quality	**PA level**		
	Low	2.739 (1.137-6.600)*	6.018 (1.555-23.286)*
	Moderate	1.129 (0.441-2.890)	1.504 (0.519-4.357)
	High	Reference	-
	PA type		
	Vigorous	0.528 (0.254-1.098)	1.990 (0.622-6.361)
	Moderate	0.654 (0.354-1.207)	2.090 (0.795-5.494)
	Walking	Reference	-
	Level of education+		
	under-graduate	0.722 (0.412-1.266)	0.602 (0.338-1.074)
	Post-graduate	0.904 (0.479-1.706)	0.765 (0.399-1.467)
	PhD scholar	Reference	-

*: p < 0.05; **: p < 0.01; ***: p < 0.001; +: covariate; COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; PA: physical activity.

Tab. III. Association of physical activity with sleep latency and sleep duration.

Predicted variable	Predictor variable	COR (95% CI)	AOR (95% CI)
Sleep latency	**PA level**		
	Low	2.838 (1.579,5.101) ***	5.094 (2.184, 11.881) ***
	Moderate	1.438 (0.783, 2.639)	1.920 (0.964, 3.825)
	High	Reference	-
	PA level		
	Low	0.654 (0.407, 1.051)	1.932 (0.959, 3.895)
	Moderate	0.641 (0.417, 0.985)	1.507 (0.833, 2.727)
	High	Reference	-
Sleep duration	**PA level**		
	Low	0.361 (0.153, 0.852) **	0.139 (0.023, 0.843) **
	Moderate	0.538 (0.158, 1.838)	0.104 (0.01, 1.073)
	High	Reference	-
	PA type		
	Vigorous	1.073 (0.428, 2.694)	0.992 (0.393, 2.503)
	Moderate	0.401 (0.119, 1.353)	0.372 (0.11, 1.259)
	Walking	Reference	-
	Age (+ 1 year)+	0.935 (0.842, 1.038)	0.928 (0.831, 1.035)
	Type of residence+		
	Hostel in college	0.942 (0.423, 2.096)	1.155 (0.503, 2.655) **
	Rent outside the college	0.389 (0.138, 1.094)	0. 392 (0. 138, 1.113)
	Home (with family)	Reference	-

*: p < 0.05; **: p < 0.01; ***: p < 0.001, +: covariate; COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; PA: physical activity.

Tab. IV. Association of physical activity with habitual sleep efficiency.

Predicted variable	Predictor variable	COR (95% CI)	AOR (95% CI)
Habitual sleep efficiency	**PA level**		
	Low	0.645 (0.350, 1.187)	0.692 (0.168, 2.668)
	Moderate	0.123 (0.017, 0.914) *	0.127 (0.012, 1.339)
	High	Reference	-
	PA type		-
	Low	Reference	0.920 (0.239, 3.540)
	Moderate	1.177 (0.322, 4.294)	0.669 (0.168, 2.668)
	High	2.442 (0.853, 6.99)	-
	Age (+ 1 year)+	1.052 (0.971, 1.138)	1.105 (0.927, 1.317)
	Gender		
	Male	0.623 (0.350, 1.107)	0.527 (0.284, 0.978) **
	Female	Reference	-
	Level of education+		
	Under-graduate	0.735 (0.369, 1.463)	1.210 (0.314, 4.659)
	Post-graduate	0.506 (0.209, 1.227)	0. 617 (0. 214, 1.778)
	PhD scholar	Reference	-
	Academic year		0.766 (0.331, 1.769)
	Freshman	0.564 (0.289, 1.100)	-
	Senior	Reference	

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; +: covariate; COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; PA: physical activity.

physical activity had a significant association with sleep latency after controlling for the level of education, age, gender, BMI, type of residence, and type of physical activity. Those who were engaged in lower physical activity were five times more likely to have sleep disturbances than high-level physical activity achievers. The level of physical activity had a significant association with daytime dysfunction after controlling for BMI, type of residence, type of physical activity, and education level. Those who were doing lower physical activity were more than 5.5 times more likely to have moderate to severe levels of daytime dysfunctions than those with a high level of physical activity. (Tab. V).

Discussion

The level of physical activity had shown to influence the components of sleep, such as sleep latency, sleep duration, sleep efficiency, subjective sleep quality, sleep disturbances, and day time dysfunction. This indicates that an increased level of physical activity influences sleep components, which resulted in better-improved sleep quality. It was also observed that type of physical activity did not affect sleep quality or its components.

The results of this study demonstrated that the prevalence of short-term insomnia symptoms (51.5%) was higher among university students who had lower self-reported levels of physical activity. The study also found that males had poorer sleep quality as compared to females. The findings of the present study were also consistent with a previously reported prevalence ranging from 19.2 to 57.5% [26]. The results are also broadly in line with a recent survey showing that a minimum of 18% of adults in the US had inadequate or poor sleep [27]. Many college and university students are poor sleepers, with 70.6% of students having less than 8 hours of sleep. Students who frequently report having sleep disturbances because of academic stress further experience a harmful influence on their academic performance [28]. A key factor or "main problem" in this vicious cycle is daytime sleepiness, which is reported by 50% of university students [5].

Since the objective of the current study was to find out the association of physical activity levels and subjective symptoms of short-term insomnia, the predictor variables, physical activity levels, were categorized into low, moderate, and high. The predicted variables related to subjective symptoms were also categorized as mentioned in the statistical analysis part. This categorization of scores was done according to the scoring criteria recommended for both the scales [12, 19, 20]. The results of the present study showed that physical activity level is a predictor of sleep quality among college students. An inverse association was found between physical activity level and sleep quality score. The findings of the present study in Indian students were similar to those carried out in other countries. A review by Lang et al. found that, despite differences in methodology, it was still possible to conclude that participants who had higher levels of physical activity were more likely to have a better quality of sleep [29]. More specifically, it was found that persons with better self-perceived exertion during exercise had reduced light sleep and increased deep sleep when compared to those who reported less self-perceived exertion. Thus supporting the recommendation that exercise should be included as a part of person's daily routine; the likely benefits of which would be an improved level of sleep quality [30].

The acute exercise was reported to have only limited effects on factors such as total sleep time, slow-wave sleep, sleep onset latency (SOL), and decreased REM sleep. Regular exercise was demonstrated to have moderate to strong positive effects on overall sleep quality while exhibiting moderate-to-largely

Tab. V. Association of physical activity with sleep disturbances and daytime sleep dysfunction.

Predicted variable	Predictor variable	COR (95% CI)	AOR (95% CI)
Sleep disturbances	**PA level**		
	Low	2.929 (1.443, 5.945) *	4.889 (1.666, 14.351)* p = 0.004
	Moderate	1.162 (0.549, 2.462)	1.342 (0.567, 3.179)
	High	Reference	-
	PA type		
	Low	0.584 (0.331, 1.029)	2.105 (0.859, 5.157)
	Moderate	0.525 (0.311, 0.888)*	1.617 (0.743, 3.522)
	High	Reference	-
	Age (+ 1 year)+	0.948 (0.898, 0.999)	0.981 (0.887, 1.086)
	Gender		
	Male	0.730 (0.507, 1.052)	0.780 (0.501, 1.214)
	Female	Reference	-
	BMI+		
	Underweight	0.474 (0.292, 0.772)*	1.337 (0.445, 3.926)
	Healthy weight	0.257 (0.130, 0.507)**	0.665 (0.251, 1.760)
	Overweight	0.654 (0.246, 1.741)	0.378 (0.130, 1.104)
	Obese	Reference	-
	Level of education+		
	Under-graduate	1.371 (0.833, 2.257)	0.805 (0.333, 1.944)
	Post-graduate	1.024 (0.572, 1.836)	0. 672 (0. 325, 1.389)
	PhD scholar	Reference	-
	Type of residence+		
	Hostel in college	0.714 (0.449, 1.135)	0.855 (0.520, 1.408)
	Rent outside the college	0.862 (0.534, 1.389)	1.039 (0.600, 1.799)
	Home (with family)	Reference	-
Day time sleep dysfunction	**PA level**		
	Low	5.237 (2.429 -11.292) **	5.592 (1.817-17.206) *
	Moderate	1.321 (0.583-2.991)	1.204 (0.471-3.081)
	High	Reference	-
	PA type		
	Low	0.265 (0.137-0.512) **	1.044 (0.396-2.755)
	Moderate	0.373 (0.220-0.633) **	1.337 (0.621-2.881)
	High	Reference	-
	BMI+		
	Underweight	2.280 (0.778-6.684)	2.716 (0.844-8.741)
	Healthy weight	1.380 (0.503-3.784)	1.615 (0.548-4.756)
	Overweight	0.899 (0.302 -2.672)	1.073 (0.340-3.382)
	Obese	Reference	-
	Level of education+		
	Under-graduate	1.193 (0.748-1.902)	0.739 (0.433-1.263)
	Post-graduate	0.835 (0.480-1.454)	0.540 (0.293-0.995) *
	PhD scholar	Reference	-
	Type of residence+		
	Hostel in college	0.766 (0.485-1.209)	0.851 (0.518-1.399)
	Rent outside the college	1.102 (0.694-1.752)	1.118 (0.680-1.840)
	Home (with family)	Reference	-

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; +: covariate; COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; PA: physical activity.

strong positive effects on all subscales of the PSQI. Furthermore, regular exercise has been found to increase total sleep time and sleep efficiency to some degree [31,32]. A study, including adults, tested the chronic effects of exercise by combining a twice-weekly aerobic training program for six weeks with everyday physical activity. They found a positive linear association between global PSQI outcome and daily physical activity. The results of the study support the use of long-term exercise programs as an intervention for poor sleep quality in adults [33].

The time frame for assessing sleep quality was the last month, whereas physical activity levels were the past week. This gave rise to a difference in the assessment time frames of the two variables. However, the usually recommended time frame for assessing sleep quality is within the past one month, sleep problems persisting beyond three month is considered to be chronic sleep disorders [34]. The amount of physical activity recommended is based on per week basis [35]. Studies may be done by keeping both the time frames equal.

The sample size of the present study is relatively large, thus helps to increase the potential generalizability of the results. There are some limitations to the present study. First, this type of study design (cross-sectional) limits the strength of relationships since it does not

investigate cause and effect relationships. Second, the self-report questionnaires were used to indentify the partcipants rather than based on clinical diagnosis with more objective methods.This fact may have affected the accuracy of the variables of interest. We recommend future longitudinal studies with a large sample size to further clarify the cause-effect associations between physical activity level and sleep quality.

Conclusions

Level of physical activity can influce sleep and its related doimains.Physical activity is very important component influencing sleep quality both at subjective and global score, it also influes sleep latency, sleep dutation, daytime sleepiness and sleep disturbnaces also. There should be active and continuous effort from the educational institutions and other stakeholders to promote the physical activity among the students.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

AKG: conception, design of study, data collection interpretation of results, drafting manuscript and approval of the final version of manuscript; MMN: conception, design of study, data collection, data analysis interpretation of results, drafting manuscript and approval of the final version of manuscript; Md.DM: design of study,data analysis interpretation of results, drafting manuscript and approval of the final version of manuscript; BBB: data analysis interpretation of results, drafting manuscript and approval of the final version of manuscript, SRPP: design of study, interpretation of results, drafting manuscript and approval of the final version of manuscript; ASB: design of study, interpretation of results, drafting manuscript and approval of the final version of manuscript.

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RESEARCH PAPER

Reach, accessibility and acceptance of different communication channels for health promotion: a community-based analysis in Odisha, India

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Keywords

Health communication • Media • Interpersonal communication • Information education and communication • Health literacy

Summary

Introduction. *To achieve universal health coverage, improving demand generation at community is necessary. Media plays an important role by acting as a linking pin between health service providers and the community. This study intended to assess the penetration and acceptability of various forms of media for health communication in Odisha, India.*
Methods. *A cross-sectional mixed method study was conducted in 2016 in four districts. Following a desk review, a situational analysis was done at state, district and sub-district level. Data was collected through direct observation of study sites using a predefined checklist on knowledge awareness and practice, focussed group discussion and in-depth interviews using semi-structured questionnaire. Qualitative data was analyzed using framework approach while for quantitative data, we used SPSS 20.0.*
Results. *Major identified media houses were television (TV), radio and newspaper. Many health programs were being broadcasted in regional TV channels of the state, whereas leading public radio channel broadcasted highest number of health programs almost daily. The major source for information on disease symptoms and prevention was television (63.6%), remove hyphen (36.6%), newspaper (21.6%), health facility/service providers (17.7%), radio (9.2%), and other media like posters, pamphlets and folk dance (5.5%). Information on disease treatment or management was received mostly from television (61.2%), poster/leaflets (39.2%), remove hyphen (35.2%) and newspaper (19.7%). Only 8% of people received any health related message in mobile in past one year. Boards and hoarding provided information to 16.5% of study population. Nearly 36% respondents got information from healthwall, which are used to promote health awareness through wall paintings, graffiti etc. For immunization related information, interpersonal communication through frontline health workers was the most preferred.*
Conclusion. *Interpersonal communication is believed to be most acceptable source of information on maternal and child health, immunization and neonatal care. For people with low literacy, remove hyphen campaign, folk media and interpersonal communication were found to be effective.*

Introduction

The maternal and infant mortality rates in Odisha, a state in eastern India, are higher than the national average of 93 per 100,000 and 34 per 1000 live births respectively. Further, malnutrition is another key health challenge where 34% of children under age five are stunted and around 27% are wasted [1]. Despite implementation of various programs and initiatives towards improving reproductive, maternal and child health (MCH), the state is yet to achieve expected progress. One of the major cited reasons could be low healthcare seeking attitude in the community owing to poor knowledge and awareness [2]. People's bent of mind for seeking healthcare is often governed by factors like travel distance, expense, closeness to stores, quack availability of healthcare services, ownership etc. It therefore becomes paramount to rein these middlemen and bring them under jurisdiction before trying to tame the community's behavior. While knowledge and awareness are ingredients which can be provided and accepted by the people, attitude needs to be developed within in order to bring a change in the external being. However, these three ingredients need incessant endeavor from the provider as well as the beneficiaries.

The National Family Health Survey of 2015-16 indicates below-optimal health related knowledge among the community with only 20% women and 33% men having knowledge about life threatening and preventable infections like HIV followed by AIDS. Consequently, inadequate access to healthcare services is also shown by an unmet need of family planning of 13.6% and a mere 62% women availing four Antenatal Care (ANC) visits, despite it being free of cost [1]. Studies have shown a possible correlation between levels of knowledge regarding diseases and actual access to healthcare services [3]. But there appears to be sparse literature revealing the reasons for such observed low level of knowledge.

Odisha's five year health communication action plan

envisions the need for communication across all programs for improved health outcomes, by giving special focus to marginalized and vulnerable groups, which contribute more than 60% of the population [4]. A framework analysis of barriers to access for healthcare services in low-income Asian countries has shown that an important demand side barrier in the community is knowledge on diseases, and services available [5]. Informed knowledge of the services they are entitled to, and provision of services at the facility level will increase not only the demand, but also improve the health seeking behavior of an individual or community. Demand generation is also imperative for achieving universal health coverage. Towards this, communication interventions need to be operated at multiple levels involving both the target beneficiary and key stakeholders like service providers, community leaders and influencers, and health system officials.

In this regard, media interventions play an important role by serving as a linking pin between service providers and community beneficiaries. However, till date, there is paucity of evidence on the effectiveness of such strategies on care seeking and health behaviors. It is pertinent to understand the present status of different media forms in creating awareness and behavior change, the impact of different media for this. This, in turn, will lead to designing a correct media mix method to derive the maximum benefit out of it.

In Odisha, creating awareness could be challenging since the state has over 83% of its population residing in rural areas [6]. Moreover, for any behavior change to occur, the perceptions and beliefs at family and community levels have to be explored first, with special attention to maternal and child health related awareness. Further, the various cultural and social barriers prevailing in the community need to be understood prior to designing any behavior change interventions for accepting services under different programs. Given this background, the present work aimed to understand the current reach, penetration, accessibility and acceptance of various media in different regions of Odisha regarding delivery of health messages. The study intended to assess the reach of different media like TV, radio, mobile phone, newspaper, magazine, cinema, hoardings, wall paintings, street theatre, interpersonal communication by front-line health workers, community groups, self-help groups/non-governmental organizations, health fairs and exhibitions among urban and rural population. Additionally, the study explored the community need for type and pattern of communication channels to get health and related information.

Methods

Study design

This cross-sectional mixed method study was undertaken in the state of Odisha, India, during January-March 2016. The study was assigned by the State Institute of Health and Family Welfare, Government of Odisha.

Selection of study participants

A stratified random sampling process was adopted to select the participant for data collection. One district was selected randomly from each of the four regional divisions of the state i.e. Southern, Western, Coastal and Northern. From each district, two blocks were selected and in each block, village names were listed and 2 revenue villages were selected by taking into account total population, caste of the people in the village and distance from block headquarter.

Data collection

A two-step approach was followed for data collection. First step involved desk review and secondary data analysis. Following a desk review, a situational analysis through multi-stakeholder perspective was carried out at the state, district and sub-district level. This included mapping of media houses currently working in Odisha, mapping of heath communication interventions at the facility level and the types of media approaches being followed. In order to understand the general perceptions on the media effectiveness on health with focus on enablers, limiting factors, both qualitative and quantitative techniques were used. Data collection comprised direct observation of study sites using a predefined checklist on knowledge awareness and practice, interviews with the help of a semi-structured questionnaire, Focused Group Discussions (FGDs) and In-Depth Interviews (IDIs) of key informants. All data collection tools were pretested and necessary modifications made.

FGDs were held with adult married men and women to understand their perspective, use, impact and importance on health information received through media and interpersonal communications. While FGDs provided mixed perspectives from a relatively homogenous group of both genders, the interviews were limited to key representatives of multiple stakeholder groups.

Quantitative data related to socio-demographic information, house hold characteristics, economic and occupation influencing media practice was collected from different categories of stakeholders at community level over a pre-tested semi-structured questionnaire. Assuming 50% of the people (p = 0.5) were aware about the health messages through media, the required sample size for quantitative data collection was decided by using the Schwartz formula:

$$\text{Sample size } (n_0) = (1.96)^2 pq / l^2,$$

Considering 95% confidence level and precision (l) of 5%, assuming a dropout rate of about 10% and a design effect of 1.5 due to multistage sampling, a minimum total of 660 study participants needed to be interviewed.

Data handling and analysis

The interviews and FGDs were transcribed verbatim and translated to English. Qualitative data was analyzed using "framework approach". In this approach, the research team will familiarize with the responses by listening to the audio recordings and by going through the transcribed data repeatedly. During the familiarization process, broad thematic areas emerging from the data

was identified. The next step was assigning the data to different themes, i.e. the coding. The responses based on the codes were grouped under each theme called thematic charts. Based on these charts, interpretation of the data was done and report was presented under different themes. The steps of coding and charting were done by using qualitative data analysis software.

The data collected over the semi-structured questionnaire was entered and analyzed by using SPSS software package, version 20.0. Different socio-demographic correlates like age, gender, education, occupation and other variables influencing the media practice on health was examined. Further, the reach, access and utility of different health messaging approaches and its acceptance was determined. These findings were corroborated with the audience analysis reports of different media houses.

Quality assurance

Quality control for the information generated from the study was carried out at various levels starting from questionnaire designing to analyzing the data. Before starting the data collection, the questionnaire was pilot tested and checked for its reliability and validity. All the field investigators were trained for maintaining the uniformity in the data collection. The lead investigator and co-investigators personally observed few interviews conducted by the field investigators. Forward and backward translation of randomly selected qualitative data was done to validate the quality of translation. Quality control steps were taken during data management by random checking of 10% of the data entered to verify accuracy of the data entered.

Ethical considerations

Ethical approval to conduct this study (protocol number - 30/23/02/2015) was obtained from the state research ethics committee, Odisha (vide number - 47/SHRMU dated 10.03.2015). Necessary permission was obtained from the district health authority prior to data collection. Participants were briefed about the study's objective, potential benefits and harms, and procedure, following which informed consent was obtained from them. They were also informed that participation in the study was purely voluntary and that they could withdraw from the interview process at any time. Each participant was allotted a unique identification code to maintain anonymity. The study was carried out in a manner that ensured the privacy, anonymity and data confidentiality at every stage.

Results

Mapping media houses currently working in Odisha

Various electronic and print media houses were identified and contacted for collecting information on types of programs being broadcasted, topics covered and the coverage. Major identified media houses were TV, radio and newspaper.

With regard to TV, except all national channels, many health programs are being broadcasted in regional channels of Odisha. Most of the programs focus on phone-in discussion on a special topic. The programs were sponsored by many organisations and some were organised by the channel itself. Besides that, the channels broadcast the national programs and other short term advertisements on sanitation, condom use, TB, HIV/AIDS etc. in between different programs.

All India Radio was seen to be broadcasting highest number of health programs amongst all channels. Almost every day discussion on health topics were done by some experts on some topics. Other FM channels catering mostly the youth and urban population were also found to be broadcasting health related programs on special days. Most of these programs were sponsored by some organisations or hospitals. Many of these programs were repeated frequently based on the importance of the topic. Newspapers, the Samaja and the Sambada carried health related information on topics such as TB, HIV, leprosy, filaria, malaria, heat stroke, cancer, kidney disease, skin disease, heart disease, allergic reaction, family planning, diabetes, immunization, mental health, Rashtriya Swasthya Bima Yojana (RSBY), Janani Shishu Suraksha Karyakaram, Data pertaining to programs in TV and radio is shown in Table I.

Besides the electronic and print media, boards, hoardings, posters and leaflets were displayed by the health departments and different national and international organisations at strategic points in villages and towns. Most common places to find a hoarding were bus stop, railway station, highway corridors, health facility, and municipality and panchayat offices. Major health issues covered were malaria, dengue, tuberculosis, HIV/AIDS, different health schemes, RSBY, sanitation programs, non-communicable diseases (NCDs). The key messages given on these hoarding targeted on prevention and management of these diseases.

Socio-demographic detail of the study participants from the 4 districts in Odisha

In total we could collect data from 668 people aged 18 years or more from four districts which participated in the study during two months of data collection period. The age of the study population ranged from 18-65 years and the mean age was 36.8 years. In the study, 41.2% participants were male and 43% were from either a scheduled caste or tribe (Figure 1). Out of the sampled participants 19.9% had no schooling exposure and 28.3% were from a joint or extended family. Values are in line with the Odisha Census data [6]. The mean family size was 4.8 persons. The mean family income per month was Rs.4850 (67 USD).

Penetration and accessibility of people to media and communication channels

Figure 2 provides a matrix showing the penetration and accessibility of people to media and communication channels. As depicted in the figure, the major source for information related to identification and prevention of

Tab. I. Programs in television and radio.

Name of the program	Channel	Time	Frequency	Types of program	Language	Topic	Coverage
Television							
Doctor-doctor	O TV	Sunday - 12 pm-12:30 pm	Weekly	Question-answer (telephonic)	Odia		40,000-50,000
Health plus	O TV		Weekly	Discussion	Odia		50,000-65,000
Chikitsaka	Kalinga TV	Sunday - 5:30 pm Tuesday - 4:30 pm	Five times a month	Discussion	Odia		TRP-2
Arogyam	Naxatra news	Friday - 2 pm-3 pm	Once in a week and special days	Phone-in	Odia	MCH, diabetes	10,000-20,000
Fit rahu odisha	NEWS-7	Sunday - 2:30 pm	Once in a week	Discussion Phone-in Story type Model features	Odia		2,00,000-2,50,000
Fitness mantra and yoga	NEWS-7	8 am-9 am	Two days	Discussion Phone-in Story type Model features	Odia		1,50,000-2,00,000
Health show	MBC TV	Sunday - 10:00 am-11:00 am Aids day and cancer day	Once in a week	Discussion	Odia		Average
Health shows	Kanak TV	Aids day Polio day	Occasionally		Odia		
Hello doctor	DD Odia	Monday - 7 pm	Once in a week	Discussion phone-in	Odia		Average
Arogya bharatam	DD Odia	Tues day and friday	Twice a week	Discussion	Odia		Average
Radio							
Agana sata	104 FM	20 min	AIDS day	Discussion	Odia	HIV/AIDS	
Awareness campaign	104 FM	1 min	Each hour for 7 days	Advertisement	Odia	HIV/AIDS	
Aids victism	104 FM		Dec 1st-7th	Live show	Odia	HI/AIDS	
Cancer awareness	104 FM		Cancer day	Talk show	Odia	Cancer	
Quit tobacco	104 FM						
Take care	104 FM		1 day per week (sunday)	Discussion	Odia	Health Issues	
Polio campaign	104 FM	1 min	Each hour	Advertisement	Odia	Polio	
Chocolate top 10	104 FM	5 min	All health day		Odia		
Sustha niramaya jeevan	92.7 FM	20 sec	10 days	Advertisement	Odia	HIV/AIDS	
Cancer awareness	92.7 FM	3 hours		Discussion	Odia	Cancer	8,00,000
Cold allergy	92.7 FM	30 sec	1 week	Advertisement	Odia		8,00,000

disease was television (63.6%) followed by health wall (36.6%), newspaper (21.6%), health facility/service providers (17.7%), radio (9.2%), and other media like posters, pamphlets and folk dance (5.5%). Information on treatment or management of the diseases was received mostly from television (61.2%), poster/leaflets (39.2%), health wall (35.2%) and newspaper (19.7%). In total, 29% of the study population read newspaper daily and Odia, the local language, was the preferred choice for newspaper. Only 14.8% of total participants read health related news in a paper.

Different disease domains and their common sources of getting information

Table II depicts the common sources of getting information which varies for different domains in health. For general information, people rely on TV and health walls most; however for information related to management, they also look for posters/ pamphlets along with TV news. Information regarding the immunisation are always better dispersed by the health worker cadres in our country as is depicted here. The social diseases like HIV/AIDS are mostly

Fig. 1. Socio demographic detail of the study participants from the 4 districts in Odisha.

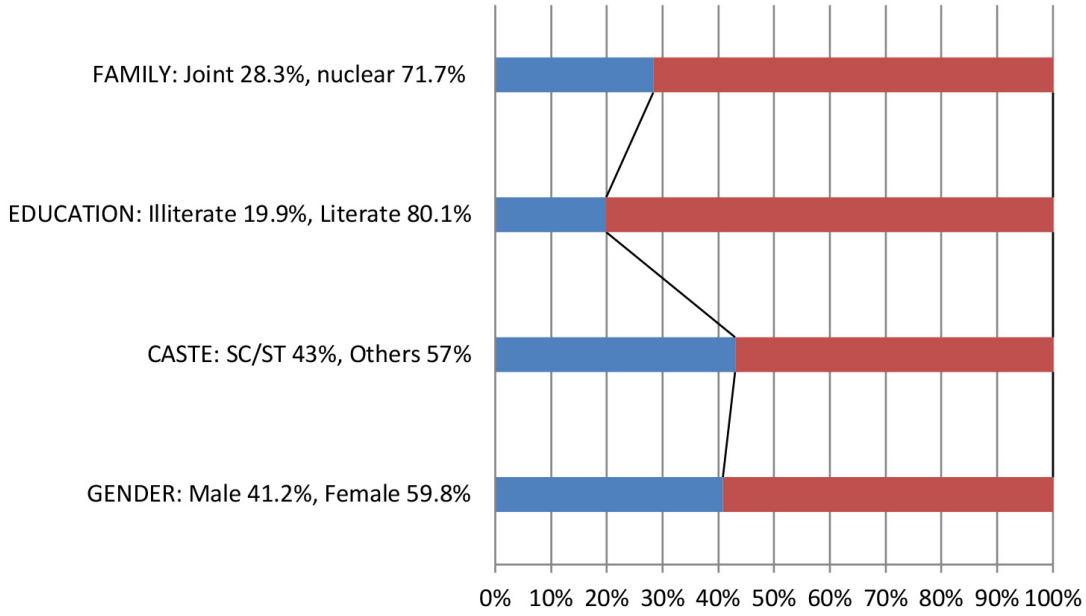
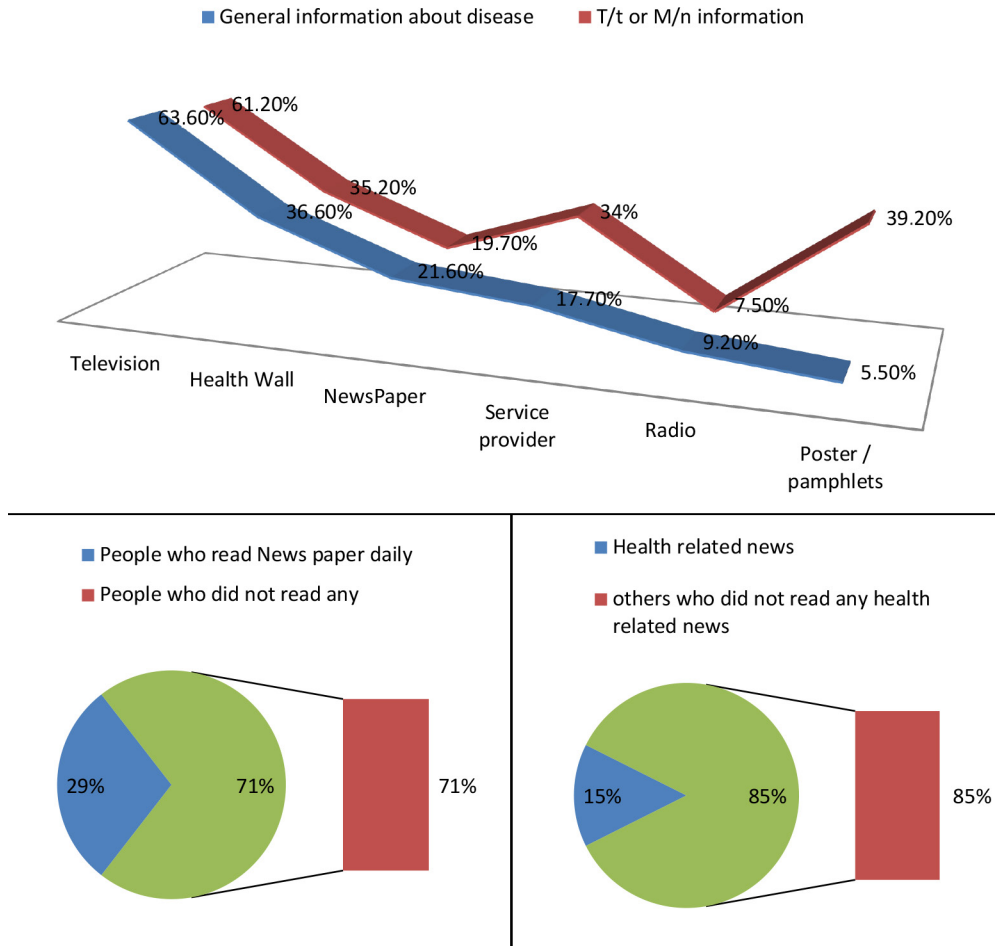


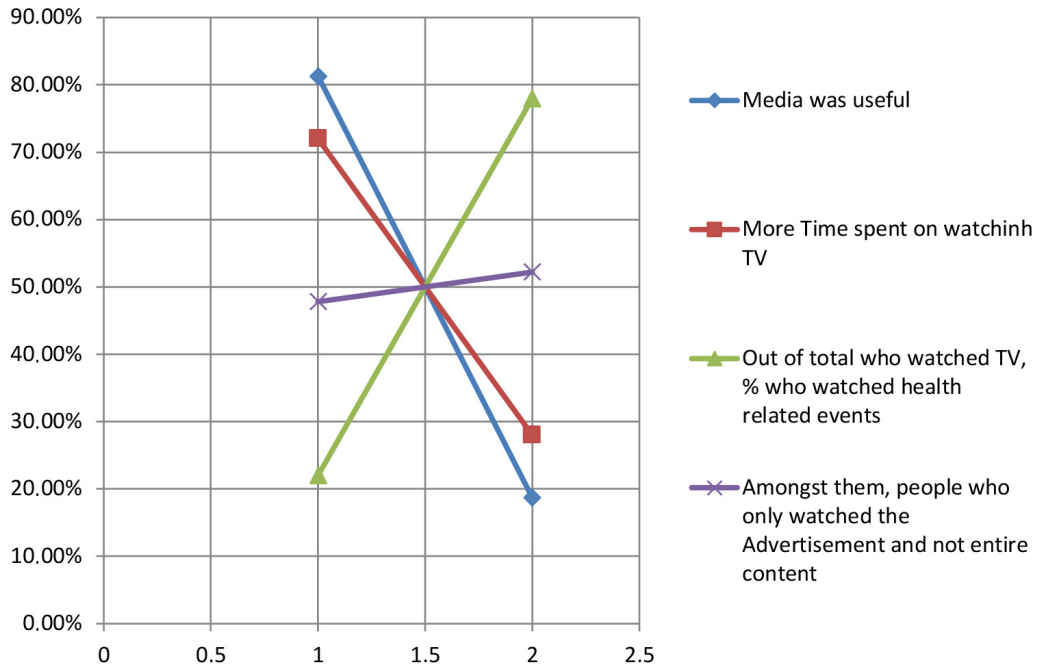
Fig. 2. Matrix showing penetration and accessibility of people to media and communication channels.



Tab. II. Different disease domains and their common sources of getting information.

Sl.No	Health domain	Most common source of getting information	Percentage
1	General information on causation, prevention of disease	Television > health wall	63.6 > 36.6%
2	Information on treatment and management aspects	Television > posters pamphlets	61.2 > 39.2%
3	Immunisation and vaccination	Health service providers like ASHA/AWWs etc.	-
4	Vector borne diseases like dengue , malaria etc.	Health centre facilities > newspapers	50 > 40 %
5	Social diseases like HIV/AIDS	Electronic Media > print media	90 > 80%

Fig. 3. Usefulness of media and its impact on people.



dependant on electronic media like personal messages on mobiles etc. For mosquito borne disease, people seem to look for the health centre hoardings, messages or staff.

Usefulness of media and its impact on people

As shown in the scatter plot in Figure 3, there were 81.3% of the participants who expressed their opinion regarding the usefulness of the newspaper in providing health related information positively. In total 72.8% of total participants watched television on regular basis and among them 70% watched during evening hours. Only 22% of the total population watched any health related programs on TV being run on Sunday and Saturday and among them 47.8% watch only advertisements and not the entire program. The left portion of the plot shows the first values and right ones shows the rest. The greatest variation was shown by people's preference to watch health related events among all the programs and least variation among those who didn't watch the entire content of the advertisement.

Summation of opinions and need assessment of informants

Table III gives a summation of opinions and need assessment of informants based on thematic areas. Out of the total 20 FGDs and 90 IDIs conducted, only 6% of the total study population listened to radio and 3.2% listened to health related program on radio. In total 11% of total study participants used internet either on mobile or computer. The major purpose of the use of internet was for using social media and browsing some websites among the young population. The use of mobile message was not seen to be active in Odisha. Only 8% of people have received any health related message in mobile in past one year. Boards and hoarding provided information to only 16.5% of the study population. The common places to see those were bus stops, hospitals, roads and key traffic junctions. Heath wall was seen in almost all villages of four districts. These walls contained information on various health topics. These were located in important places of the villages. Nearly 36% respondent get health related information from the health wall. The

Tab. III. Summation of Opinions and Need Assessment of informants based on thematic areas.

Thematic areas	Opinions and need assessment	Informant	Quotes
Motif to gather information	Most of them were keen to read newspaper, but search further when they want to know more about something important. They rely more on the Doctor's column since its by renowned experts and whom they cannot get to visit that easily	A 30-35 years old participant from Nawarangpur	"We read newspaper most of the time during leisure time at the shop. Yes, I like the main page and sports news. Recently i have read about the kidney disease. I want more information on diabetes, as one of my relative is having sugar. I prefer the question-answer section most as it is written by the professor of the medical colleges. We cannot visit them for small matters but these provide us very important information"
Faith on health service providers (HSPs)	Many were found to only listen to what their HSP would inform them. This might be due to the faith that HSPs are closest to doctors and give first-hand information	A 45-50 years old participant from Keonjhar	"I do read newspaper but very rarely. Whenever i have any problem i ask the ASHA didi (a frontline community health worker) and get most of the information. She gives us the medicine for small diseases like cold and cough. When we had any big disease, we prefer to go Cuttack. The doctor gives us all information about the disease"
Time	Many watched TV and would mostly see the health related Ads only when it came in the Break slot or change slot. Health Talk shows were also an instant Hit	An elderly participant from Puri	"We do not watch the program as such, but we watch the advertisement comes in between serials. I remember last time I have seen one talk show on childhood illness in O TV. Two doctors from medical colleges were there. I tried the number to ask my question but i could not talk to them. However they answered very nicely to all the questions being asked. I got to know about many things from that show. I will try to watch is regularly"
Reliability	Youngsters were seen showing their reluctance and not believe whatever was surfed on internet, Rather, they said they would opt clarifying from doctor himself	A30-35 years old farmer from Puri	"We use internet for Whatsapp and Facebook. Sometimes I browse for jobs and other documents. I have not used internet to know about any disease, as I get most of the information from the doctor we visit"
Mode of transmit	Few young adults were found to be keen on getting messages on mobile phone especially related to advice on diet. They wanted to receive more such messages	A young adult from Keonjhar	"Last time I remember to get a message in my mobile was on use of fruits, vegetables and life style changes from AYUSH department. After that I have not received any such messages. It is good to see messages but how many people can read it? It should be more regular and on the disease or problem specific to our area like TB or Malaria"
Preferences	It was found that waiting areas, whether shop, hospital, railway, bus stop etc. are the perfect areas where one gets to or is bound to go through. These needs to be catchy, crisp and updated	A 35-40 year old businessman from Puri	"Most of the boards I see when I visit any hospital. Not every time I read those but when I was waiting for my turn or accompanying any patients I prefer to read those. Here most of the hoardings are old and colour faded. Some are placed by the NGOs. That need to be more attractive and more in number within our block"
Preferences	Some prefer close and secluded places especially females and so they prefer the lady of the village to call them and speak	A 40-45 years old housewife from Bargarh	"It is the VHND session (Village health and nutrition day) where i get information on mother and child health. ASHA didi, ANM didi provides us information on immunization, nutrition and check our health. They personally contact us during the time of immunization. I think besides that i get information about pulse polio from television that comes in between the serials"
Sensitive information	Social issues or sensitive talks need to be addressed on a one to one basis and then gradually in groups. Some prefer to keep it open but many need closed door discussions. HSPs should also be trained on how to disburse information with all cares to privacy and autonomy	A shopkeeper from Keonjhar	"Everyone in our village is aware of HIV/AIDS but no one talks about it. I got the information from the dance show done five years back. Then I saw in the big hoarding and posters near bus stop with clear messages on spread of the disease. I remember when I initiated the discussion at my shop few people walked away. Now the situation has changed. Even in TV during films and serials we get advertisement on this. As this is little sensitive issue the health workers are not discussing with us. I do not know if they are discussing with the women or not"

preferred source of information changes according to the disease and health information.

Immunization related information, interpersonal communication through grass root health workers (Accredited Social Health Activists-ASHA, Anganwadi worker (AWW), Auxillary Nurse Midwife-ANM) was found to be more effective and preferred among the population. They got more information on these during the village health and nutrition days (VHND). Other media like posters, health wall and TV played equal role in providing information on immunization.

In all the districts, interpersonal communication was seen to be accepted as a strong medium of communication for having knowledge and awareness on breast feeding and safe motherhood practice. The health worker's direct interaction with the target beneficiaries during VHND sessions were found to be an effective strategy. Nearly 30% of the respondents mentioned about the health wall and TV as their source of information. Similar responses were seen for having information on family planning along with higher contribution from electronic and print media.

Electronic (90.2%) and print media (80.5%) were cited to be major source of information on HIV/AIDS followed by posters among the respondents. More than 10% of the respondent mentioned about folk media and hoardings/ boards as their source of information on the disease.

Health centres or facilities (50.1%) and newspaper (41.3%) were cited to be leading sources of information on infectious diseases like malaria, filarial, TB and diarrhoea as well as NCDs. Folk media had a major role here as 32.3% of the study population got information regarding infectious diseases from folk media.

Discussion

The Ottawa Charter of 1986 for health promotion conveys a set of actions to foster well-being and good health. Built upon the construct of 5 principles of positive health, participation, competence, perspective and equity, it strategizes essential components for health promotion. If we notice, all the essential strategies in the Charter hinge upon creating effective communication and mass media coverage for taking up the desired shape, whether it is building healthy public policies, creating supportive environment, developing personal skills or reorienting health services. Once these key actions are incorporated by the 3 pillars of enabling, mediating and advocating processes, we can speculate a community of health literate people capacitated enough to obtain, process, and understand basic health information and services needed to make appropriate health decisions. This is what our tree of vision is; which is possible only with effective communication strategies as the roots. The firmer the rootlets are, the faster is the vision shaped up.

Communication constructs: penetration, acceptability, accessibility and delivery

The major source of information on prevention and treatment of diseases for the households was TV followed by health wall and newspapers. These avenues should be exploited adequately by the healthcare system to optimize delivery of key health messages. A systematic literature review of effectiveness of community based strategies in increasing screening access showed that strategies that combining mass media campaigns with direct tailored information transmission to beneficiaries by service providers seemed most successful [7]. Customizing and tailoring the health messages is one of the major benefits of flexible mass media campaigns using social media and personalized situation based targeted messaging services. Inclusion of health promotion practices in routine care is imperative for a strong healthcare system. Individual counselling for improved nutrition, physical activity, smoking cessation, stress management, weight control and other health related behaviours is based on this approach of health promotion [8].

Interpersonal communication is a key skill among service providers, especially in communities with low levels of education. In this study less than 18% of the respondents had received information on identification and prevention of diseases from the healthcare service providers. Lack of confidence and absence of structured mechanisms of message communications by the service providers might be the reason for this. Additionally message framing also plays a key role in the decision making process regarding access to healthcare. Positively framed messages based on social variables tend to have a strong impact on an individual's acceptance of the message [9].

Although less than 15% participants got their health related information from newspapers, more than 81% expressed their opinion regarding the usefulness of the same in providing health related information. However, optimum use of this media may be made to advocate the public adoption of basic preventive measures, like handwashing, while such messages may be displaced in a mass media dominated by discussion of technical interventions [10].

Penetration of TV for media consumption was high at over 72%, but around 48% of the participants did not watch the entire show related to health information. TV shows like health talks and phone in programs are preferred by the people because of the chance of getting information from specialist. Penetration of radio as a medium is poor with only 3% of the population listening to health related programs on the radio. Exposure to messages by such media is generally passive, resulting from an incidental effect of routine use. The likelihood of success of such messaging is substantially increased when the target behaviour is one-off or episodic (e.g., screening, vaccination, children's aspirin use) rather than habitual or ongoing (e.g., food choices, sun exposure, physical activity) [11].

The use of internet and social media is on the rise with 11% accessing this media. However, the use of mobile messaging services for delivery of health information does not seem to be active in the state, with only 8% receiving any health information related SMS in the past year. Lack of control in onward movement of

health messages can pose a serious challenge to the widespread use of social media for this purpose. The message can be distorted during chains of sharing and unintended results attained. With increasing penetration of internet, health information should be disseminated in a structured manner. There is also the added risk of emerging health hazards being over-reported in mass media in comparison to common threats to public health [12]. Therefore frameworks for health promotion education, as well as evidence based and ethical health promotion methods which have been developed may warrant further studies in detail [13].

Boards and hoarding provided information to only 16.5% of the study population. Hoarding and boards at strategic places are cited to be important source of information for male members, as they travel out for work for most of the time. These could be efficiently used for 'negative advertising' as evidenced by anti-tobacco messaging in recent decades. Literature suggests that 'negative advertising' is an effective way to encourage behavioural changes, but it has enjoyed limited use in public health media campaigns. However, as public health increasingly focuses on NCDs prevention, negative advertising could be more widely applied [14].

The penetration of the health wall strategy was very good with nearly all study villages having these at important places in the village. Nearly 36% respondent get health related information from the health wall. Health wall or "Swasthya Kantha" in local language is an initiative by the State Government to communicate health messages by using an Integrated Behaviour Change Communication strategy and the Information and Needs Assessment in tribal districts undertaken by State Government. Odisha is a state, rich in folk art. It is also a land where stories and legends appeal to people. It was anticipated that using the 'Kantha Kahe Kahani' (wall tells a story) format to transmit health messages, people would shed old habits and adopt new and healthy behaviours [15].

Health workers using interpersonal communication was more preferred and effective within the community for immunization, breastfeeding and safe motherhood practices related information. The direct contact sessions with the health workers occurred during VHND sessions, which were found to be an effective strategy. VHND is a monthly village level activity for dissemination of information and service packages ranging from MCH, immunization, nutrition, family planning, sanitation, health promotion, counselling and others.

Print media and electronic media contributed more to the information accessed on family planning. These media types were also major sources of information on HIV and AIDS which lacked interpersonal communication due to social taboo in the community. Choice of television as medium of communication seems to be effective in addressing these concerns arising from behavioural and access differences between different socio-economic strata [16].

Health centres and newspapers were the major source of information on diseases which were the focuses of national control programs such as Malaria, Filaria, TB and NCDs. Folk media had a major role regarding information on prevention and control of infectious diseases. But information on NCDs are lacking in the community. The FGD members expressed that the health workers are more focusing on MCH. It has been observed that socio-demographic factors such as education and age affect individuals' use of and access to communication channels [17]. The receivers trust in the media of communication is an important factor at play in selection of the choice of media by policy makers. This trust by individuals is related to both their perception of the mass communication process and also to socio-demographic factors, but is more strongly related to the former [17-19].

Community need assessment

A detailed view point of people of the Odia community in the four districts of Odisha as selected by random sampling showed that most of them are literate, watch TV, use mobiles mostly for entertainment and social surfing, are health conscious and sufficiently motivated to know more about diseases and take care of their health. The government has a strong mandate of fulfilling the health care needs of its citizens and has introduced many programs through the National Health Mission. In addition to a robust policy and responsive leadership, the active participation of community is the catalyst for seamless and effective implementation of these services. On one end of the spectrum, we have the societal norms of the community which are deeply embedded, whereas, on the other end is the intervention and policies designed to influence behaviour. Thus, a judicious balance between the norms and values of people and public regulations has to be created; where the provider needs to synchronize their services with the societal mind-set and cultural acceptability of people, and adopt appropriate steps as per the contemporaneous need to achieve their desired outcomes [20-22].

The coverage of media in the state is widespread too. Daily newspapers like vernacular language also have online links too. Most of them watch Odia daily soaps regularly like a ritual. Besides, there are many health shows which discuss important diseases and consult telephonically too. Institutes of media studies can nurture health journalists and intellectuals who further aid in preparing crisp messages to capture audience. The Health Management Information System is yet one such umbrella platform which works with harmonious coordination within the state and also has been applauded from time to time. It manages all information obtained from various sectors and gives a first-hand information about the what and how. With data delivery at click of our fingertips, it becomes easy to move further to communicate with the people as per their demands and needs [23, 24].

Therefore, when the providers and beneficiaries are ready, the sole thing to diligently work upon is the generation of demand. Individual demands like in our survey are like wishes, which might fade or might take a backseat in due

course of time. However, when the demand generation comes as a force from the community as whole, it becomes reckoning. The presence of stakeholders, experts, community leaders and other members officiate the demand generation which becomes a command. The realisation that cultural beliefs are deep rooted and imbibed and needs to be uprooted gradually has to start from the people themselves. It is then that providers can aid and help them come out [24, 25].

Conclusions and recommendations

Interpersonal communication is believed to be most acceptable source of information on MCH, immunization and neonatal care. Appropriate skill building of service providers needs to be taken up for optimum use of this media. Educational level and media habit was found to be strongly correlated. For people with low literacy, health wall campaign, folk media and interpersonal communication was found to be effective. Tailoring of messages for different socio-economic and education strata can help uniform dissemination of key health messages.

The community tends to obtain information from particular sources for specific diseases like physician's communication, posters and TV shows for infectious diseases and newspapers for non-communicable diseases. This fact can be used to determine the choice of media for specific health messages. Internet is yet to percolate a large section of population and geography in the state. People prefer to receive messages on mobile on health related topics at regular interval. While the use of social media expands rapidly, frameworks need to be adapted for source controlled, secure, truthful and ethical transmission of communications related to health.

VHND is considered a great platform for transmission of the information and key messages to the beneficiaries and an intensive and structured health communication towards locally sensitive health promotion needs may be developed. Awareness on the sanitation and hygiene programs, projects and different national health programs was adequate, and newspaper, wall posters and health workers were the major source of information on such programs.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

SP, SKP and SS conceptualized the study. SP, PM, SS designed the study's tool. SS and SKP, MP were involved in the data collection. SS, MP, RS and PM analysed the data. JSK, SKP and MP wrote the first draft which was further refined by SP, RS and PM. All were involved in writing and reviewing the manuscript. All authors have gone through the manuscript and approved the final version.

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RESEARCH PAPER

Public awareness of environmental risk factors of cancer and attitude towards its prevention among the Lebanese general population

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Keywords

Awareness • Cancer • Risk factors • Lebanese • Prevention

Summary

Introduction. *Since the majority of cancers occur as a result of modifiable risk factors, cancer is being seen more as a preventable disease. The primary objective of our study was to assess the level of awareness of environmental risk factors of cancer among the Lebanese general population. The secondary objective focused on identifying the predictors of the preventability of the disease.*
Methods. *We conducted a cross-sectional study between June and July 2020. An online questionnaire was used to collect data pertaining to the knowledge of environmental risk factors of cancer, source of information and personal practice of the participants. Bivariate and multivariate analyzes were performed.*
Results. *About 387 respondents agreed to participate in the study. The study showed low awareness regarding infectious agents, lifestyle, diet and many work exposures. The predictors of the attitude of respondents regarding the preventability of cancer were: believing that cancer has an environmental cause (p=.014), not having a healthy lifestyle (p = 0.004), not smoking waterpipe (p = 0.023), being single (p = 0.013), and having a university degree (p = 0.049).*
Conclusions. *Efforts should be made to improve awareness of the cancer risk factors regarding infectious agents, lifestyle, diet and many work exposures. This can also be followed by further studies assessing the impact of these community and governmental cancer prevention initiatives on cancer risk factors level of awareness.*

Introduction

Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or one in six deaths in 2018 [1]. In Lebanon, the risk of being diagnosed with cancer before the age of 75 is estimated to be 17.5% and 7,100 new cases of cancer are diagnosed each year [2].
According to the World Health Organization research, 35% of deaths caused by cancer worldwide are due to potentially preventable or modifiable risk factors. These risk factors are related to lifestyle, including smoking and alcohol consumption, infections, parasites, exposure to ultraviolet (UV) light and tanning using devices that emit UV radiation, environmental exposures, dietary factors, hormone replacement therapy, as well as exposure to ionizing radiation [3-6]. Worldwide, tobacco use causes the death of around 6 million people every year [7]. Cigarette smoking is the most harmful form of tobacco use, causing the largest cancer burden. Passive smoking, like actual smoking is also carcinogenic. Substances contained in tobacco smoke sediments remains chemically active and are harmful to health [7-9]. Moreover, the international agency for research on cancer (IARC) has classified alcohol as a Class I carcinogen for liver cancer [10, 11]. It also increases the risk of cancer of the mouth, throat, larynx, esophagus, liver and breast [10-12]. Diet also plays an important role in contributing to cancer development. Indeed, the World Cancer Research Fund Report 2007 estimates that 35% of the incidences of cancer worldwide can be linked to nutrition and lack of physical activity [13]. Epidemiological studies have also shown that obese patients with oncological treatment have worse prognoses and greater morbidity and mortality than those with normal Body Mass Index (BMI) [14, 15]. According to a synthetic analysis, infections are linked to about 15.4% of cancers worldwide [16], this percentage is variable between countries and was found to be approximately equal to half of the worldwide burden in Italy [17]. Another cancer risk factor is certain workplace exposures. The Centers for Disease Control and Prevention (CDC), estimates 3 to 6% of all cancers worldwide to be caused by exposures to carcinogens in the workplace [18]. Additionally, over 120 chemical or biological agents are classified as carcinogens by the IARC [19]. The main agents found to be contributing to the workplace cancer are asbestos, shift-work involving night work, mineral oils, solar radiation, silica, Diesel Engine Exhaust (DEE), coal tars and pitches, occupation as a painter or welder, dioxins, environmental tobacco smoke, radon, tetrachloroethylene, arsenic and strong inorganic acid mists [20]. Indoor radon could explain 10% of all

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lung cancer deaths each year in France [21]. To add, according to a recent study done in South-Eastern Italy, areas at higher radon concentrations seem to overlap with those characterized by the highest pulmonary cancer mortality and incidence rates, thus indicating that human exposure to radon could possibly enhance other individual or environmental pro-carcinogenic risk factors (i.e. cigarette smoking, air pollution and other exposures) [22]. Other important carcinogens that are found to be linked to cancer include bisphenol A, phthalates and naphthalene [23, 24], household cleaning products, plastic containers, indoor combustion, soot and wood dust [25].

Cancer prevention is a crucial step and the most cost-effective long-term strategy for the control of cancer specially in middle and low-income countries [26]. Prevention programs are an important weapon to fight against cancer, because they can contribute to reducing both the incidence of cancer and mortality [27]. The risk of getting cancer can be also reduced by making healthy choices. Keeping a healthy weight, avoiding tobacco, limiting the amount of alcohol you drink, eating a healthy diet with plenty of fruit and vegetables, exercising regularly, limiting alcohol use, practicing safe sex, reducing exposure to UV and ionizing radiations (occupational or medical diagnostic imaging), avoiding urban air pollution and indoor smoke from household use of solid fuels can all contribute to decreasing the risk of cancer [1].

Awareness of evidence-based risk factors is considered an important part of cancer prevention. Many studies were done in the US [28], UK [29]causing an estimated 9.6 million deaths in 2018. Low cancer symptom awareness has been associated with poor cancer survival for all cancers combined. The Cancer Awareness Measure (CAM, Japan [30], Tanzania [31], Nepal [32], Iran [33], UAE [34], Oman [35], Saudi Arabia [36], India [37]) to estimate the knowledge of people about cancer and its risk factors and to implement many public health interventions to increase awareness. The knowledge level differed between these countries. Other studies suggest that awareness of specific risk factors vary for different cancer types [38].

In Lebanon, several studies estimated the knowledge of risk factors of specific types of cancer like colorectal cancer [39], breast cancer [40] and cervical cancer. However, no studies were done to assess the level of public awareness concerning the evidence-based risk factors of cancer in general among the Lebanese general population. There is a need for such studies in Lebanon in order to know how to intervene and implement a prevention strategy specially that the cancer incidence in Lebanon is among the highest in the region and is expected to remain as such over the coming decade [41, 42]. Thus, the primary objective of this study was to assess the public awareness of environmental risk factors for cancer among the Lebanese general population. The secondary objective focused on identifying the predictors of the attitude of respondents regarding the preventability of the disease.

Materials and methods

Study design and participants

A descriptive cross-sectional study was conducted over a period of two months from June until July 2020 to estimate the awareness about the environmental risk factors of cancer among the Lebanese general population. The inclusion criteria included: being Lebanese aged 18 or more, residing in Lebanon, and speaking Arabic or English.

Sample size calculation

To calculate the minimum sample size needed, Epi info was used. The expected frequency was set 50% because no similar study was conducted in the region and a margin error of 5% was also considered. Accordingly, 384 participants were required and targeted.

Data collection tool

The tool used in this study was an online standardized questionnaire developed using google form. The questionnaire was based on literature review [19, 28-30, 34-36]. It consisted mainly of closed-ended, dichotomous (yes/no), multiple choice questions or a 5-point Likert type scale (1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly Agree).

The questionnaire encompasses 3 main parts. The first part is entitled "demographic and general information" and was mainly to collect sociodemographic and background information about the participants. The second part is entitled "General knowledge about cancer and its environmental risk factors" and contained questions regarding 43 environmental cancer risk factors where the answer would be in the form of 5-point Likert scale. This part also included a question about if the participant thinks cancer is preventable or not and 3 questions regarding the participant source of information. The third part is entitled "personal practice" and was mainly designed to collect some information about the participant lifestyle. This section included questions about lifestyle habits and behaviors that can somehow reflect if the participant is trying to have a healthy lifestyle or not specially that these behaviors are self-controlled like smoking, waterpipe, alcohol consumption, red meat consumption, fruits and vegetables consumption, physical activity, high sugar food consumption and excessive exposure to sunlight. The questionnaire was first written in English, translated to Arabic and then back translated to English by another person. The objective of the questionnaire was provided at the beginning of the survey in the cover letter which included the purpose of the survey and the time needed to fill the questionnaire which is 5 to 10 minutes. To ensure face and content validity, the questionnaire was pilot tested and reviewed by three experts in the field of cancer.

Recruitment of participants

Questionnaires were first sent electronically as a link using Google forms through social media applications. The response rate was estimated based on the percentage of people responding by Yes to the question asking them if they accept to participate in the study that was mainly considered as a consent. Although we couldn't track the non-responders, reminder messages were sent again. A pilot study of 14 respondents was conducted to assess the clarity of the questionnaire in both languages and the validity and reliability of the Arabic version. Even though, this study doesn't require any definite ethical approval but a verbal consent was obtained from all participants before filling the questionnaires by asking them if they want to participate in the study. All data were collected in a manner that respects participant's anonymity and confidentiality.

Statistical analysis

Analysis of data was carried out using the Statistical Program for Social Sciences (SPSS) version 21. Descriptive analysis was first performed to evaluate the distribution of the socio-demographic characteristics of the participants, their lifestyle behaviors, their knowledge about cancer and its environmental risk factors, and their source of information. The dependent variable is a dichotomous variable: cancer preventable or not. Bivariate analysis was done for all variables related to sociodemographic, cancer history, cancer cause and practice. Since all of our variables are categorical variables, the Chi square and Fisher exact tests were used when applicable. The Cochran Armitage trend test was performed for categorical variables following a specific order such as age, BMI, income, education and variables related to practice. Differences with a two-tailed p-value < 0.05 were considered as statistically significant. Multivariate analysis using logistic regression was also performed. Since the number of participants is less than 500 the forward LR method was used. The entered variables are the variables having a p-value < 0.2 in the bivariate analysis. The adjusted odds ratio (OR) and 95% confidence intervals generated by the multiple logistic regression models were used to describe the relationship of the entered variables with the attitude of the participants toward the preventability of cancer. To test the reliability between the questions related to the same risk factor in the questionnaire, we used Cronbach alpha. To ensure construct validity of our questionnaire, a factor analysis was performed considering all the environmental risk factors. Our items were all in the form of Likert scale. Then, to ensure the reliability of the questionnaire, Cronbach alpha of the whole list of environmental risk factors was calculated.

Results

Participants baseline characteristics

Only 387 individuals accepted to participate in our study with 99.5% participation rate. In total, 207 participants were women (53.5%) while 180 were men (46.5%). Most of our participants were young where 52.7% of them were aged between 18 and 24 and only 3.1% were 65 years or above. Most of the participants were single (63.8%) and were from different regions in Lebanon. To note here, 56.3% of the participants were living in urban places while 43.7% lived in rural places. The majority of the participants (84.0%) completed one or more university degree. It should be noted that 80.1% of the participants didn't work in the medical field. The majority of the participants (95.1%) didn't undergo any cancer screening, and didn't have cancer (97.2%) (Tab. I).

Knowledge about risk factors of cancer and attitude regarding the prevention of this disease

The majority of our participants have heard information about cancer (89.9%). Internet (74.2%) was the most common source of information about cancer in general. The most preferred sources identified by the participants to receive information concerning environmental risk factors of cancer were healthcare professionals (51.9%) and internet sources (43.7%).

Approximately 86 % of the respondents agreed that the cause of cancer is both genetic and environmental and 56 % agreed that cancer could be preventable (Fig. 1).

The environmental risk factors of cancer positively identified by the participants were environmental pollution (91.5%), smoking (90.4%), industrial pollution (88.3%), nuclear rays (85.5%), UV radiation (83.5%), X rays (72.6%), tobacco exposure (72.4%), processed food (72.1%), long term use of preservatives (68.8%), excessive sunlight exposure (65.9%), artificial sweeteners (65.3%), pesticides (65.4%), genetically modified food (65.2%), uranium (64.9%), high sugar diet (63.4%), living close to high voltage transmission lines (62.0%), alcohol (61.8%), stress (58.7%), plastic bottles (58.4%), hormone in beef (51.9%), red meat (50.9%), diesel exhaust (49.9%), unbalanced diet (49.8%), mobile phones (48.3%), paints (48.3%), obesity (45.5%), and hormonal treatment after menopause (45.0%).

Low awareness was found among the following factors: benzene (43.1%), low fiber diet (40.1%), low physical activity (38.2%), infections (36.6%), naphthalene (36.4%), many sexual partners (36.4%), radon (32.3%), asbestos (31.8%), arsenic (31.5%), vitamin D deficiency (31.5%), phthalates (27.6%), bisphenol A (27.1%), breastfeeding for less than 6 months (23.5%) and wood dusts (19.4%). To note, only a small percentage of participants disagreed with the fact of considering coffee and Mediterranean diet as risk factors of cancer (33.3% and 15.8% respectively) (Fig. 2).

The participant's lifestyle characteristics

Half of the participants (51.7%) considered themselves living an unhealthy lifestyle and 82.4% considered

Tab. I. The socio-demographic characteristics of the study population.

Variable	Categories	Frequency (n = 387)	Percentage (%)
Gender	Male	180	46.5
	Female	207	53.5
Age	18-24	204	52.7
	25-44	120	31
	45-64	51	13.2
	65 or above	12	3.1
Marital	Single	247	63.8
	Married	128	33.1
	Divorced	6	1.6
	Widowed	6	1.6
Education level	Elementary/intermediate/high school	62	16.1
	Bachelor's degree	215	55.6
	Master's or PhD degree	110	28.4
	PhD		
Income	< 675 000 LBP	49	12.7
	675 000-999 000	46	11.9
	1 000 000-1 999 000	110	28.4
	2 000 000-2 999 000	76	19.6
	3 000 000 or above	106	27.4
Working in the medical field	No	310	80.1
	Yes	77	19.9
Region	North	42	10.9
	South	65	16.8
	Beirut	96	24.8
	Beqaa	27	7.0
	Mount Lebanon	81	20.9
	Nabatiyeh	30	7.8
	Akkar	21	5.4
	Baalback/hermel	25	6.5
Living place	Urban	218	56.3
	Rural	169	43.7
Cancer screening	No	368	95.1
	Yes	19	4.9
Having cancer	No	376	97.2
	Yes, I had	2	.5
	Yes, I'm currently having	9	2.3
Know someone having cancer	No	100	25.8
	Yes	287	74.2
Occupation	Unemployed	179	46.3
	Agriculture	9	2.3
	Manufacturing	4	1.0
	Trade	42	10.9
	Transport, Post and telecom	11	2.8
	Services/Financial intermediation/insurance	119	30.7
	Retired	8	2.1
	Other/not specified	15	3.9

themselves living in an unhealthy environment. About 67.7% of the participants were non-smokers and 54.0% didn't smoke waterpipe. The majority of the participants didn't drink alcohol (83.2%) and most of the participants exercised for 30 minutes 3 times per week but with different frequencies (78.9%). About 30.2% of the participants eat five fruits and vegetables per day most of the time. Only 11.9% of the participants consume red meat more than three times per week while 75.4% consume red meat less than 3 times and 12.7% don't consume red meat at all. In addition, 9.0% of the participants don't consume high sugar food and only 25.1% don't expose themselves excessively to sunlight. To note, almost half of the participants (48.3%) had a normal BMI, 35.4% were overweight, and 11.6% were obese (Tab. II).

Fig. 1. Descriptive analysis of cancer causes and preventability.

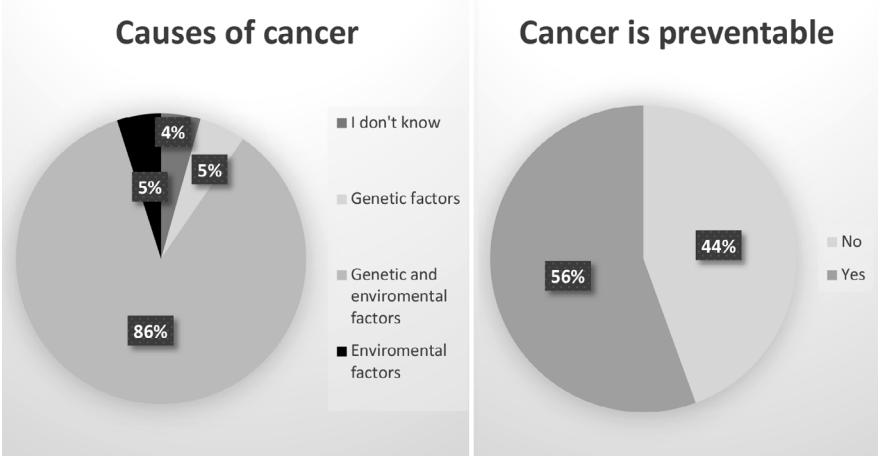
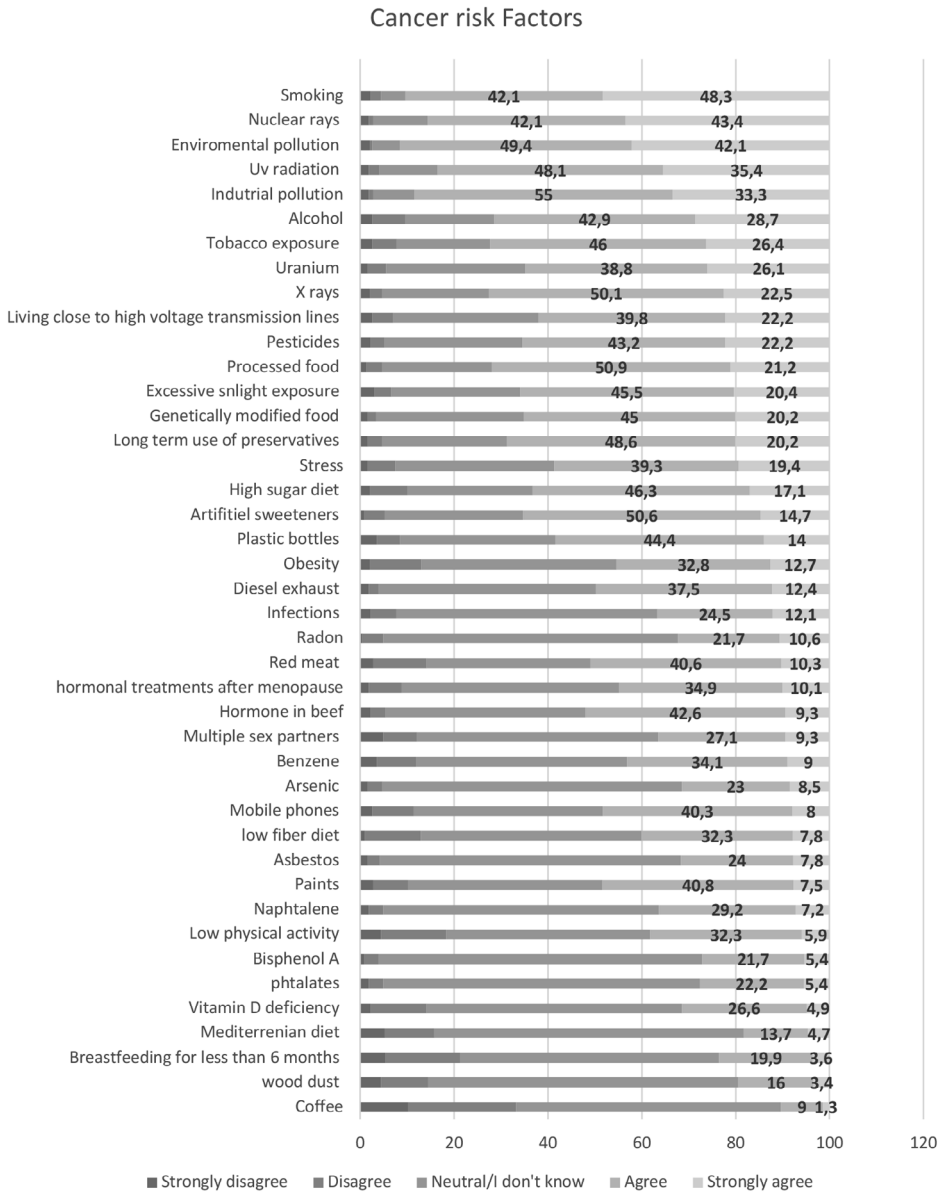


Fig. 2. Knowledge of the participants of the environmental cancer risk factors.



Tab. II. Table summarizing the lifestyle of the participants-

Variables	Categories	Frequency (n = 387)	Percentage (%)
Healthy lifestyle	No	200	51.7
	Yes	187	48.3
Healthy environment	No	319	82.4
	Yes	68	17.6
Cigarette smoking	No	262	67.7
	Yes, more than 20 cigarettes per day	28	7.2
	Yes, less than 20 cigarettes per day	48	12.4
	Sometimes	21	5.4
	Rarely	28	7.2
Water pipe smoking	No	209	54.0
	Yes, everyday	51	13.2
	Most of the times	29	7.5
	Sometimes	41	10.6
	Rarely	57	14.7
Alcohol intake	No	322	83.2
	Yes, not more than 1 drink per day	5	1.3
	Sometimes	24	6.2
	Rarely	36	9.3
Doing at least 30 mins of physical activity 3 times per week	No	82	21.2
	Yes, always	79	20.4
	Most of the times	68	17.6
	Sometimes	80	20.7
	Rarely	78	20.2
Eating at least 5 fruits and vegetables per day	No	55	14.2
	Yes, everyday	54	14.0
	Most of the times	117	30.2
	Sometimes	112	28.9
	Rarely	49	12.7
Consuming red meat	No	49	12.7
	Yes, more than 3 times weekly	46	11.9
	Yes, 3 times weekly	120	31.0
	Sometimes (up to 3 times/month)	83	21.4
	Rarely	89	23.0
Consuming high sugar food	No	35	9.0
	Yes, everyday	28	7.2
	Most of the times	73	18.9
	Sometimes	152	39.3
	Rarely	99	25.6
Being exposed excessively to sunlight	No	97	25.1
	Yes, everyday	12	3.1
	Most of the times	44	11.4
	Sometimes	104	26.9
	Rarely	130	33.6
BMI	Underweight (< 18.5)	18	4.7
	Normal (18.5 through 24.99)	187	48.3
	Overweight (25 through 29.99)	137	35.4
	Obese (30 or above)	45	11.6

BMI: Body Mass Index; Underweight < 18.5; Normal: Between 18.5 and 24.99; Overweight: Between 25 and 29.99; Obese > 30.

Sociodemographic characteristics and attitude regarding the preventability of the disease

Regarding the sociodemographic characteristics of the participants, the variables that were found to be significantly associated with the attitude of patients regarding the preventability of cancer were: gender ($p = 0.014$), age ($p = 0.000$), education ($p = 0.001$), occupation ($p = 0.000$), region ($p = 0.000$), medical field ($p = 0.064$), living place ($p = 0.041$), having cancer ($p = 0.003$), and knowing a family member or a friend having cancer ($p = 0.015$) (Tab. III).

The variables found to be significantly associated with the attitude of patients regarding the preventability of cancer were: BMI ($p = 0.000$), having a healthy life ($p = 0.015$), smoking ($p = 0.000$), waterpipe ($p = 0.000$) and alcohol ($p = 0.055$) (Tab. IV).

Tab. III. Sociodemographic characteristics and the attitude regarding preventability of cancer.

Variable	Cancer not preventable (N = 172)		Cancer preventable (N = 215)		
	n	%	n	%	P-value
Gender					
Male	92	53.5%	88	40.9%	0.014†
Female	80	46.5%	127	59.1%	
Marital					
Single	88	51.2%	159	74.0%	0.000†
Married/Divorced/Widowed	84	48.8%	56	26.0%	
Age					
18-24	76	44.2%	128	59.5%	0.000† 0.000‡
25-44	53	30.8%	67	31.2%	
45-64	33	19.2%	18	8.4%	
65 and above	10	5.8%	2	0.9%	
Education					
Elementary/intermediate/ high school	33	19.2%	29	13.5%	0.001†
Bachelor's degree	107	62.2%	108	50.2%	
Master's or PhD degree	32	18.6%	78	36.3%	
Occupation					
Unemployed	79	45.9%	100	46.5%	
Agriculture	8	4.7%	1	0.5%	
Manufacturing	2	1.2%	2	0.9%	
Trade	23	13.4%	19	8.8%	0.000¥
Transport	8	4.7%	3	1.4%	
Services	40	23.3%	79	36.7%	
Retired	7	4.1%	1	0.5%	
Not specified/other	5	2.9%	10	4.7%	
Income					
<675 000 LBP	19	11.0%	30	14.0%	
675 000 - 999 000	18	10.5%	28	13.0%	0.303† 0.759‡
1 000 000 - 1 999 000	53	30.8%	57	26.5%	
2 000 000 - 2 999 000	40	23.3%	36	16.7%	
3 000 000 or above	42	24.4%	64	29.8%	
Region					
North	19	11.0%	23	10.7%	
South	29	16.9%	36	16.7%	
Beirut	28	16.3%	68	31.6%	
Beqaa	20	11.6%	7	3.3%	0.000†
Mount Lebanon	30	17.4%	51	23.7%	
Nabatiyeh	20	11.6%	10	4.7%	
Akkar	7	4.1%	14	6.5%	
Baalbeck/Hermel	19	11.0%	6	2.8%	
Working in the medical field					
No	145	84.3%	65	76.7%	0.064†
Yes	27	15.7%	50	23.3%	
Living place:					
Urban	87	50.6%	131	60.9%	0.041†
Rural	85	49.4%	84	39.1%	
Cancer screening					
No	162	94.2%	206	95.8%	0.461†
Yes	10	5.8%	9	4.2%	
Had cancer					
No	162	94.2%	214	99.5%	0.003¥
Yes, had cancer or currently having	10	5.8%	1	0.5%	
Know a friend or family member having cancer					
No	34	19.8%	66	30.7%	0.015†
Yes	138	80.2%	149	69.3%	

†: chi square;‡: Cochrane; ¥: fisher.

Tab. IV. Association between lifestyle and attitude regarding preventability of cancer.

	Cancer not preventable		Cancer preventable		
	n	%	n	%	P-value
BMI					
Underweight	3	1.7%	15	7.0%	Variable
Normal	67	39.0%	120	55.8%	
Overweight	74	43.0%	63	29.3%	
Obese	28	16.3%	17	7.9%	
Healthy life					
No	77	44.8%	123	57.2%	0.015†
Yes	95	55.2%	92	42.8%	
Healthy environment					
No	146	84.9%	173	80.5%	0.256†
Yes	26	15.1%	42	19.5%	
Smoking					
No	94	54.7%	168	78.1%	0.000† 0.000‡
Rarely	17	9.9%	11	5.1%	
Sometimes	15	8.7%	6	2.8%	
Yes less than 20 cigarettes per day	26	15.1%	22	10.2%	
Yes more than 20 cigarettes per day	20	11.6%	8	3.7%	
Water pipe					
No	66	38.4%	143	66.5%	0.000† 0.000‡
Rarely	32	18.6%	25	11.6%	
Sometimes	26	15.1%	15	7.0%	
Most of the times	22	12.8%	7	3.3%	
Yes everyday	26	15.1%	25	11.6%	
Alcohol					
No	137	79.7%	185	86.0%	0.055¥ 0.084‡
Rarely	4	2.3%	1	0.5%	
Sometimes	9	5.2%	15	7.0%	
Not more than 1 drink per day	22	12.8%	14	6.5%	
Eating > 5 fruits and vegetables per day					
No	19	11.0%	36	16.7%	0.210† 0.023‡
Rarely	20	11.6%	29	13.5%	
Sometimes	46	26.7%	66	30.7%	
Most of the times	59	34.3%	58	27.0%	
Everyday	28	16.3%	26	12.1%	
Exercising for 30 minutes 3 times per week					
No	43	25.0%	39	18.1%	0.424† 0.479‡
Rarely	33	19.2%	45	20.9%	
Sometimes	30	17.4%	50	23.3%	
Most of the times	30	17.4%	38	17.7%	
Always	36	20.9%	43	20.0%	
Eating red meat					
No	22	12.8%	27	12.6%	0.104† 0.210‡
Rarely	50	29.1%	39	18.1%	
Sometimes (up to 3 times per month)	30	17.4%	53	24.7%	
Yes, equal or less than 3 times weekly	50	29.1%	70	32.6%	
Yes, more than 3 times weekly	20	11.6%	26	12.1%	
Eating high sugar food					
No	17	9.9%	18	8.4%	0.631† 0.195‡
Rarely	48	27.9%	51	23.7%	
Sometimes	68	39.5%	84	39.1%	
Most of the times	27	15.7%	46	21.4%	
Every day	12	7.0%	16	7.4%	
Exposed excessively to sunlight					
No	48	27.9%	49	22.8%	0.645† 0.617‡
Rarely	56	32.6%	74	34.4%	
Sometimes	41	23.8%	63	29.3%	
Most of the times	21	12.2%	23	10.7%	
Everyday	6	3.5%	6	2.8%	

BMI: Body Mass Index; Underweight < 18.5; Normal: between 18.5 and 24.99; Overweight: between 25 and 29.99; Obese > 30; †: chi square; ‡: Cochrane; ¥: fisher.

The predictors of the attitude of respondents regarding the preventability of cancer

In the multivariate model, cancer was considered more as preventable when the participants considered the cause of cancer is environmental, OR=18.648 (95% CI: 1.81-191.65, p = 0.014). People having a healthy life considered more than those who didn't that cancer is non-preventable, OR = 0.49 (95% CI: 0.3-0.8, p = 0.004). Participants smoking waterpipe with different frequencies considered that cancer is not preventable. For rarely smokers, the OR was 0.46 (95% CI: 0.24-0.9, p = 0.023). Married participants considered that cancer is non-preventable, OR = 0.52 (95% CI: 0.31-0.87, p = 0.013). Participants having a high educational degree considered that cancer is preventable, OR = 2.18 (95% CI: 1.0-4.74, p = 0.049). Participants having cancer considered more than people who didn't that cancer is non-preventable, OR = 0.14 (95% CI: 0.02-1.14, p = 0.066) (Tab. V).

Reliability and validation of the scale

The alpha coefficient of the three following risk factors: naphthalene, phthalates and paints, the two factors sunlight and UV radiation, multiple sex partners and infections, diesel and benzene were respectively 0.697, 0.619, 0.569, 0.583. Their alpha coefficients are above 0.5 suggesting that the items have good internal consistency. The alpha coefficient of the 2 items arsenic and pesticides 0.423, bisphenol A and plastic 0.423 were low suggesting low internal consistency between the items. The results of the exploratory factor analysis suggested that our items were able to explain 62.66% of the variability of our latent variable or awareness of environmental risk factors of cancer. In this study, the Kaiser-Meyer-Olkin statistic was 0.929. This means that the data are suitable for performing factor analysis. The result of the Bartlett test was also significant. This means that the opposite assumption was confirmed and there was a significant correlation between variables ($p < 0.001$). Cronbach's alpha of all scale-items was equal to 0.95.

Discussion

Cancer has a big impact on the patient's life, physically, emotionally and financially. Thus, the most important step is the prevention of cancer occurrence when it is possible. As cancer has been linked to many preventable environmental risk factors [1], having a good knowledge about these risk factors is an essential step to help prevent and reduce the burden of this disease [26].

Our study showed that more than half of our sample had recognized the following factors as risk factors of cancer: environmental pollution, smoking, industrial pollution, nuclear rays, UV radiation, X rays, tobacco exposure, processed food, long term use of preservatives, excessive sunlight exposure, artificial sweeteners, pesticides, genetically modified food, uranium, high sugar diet, living close to high voltage transmission lines, alcohol, stress, plastic bottles, hormone in beef and red meat. On the other hand, less than 50% of the participants had recognized the following factors: diesel exhaust, unbalanced diet, mobile phones, paints, obesity, hormonal treatment after menopause, benzene, low fiber diet, low physical activity, infections, naphthalene, many sexual partners, radon, asbestos, arsenic, vitamin D deficiency, phthalates, bisphenol A, breastfeeding for less than 6 months and wood dusts.

In 2001, the American Institute for Cancer Research (AICR) commissioned its first Cancer Risk Awareness Survey to gauge Americans' awareness of various lifestyle-related cancer risk factors. In 2019, they reported that less than half of Americans recognize that alcohol, diets high in red meat, diets low in vegetables, fruits, and fiber and insufficient physical activity all have a clear link to cancer development [28]. Our results were similar to that of the AICR 2019 survey except for alcohol and red meat where more than half of the Lebanese population did identify them as risk factors of cancer. This survey also showed that the awareness of other established cancer risk factors like obesity and processed meat is above 50% among Americans. This wasn't the same in our study where less than half of the participants identified obesity as a risk factor for cancer. The majority of Americans correctly identified tobacco (89%) and excessive exposure to sunlight (82%) as cancer risks [28] and this was similar to our results.

Our results were not in line with a previous Japanese study that showed that the attributable fraction of cancer-causing viral and bacterial infection was considered the highest (51%), followed by that of tobacco smoking (43%), stress (39%), and endocrine-disrupting chemicals (37%) [30]. Thus, it is worth increasing awareness about infectious agents as a cause of cancer.

A study done in Iran in 2010 to assess the public awareness of cancer risk factors and its determinants showed that a small proportion of the respondents (12.2%) had high knowledge level and most of them had mixed (56.9%) and low level of awareness (30.9%). The most important determinants of knowledge level included level of education, gender, and family history [33].

Our results were also aligned with the results of a pilot study done in Emirates showing that many of the study participants were able to identify smoking, alcohol, and nuclear radiation as cancer-causing factors, but a large number of the respondents failed to identify infections, some food-related contaminants/components, and occupation-associated carcinogens as risk factor [34]. These results emphasize on the need of an awareness campaign concerning occupation-associated carcinogens.

Our results were very close to the results of a study done in Oman. Similarly to our results, the majority of respondents identified that smoking cigarettes (83.3%), passive smoking (72.7%) and excessive drinking of alcohol (69.0%) are risks factors for cancer while fewer respondents identified that eating less fruits and vegetables (21.6%), eating more red or processed meat

Tab. V. The predictors of the preventability of cancer.

Variables	ORa	95% CI	P-value
Cancer cause			
Don't Know	1	Ref	0.013
Genetic	0.351	0.071-1.720	0.197
Environmental	18.648	1.814-191.651	0.014
Both genetic and environmental	0.892	0.281-2.829	0.846
Healthy life			
No	1	Ref	0.004
Yes	0.485	0.297-0.790	
Water pipe			
No	1	Ref	0.000
Rarely	0.462	0.238-0.899	0.023
Sometimes	0.268	0.124-0.576	0.001
Most of the times	0.114	0.040-0.323	0.000
Everyday	0.362	0.178-0.738	0.005
Marital status			
Single	1	Ref	
Married	0.520	0.309-0.873	0.013
Education			
Elementary/intermediate/ high school	1	Ref	0.008
Bachelor degree	0.913	0.449-1.859	0.803
Masters or PhD	2.179	1.002-4.736	0.049
Have cancer			
No	1	Ref	
Yes	0.135	0.016-1.141	0.066

ORa: adjusted Odds Ratio; omnibus test: significant so at least the variable is associated with the dependent variable; model summary: Nagelnerke R square 0.299 so the model was able to explain 29.9% of the variability of the dependent variable; Hosmer Lemshow was not significant (0.153) so the model is adequate; classification table showed that 71.1% of the participants had good classification; correlation matrix: all R s were < 0.8 so no variables were over correlated.

(30.2%), being overweight (32.0%), doing less physical exercise (31.0%), having a close relative with cancer (34.9%) and getting frequent sunburn during childhood (38.8%) are risk factors contributing for the development of cancer [35].

The level of awareness is high in both western and Arab countries concerning smoking. It is important to highlight that the majority of the respondents are also aware that drinking alcohol is also a risk factor for cancer, which could be explained by the cultural stigma in these countries where smoking and alcohol are seen as unhealthy [43].

Concerning the western dietary pattern and lifestyle, the level of awareness was low in all countries and similar in Lebanon except for red meat and processed food where we had a better knowledge. Indeed, the western dietary pattern including red and processed meat and refined grains and sedentary lifestyles are associated with increase in the risk of cancer [44]. Low fruit and vegetable intake, smoking, drinking of alcohol and obesity were still the leading risk factors for death from cancer worldwide [45]. Giovannucci et al, found that a healthy lifestyle can prevent 40% of cancer cases and 50% of cancer deaths in the United States. Thus, it is important to raise awareness about the importance of adopting a healthy lifestyle [46].

Concerning the source of information of our participants, internet sources was the most common source of information followed by healthcare professionals and the most preferred sources identified were healthcare professionals (51.9%) and internet sources (43.7%). While our study population favored being educated through healthcare professionals, in the pilot study done in Emirates, respondents favored being educated via the media [34].

Concerning the attitude towards the preventability of cancer, 56% of our participants perceived that cancer is preventable and 44% considered cancer as non-preventable. Our results were similar to a study done in Mumbai where 55% of the participants perceived that cancer could be preventable [47]. However, in a study done in India, the majority of the study population (42%), perceived cancer could not be preventable, and around 30% of them did not know what to perceive about the preventive methods for cancer [48].

Concerning the predictors of the attitude of our participants toward the preventability of cancer, it is important to highlight that the main predictor is believing that cancer has an environmental cause. This is a logical result, since the environmental risk factors are usually preventable unlike the genetic ones. Participants considering cancer is preventable considered at the same time that they are not living a healthy lifestyle, which showed that they underestimate the impact of taking health precautions in preventing cancer. This result can also reflect that these participants are feeling guilty and that's why they are considering themselves not living a healthy lifestyle. Another important result is that waterpipe remained in the multivariate model while smoking was removed, this reflects the Lebanese profile where waterpipe is a cultural habit and the prevalence of waterpipe smoking has increased extensively [49,50].

This result also shows that people smoking waterpipe are not aware that waterpipe can increase the risk of cancer. Married participants considered less that cancer is preventable this could be related to age and level of education. Participants having cancer considered more that cancer is not preventable, due to the fact that many of these patients take precautions but couldn't stop cancer from occurring.

To our knowledge, this is the first study assessing the knowledge of the Lebanese population toward the general environmental risk factors of cancer. Another strong point in this study is that it achieved the minimum sample size needed and this increase the power of study. Concerning the questionnaire, it was strongly built based on good literature review and covered a lot of risk factors and in some cases, the question was asked in different ways to ensure that the questionnaire truly reflects what the participant knows in order to decrease the classification bias. The Cronbach alpha reflecting the reliability of the knowledge questionnaire was high (0.95). However, the calculated alpha coefficient was low for the bisphenol A and plastic and for the arsenic and pesticides. This shows that the participants are not able to identify what is the scientific name of the substance causing cancer leading to a classification bias. The questionnaire included mainly closed ended questions which makes it easier for respondents and to have fewer missing answers. Only in questions where the respondents can be frustrated because their desired answer is not a choice (like when asked about the preferred information source etc.) an option where the respondent can write a short answer was added. In questions concerning the knowledge of the participants concerning the environmental risk factors a Likert scale was used to have more precise answers thus removing the classification bias.

On the other hand, this study has some limitations. This study was done during the COVID-19 pandemic so we couldn't fill the questionnaires face to face with the participants. First, we had difficulty reaching certain types of participants, such as those who do not have internet access and thus our sample had more young people which increase the selection bias. Second, there is no identification tool so it is impossible to know if the sample providing answers is the right person or if one person is submitting multiple responses. Third, since the questionnaire was distributed through the internet, we couldn't control effectively its spread and we couldn't know the exact response rate and the number of people ignoring our questionnaire. Finally, according to the Lebanese statistical Bulletin 2018 [51], 21.92% of the Lebanese population live in Akkar and the North, 14.46% in Beqaa and Baalbek, 7.81 in Nabatieh, 11.67% in the South, 34.85% in mount Lebanon and 9.3 % Beirut. While, in our study 24.8% of our participants were living in Beirut, 20.9% in Mount Lebanon, 16.8% in South, 16.3% in North and Akkar, 7.8% in Nabatieh,13.5% in Beqaa and in Baalback/Hermel. Thus, our results may overestimate the results in Beirut and South and underestimate it in Mount Lebanon. To add, our sample was selected using mostly the convenience sampling method, this can lead to selection bias and can affect the generalizability of the results.

Conclusions

Cancer is a multi-factorial disease having both environmental and genetic risk factors. Our results increase the need for more health campaigns to increase awareness on these risk factors specially those related to toxic substances and infections and lifestyle habits. This can also be followed by further studies assessing the impact of these community and governmental cancer prevention initiatives on cancer risk factors level of awareness.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MK performed study, collected data, analyzed data and drafted the manuscript.

MEH, DK, SA, SR, AAH reviewed, edited the manuscript and approved the final version of the manuscript to be submitted.

RA designed study, analyzed data, reviewed and approved the final version of the manuscript to be submitted.

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Research paper

Screening and isolation of microbes from a Mud Community of Ischia Island Thermal Springs: preliminary analysis of a bioactive compound

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Keywords

Microbes • Thermal springs • Ischia island • Antimicrobial activity • Antibiofilm activity

Summary

Introduction. *Balneotherapy centers of Ischia island (Italy) offer treatments for different dermatological diseases (psoriasis, acne, atopic dermatitis) and upper respiratory tract infections. In this study, we integrated morphological and molecular approaches to give a focus on isolation and screening of extremophile bacteria from Ischia thermal mud for potential antimicrobial applications.*
Methods. *Samples were collected during 2019 at four sites. Some bacterial strains ATCC for antibacterial and antibiofilm activity were tested. After morphological characterization, screening for antagonistic isolates was made. The colonies isolated from thermal mud samples were submitted to molecular characterization. Susceptibility testing by dilution spotting was carried out and antibacterial efficacies of most active isolate were evaluated with a Minimal inhibition concentration assay. Biofilm formation, inhibition, eradication were examined. Statistical analyses were carried out utilizing Microsoft® Excel 2016/XLSTAT©-Pro.*
Results. *We isolated a natural compound with antimicrobial and antibiofilm activities.*
Conclusions. *The results obtained in this study are discussed in the context of how hydrothermal systems are important environmental source of uncharted antimicrobial and antibiofilm compounds. In conclusion, to the most effective of our knowledge, this work presents the primary report on the preliminary investigation of thermophile microbial diversity and their antimicrobial and antibiofilm activities for future biotechnological interest.*

Introduction

The use of hot spring waters for health and recreation in Italy may be a traditional activity dating back to Roman times. This tradition continues today; thermal waters are used in the form of baths, inhalation, irrigation and mud therapy and are usually recommended as a therapeutic and prophylactic measure against many varieties of illnesses and toxicity [1, 2]. The immersion in mineral-medicinal water and the application of mud to improve the prognosis of various diseases are still unknown, but it is known that the neuroendocrine and immunological responses to these treatments lead to anti-inflammatory, analgesic and antioxidant effects [3, 4].
The chemical, physical and microbial characteristics of thermal waters can indirectly contribute to their curative effects [5].
Temperature, pH and concentration of salts can create suitable habitats for the multiplication of different bacteria: *Legionella*, *Pseudomonas*, *Mycobacteria*, protozoa, amoebae, algae and other microorganisms. They can become a danger to users if not properly controlled [6, 7].
Thermal muds are obtained by mixing clayey materials with thermo-mineral waters, enriched with organic materials [8]. They have different properties depending on the type of clay, the properties of the thermal water contained and the microorganisms present [9].
In Southern Italy, the Campania region is one of the richest regions in terms of thermal and mineral water resources. These waters have been used for therapeutic purposes since Roman times [10, 11].
This Mediterranean Island (originally called Pithacusae) was included in the first century AD Plinio's description of the interactions between earthquakes and water sources [12, 13].
The therapeutic effect of Ischia mud is said to its high content of mineral. It's been demonstrated that Ischia muds are useful in treating skin disorders and skin diseases like psoriasis, dermatitis [14].
This specific maturation procedure will be considered as an ancient biotechnological process. This maturation procedure allows a microbial community, mainly represented by cyanobacteria [15, 16], to grow on the mud surface. The microorganisms, associated in a polysaccharide matrix, produce a green biofilm which shows the correct maturation of the mud. Before using the mud for therapies, this can be mixed and put in tanks during which thermal water at nearly 60°C is present, so as to cut back the natural microbial load and maintain the fluidity of the merchandise. Some studies contributed to defining the properties of this mud, suggesting that its effectiveness isn't only thanks to the warmth and therefore the thermal water proprieties, but also to substances produced by cyanobacteria [17-19]. Cyanobacteria are

known to synthesize an outsized type of high-value bioactive compounds, including substances with UV protection, antiviral, antibacterial, and anticancer activities [20, 21]. Looking on the habitat, biofilms can include prokaryotic and eukaryotic microorganisms, like archaea, bacteria, cyanobacteria, microalgae, and fungi [22, 23].

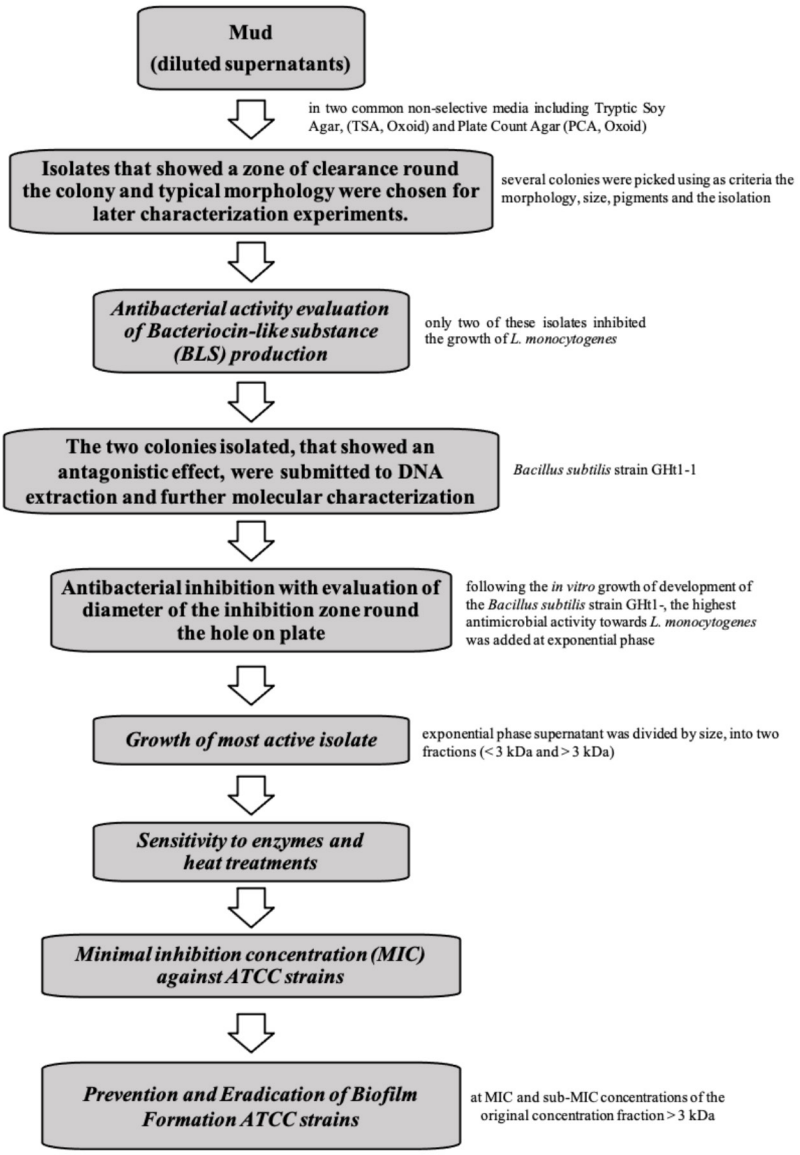
Currently, interest dedicated to isolation and identification of bacterial strains from thermal springs. The target is that the exceptional and also the distinctive adaptation of those microorganisms under the influence of both heat and thermal stress. This special heat stability makes them prospective producers of high value thermostable bio-products and an important source for exploitation in new biotechnological developments. The tolerance of thermophilic microorganisms to thermal environments is usually attributed to exopolysaccharides (EPS). EPS are defined as high mass biopolymers that put together a considerable component of the extracellular polymers surrounding microbial cells membrane within the aquatic environment [24].

Ischia mud is comprised of specific minerals like argil and non-pathogenic microbes which produce more organic substances than other not of volcanic origin.

Despite the intense thermophilic environment, also the Ischia mud could be a unique ecosystem housing various microorganisms adapted to hot temperature that are growing interest because they might produce some biocatalysts that function under extreme conditions so useful in various industrial processes. In addition, as many antibiotics are now less effective for bacterial resistance, the demand for new stable and efficient molecules is increasing worldwide. The present study focuses on isolation and screening of extremophile bacteria from Ischia thermal mud for potential antimicrobial applications.

An integrated approach was wont to understand the microbial diversity and to spot microorganisms which could grow at extreme temperature, using microbiological, morphological, and molecular identification so to bring new information on the extremophile bacteria in thermal environment (Fig. 1).

Fig. 1. Flow chart of the study design.



Methods

Bacterial strains for antibacterial and antibiofilm activity testing

The following strains were utilized in this study: *Staphylococcus aureus* ATCC 6538, *Listeria* monocytogenes ATCC 7644, *Escherichia coli* ATCC 11229, *Pseudomonas aeruginosa* ATCC 9027. They were grown in Tryptone Soya Broth (TSB) at 37°C, for 16-18 h and maintained in Triptone Soy Agar (TSA) containing glycerol at -80°C respectively. Overnight cultures of them were washed twice using sterile phosphate buffered saline (PBS) and standardized to 10^6cells/mL for next experiments.

Sampling Collection

Samples were collected during winter and spring months 2019 at four sites distributed throughout the thermal springs of the north and south part of island. Samples, marked A, B, C, D, were chosen to vary the nature and location of the sampling.

Mud temperature and pH were measured by a transportable conductivity and pH meter.

Samples containing a combination of water and dust (four samples for every site) were collected approximately 10-15 cm below the surface, placed into sterile 50-mL polypropylene tubes, fixed using 5% formaldehyde, and transported to the laboratory at ambient temperature.

Morphological characterization

To identify the microorganisms in our collected samples, eight grams of every sample were homogenized using 10 mL NaCl. So as to be ready to culture the very best number of bacterial species, supernatants were diluted and plated in two common non-selective media including Tryptic Soy Agar, (TSA, Oxoid), Plate Count Agar (PCA, Oxoid), and so incubated at 37°C for 24-48 h, under aerobic conditions. Growth media were prepared using filtered water from Ischia Thermal spring to keep up original chemical composition of this environment. Then several colonies were picked using as criteria the morphology, size, pigments and the isolation. Isolates that showed a zone of clearance round the colony and typical morphology were chosen for later characterization experiments.

Antibacterial activity evaluation of bacteriocin-like substance (BLS) production

Preliminary screening for antibacterial activity was performed by a method that allows the observation of antagonistic interactions among our strains and several target strains as reported previuosly by agar well diffusion assay [25].

Agar plates were previously spread with 100 mL of target microorganisms suspension, which corresponded to a 0.5 McFarland turbidity standard solution (10^{6-7} CFU/mL). With the help of a sterilized borer, 6 mm diameter wells were made in the agar plates, then 100 mL culture of 25 selected colonies or/and cell-free supernatant of the isolates were poured into the wells and incubated for 8 h at 37°C, and zone of inhibition was measured for the antimicrobial activity. An isolated exhibiting a statistically larger inhibition zone was finally selected for further investigation. 5 µl of 25 mg/ml of Ampicillin (AMP) and 5 µl of sterile 0.9% NaCl were used as positive and negative control respectively.

Molecular characterization

The two colonies isolated from thermal mud samples, that showed an antagonistic effect, were submitted to DNA extraction and further molecular characterization. Colonies were recovered reconstituted with 70µL Milli-Q Type 1 Ultrapure Water: extraction of DNA was obtained by denaturing samples at 98°C for 10 min and subsequent centrifugation (8,000 rpm for 5 min at 4°C) and supernatant recovery [26]. Amplification was meted out employing universal oligos, which are complementary to the V3-V6 16 S rRNA gene conserved regions [27]: V3f (5'-CCAGACTCCTACGGGAGGCAG-3') and V6r (5'-TCGATGCAACGCGAAGAA-3'). PCR reactions were performed with a Techne Prime PCR Thermal Cycler (TECHNE), using VWR Chemicals reagents, obtaining a final 55 µL volume: 5.5 µL PCR Key Buffer Tripton Free (Tris-HCl pH 8.5, KCl, 15 mM McCl2), 1.0 µL dNTP 12 µM, 0.44 µL forward and reverse oligos (50 µM), 0.5 µL Taq polimerase, 1.5 µL DNA template, and 47 µL sterile deionized water. Polymerase chain reaction conditions were the following: an initial denaturation stage (95°C for 2 min); 35 cycles of 95°C for 30 s, 62°C for 30 s, and 72°C for 30 s; a final extension stage of 72°C for 5 min. Obtained amplified samples were run on a 1.5% agarose gel, disposing as a base pairs size reference a 100 bp DNA ladder, and stained using GelRed (BIOTIUM). PCR samples were delivered to an external service for the purification step and sequencing evaluations. Resulted sequences were identified through the comparison with sequences available on NCBI Sequence Database [28, 29].

In vitro growth of most active isolate

The identified isolate was used for further study. Bacteria were cultured in M9 medium at 30°C and 250 rpm. Until the late stationary phase, centrifuged and supernatant were filtered (0,22 µM Millipore, Bedford, MA, USA). After the supernatant was split up with a *cutoff spin column* of 3-kDa and 10-kDa, (Centricon, Millipore). The two fractions were tested for antibacterial inhibition with evaluation of diameter of the inhibition zone round the hole on plate.

Sensitivity to enzymes and heat treatments

The two aliquots of supernatants from *Bacillus* strain GHt1-1 were also screened for sensitivity to enzymes and heat treatments. For the results of proteinase K and trypsin activity, diluted supernatant was treated with 2.5 µL (100 µg/ml) 1 h at 42° and 37°C respectively. For temperature effect, supernatant was also heated at at 60°, 80° e 100°C for 15 min. All processed samples

were then tested for antimicrobial activity by using the well diffusion method.

Minimal inhibition concentration (MIC)

The antibacterial efficacies of our supernatant were assessed with a MIC assay, in line with Clinical Laboratory Standards Institute guidelines (CLSI, 2006 M7-A6). Briefly, 10 mL of exponential bacterial culture grown in low-nutrient medium (M9 minimal medium Sigma-Aldritch) [30], was centrifuged and filtrated with a 0.22 µM filter (Millipore, Bedford, MA, USA). Supernatants were divided by size (cutoff spin column 3-kDa; Centricon, Millipore). Then, aliquots of the suspension higher 3 KDa were inoculated into each well of sterile, 96-well, polystyrene. Serial dilutions of sample were settled from a 50% (w/w) supernatant solution, leading to final concentrations of 50, 25, 12.5, 6.25, 3, 1.5%. After 18 h of incubation at 37°C, bacterial growth inhibition resolve by monitoring the optical density at 600 nm wavelength with a plate reader (SYNERGY H4 BioTek) [31]. The MIC was defined as the lowest concentration of supernatant capable of inhibiting the growth of each microorganisms. Positive control group composed of the microrganisms solution and liquid medium and negative control group composed of liquid medium only were used. All tests were executed in triplicate and repeated thrice.

Biofilm formation, inhibition, eradication

The selected strains were examined for the ability to provide biofilm and categorized as active biofilm former within the polystyrene microplates using the *in vitro* biofilm model as previously described by Stepanović et al. [32]. Each well of a microplate was inoculated with 100 µL of PBS containing 1 x 10^7 cells/mL, incubated at 37°C to permit the adhesion of cells on the solid surface. The inhibition activity of supernatant on biofilm formation and the eradication activity against preformed biofilm were evaluated by using sub-MIC concentrations ranging from 6.25, 3, 1.5, 0.75% of the original concentration supernatant > 3 kDa.

For biofilm inhibition assay, 100 µL of bacteria in TSB were seeded into individual wells of microtiter plates with different concentrations of supernatant for 24 h. Data from dose-response experiments were represented because the percentage of inhibition compared to regulate. The MBIC50 corresponds to the concentration that will yield an inhibition of fifty of biofilm.

The effect on mature biofilms was evaluated adding the supernatant at different concentations after 24 h. After other 24 h, biofilm was washed with PBS buffer to get rid of planktonic cells.

Biofilm growth was analyzed using the CV (crystal violet) assay. The remaining attached cells were heat-fixed at 60°C for 60 min and therefore the adherent biofilm layer was stained with 0.4% (w/v) bactericide for 25 min at 25°C. After washing with water, the stain sure to the biofilm was solubilized with ethanol (15-min incubation) and therefore the absorbance was measured at 570 nm. The MBEC was calculated as percentage of eradication compared to regulate.

Statistical analysis

Statistical analyses were carried out utilizing Microsoft® Excel 2016/XLSTAT©-Pro (version 7.2, Addinsoft, Inc., Brooklyn, NY, USA). Values are expressed because the mean ± variance (± SD). The importance of the differences between different treatment groups was assessed by analysis of variance (ANOVA) with a 0.05 significance level. Moreover, the post-hoc analyses were kept on with Dunnet's test for MIC and Tukey's test for MBIC and MBEC.

Results

Physiological and microbiological properties of the samples

For each sites, we reported geographic location and chemical-physical characteristics as showed in Table I. Samples for physical, chemical and biological analyses were gathered from four pools at the hydrothermal Ischia stations at the end of the dry season and the beginning of the wet season (during April-November 2019).

The mud samples had pH values between 6.4 to 7.5 and relatively high temperature with the range 50.3°C to 67.8°C. Despite these particular conditions, the microorganisms developed well in diverse colonial morphology on growth media used. The isolates showed different types of colonies in shape, color and surface (yellow, white or creamy, circular, smooth or transparent colonies), with a diameter of 0.5-2 mm. The colonies were collected on the basis of the morphological difference and to be more detached on the culture medium than the others.

Screening for antagonistic isolates

Twenty-five isolates were chosen based on colony morphology and used in a screening for antagonistic isolates by agar plate assay. This screening was repeated for all considered ATCC strains. Only two of these isolates inhibited the growth of *L. monocytogenes* and they showed the same inhibition zone only for *L. monocytogenes* and no inhibition zones for the other bacteria strains tested (Tab. II).

Identification and molecular characterization

In this study, the two isolates, which inhibited *L. monocytogenes* ATCC 7644 were identified based on 16S rRNA analysis. Analysis of the 16S rRNA revealed that the two isolates were found to be very close to *Bacillus* species with identity > 99%. These two isolates were identified as the same strain: *Bacillus subtilis* strain GHt1-1 (Max Score: 1293; Total Score: 1293; Query Cover: 100%; E value: 0.0; Identity: 99.86%; Accession: GU434356.1). They were gram positive and catalase and oxidase positive.

Tab. I. Physicochemical and geographical characteristics of samples collected from Ischia island.

Samples	Spa area	Temperature (°C)	Conducibility (mS/cm³)	pH	Geographical location
A	Ischia (NA)	50.8	10.82	7.07	Latitude: 40°43.00′ N Longitude: 13°54.00′ E
B	Ischia (NA)	50.3	45.8	6.40	Latitude: 40°44.3477′ N Longitude: 13°57.02′ E
C	Ischia (NA)	67.8	9.80	7.50	Latitude 40°43′8″40 N Longitude 13°55′54″48 E
D	Ischia (NA)	62.5	45.6	6.91	Latitude 40°32′48″84 N Longitude 13°33′35″28 E

Tab. II. Screening for antagonistic activity of mud isolates against *Staphylococcus aureus* ATCC 6538, *Listeria monocytogenes* 7644, *Escherichia coli* ATCC 11229, *Pseudomonas aeruginosa* ATCC 9027. G: Gentamicin; R: Resistant; I: Intermediate; S: Sensitive (Rasooli I, Owlia P. Chemoprevention by thyme oils of Aspergillus parasiticus growth and aflatoxin production. Phytochemistry 2005;66:2851-6. https://doi.org/10.1016/j.phytochem.2005.09.029).

Samples	*S. aureus* ATCC 6538	*L. monocytogenes* ATCC 7644	*P. aeruginosa* ATCC 9027	*E. coli* ATCC 11229
	Means ± SD (Ø mm)			
1	< 6.0	6.1 ± 2.2	< 6.0	< 6.0
2	< 6.0	< 6.0	< 6.0	< 6.0
3	8.5 ± 1.5	25.0 ± 1.0	< 6.0	< 6.0
4	< 6.0	< 6.0	< 6.0	< 6.0
5	< 6.0	< 6.0	< 6.0	< 6.0
6	< 6.0	< 6.0	< 6.0	< 6.0
7	< 6.0	6.8 ± 1.9	< 6.0	< 6.0
8	< 6.0	< 6.0	< 6.0	< 6.0
9	< 6.0	< 6.0	< 6.0	< 6.0
10	< 6.0	< 6.0	< 6.0	< 6.0
11	< 6.0	< 6.0	< 6.0	< 6.0
12	< 6.0	< 6.0	< 6.0	< 6.0
13	< 6.0	< 6.0	< 6.0	< 6.0
14	< 6.0	7.3 ± 3.1	< 6.0	< 6.0
15	< 6.0	< 6.0	< 6.0	< 6.0
16	< 6.0	< 6.0	< 6.0	< 6.0
17	< 6.0	< 6.0	< 6.0	< 6.0
18	6.7 ± 1.3	12.0 ± 2.3	< 6.0	< 6.0
19	< 6.0	6.9 ± 1.1	< 6.0	< 6.0
20	< 6.0	< 6.0	< 6.0	< 6.0
21	< 6.0	< 6.0	< 6.0	< 6.0
22	< 6.0	< 6.0	< 6.0	< 6.0
23	< 6.0	< 6.0	< 6.0	< 6.0
24	< 6.0	< 6.0	< 6.0	< 6.0
25	< 6.0	< 6.0	< 6.0	< 6.0
Gentamicin	S	S	S	S

Tab. III. Influence of the two fractions (> 3 kDa , < 3 kDa) on microbial cells growth. Values are expressed as the mean of three independent experiments ± Standard deviation; G= gentamicin.

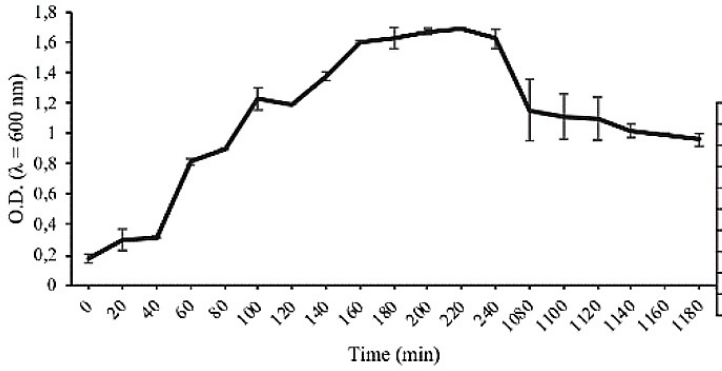
Strains	Mean±SD (Ø mm)	Control positive	
	> 3 kDa	< 3 kDa	G
S. aureus ATCC 6538	8.1 ± 2.2	< 6.0	S
L. monocytogenes ATCC 7644	25.0 ± 1.0	11.1 ± 2.3	S
P. aeruginosa ATCC 9027	< 6.0	< 6.0	S
E. coli ATCC 11229	< 6.0	< 6.0	S

Following the *in vitro* growth of development of the *Bacillus subtilis* strain GHt1-, the highest antimicrobial activity towards *L. monocytogenes* was added at exponential phase. (Figure 1). Indeed, inhibition zones diameter (mm) for *L. monocytogens* was 20 ± 1 after 80', while it was 25 ± 3 and 25 ± 1, respectively after 100' and 120' (exponential growth phase). No activity was shown for the other tested strains [33] (Fig. 2).

Exponential phase supernatant was divided by size, into two fractions (< 3 kDa and > 3 kDa).

Only aliquots of the fraction higher 3 KDa showed growth inhibition against *L. monocytogenes* (Tab. III), forming an inhibition zones diameter of 25,0 ± 1,0 mm. The

Fig. 2. *In vitro* growth *Bacillus subtilis* strain GHt1-1 in M9 medium at 30°C as defined by measurement of the OD600. Data figure the means of three independent cultures ± standard deviation (SD).



Time (min)	*L. monocytogenes* Mean ± SD (Ø mm) ScA
0'	-
20'	-
40'	-
60'	-
80'	20 ± 1
100'	25 ± 3
120'	25 ± 1

Tab. IV. Effects of enzymes action and temperature on microbial growth. Values are expressed as the mean of three independent experiments ± Standard deviation.

	L. monocytogenes ATCC 7644
	> 3 kDa
	Mean±SD (Ø mm)
Control	25.0 ± 2.0
Trypsin	10.0 ± 1.1
Proteinase k	9.5 ± 2.8
60 °C	10.0 ± 1.5
80 °C	9.5 ± 1.2

fraction < 3 KDa formed an inhibition zones diameter of 11,1 ± 2,3 mm. For the other strains the inhibition zones diameter is always < 6 mm, indicating no growth inhibition activity of the suspension higher 3 KDa. Gentamicin, the antibiotic to which all tested strains are sensitive, was used as a positive control (S = diameter of inhibition zones > 23 mm).

Sensitivity to enzymes and heat treatments

Further to better characterize the > 3 kDa fraction, effects of proteinase K, trypsin and temperature action were evaluated. Table IV reports results showing the reduced persistence of inhibitory effects against *Listeria monocytogenes.*

MIC determination

The active > 3 kDa fraction was tested for establishing the Minimal inhibitory concentration (MIC) against *S. aureus, L. monocytogenes, P. aeruginosa* and *E. coli* (Fig. 3). The absorbance of the negative control (TSB only) was found to 0.093 ± SD; therefore, based on this value, positive culture growth was considered when absorbance was found to > 0.2. The MIC of > 3 kDa fraction against *L. monocytogenes* was 6.25% of the original concentration. The MIC against *S. aureus* was (25%) of the original concentration. *P. aeruginosa* and *E. coli* growths were not inhibited at any tested fraction concentration.

Fig. 3. Bactericidal effect of > 3 kDa fraction on selected strains. The absorbance of negative control (only TSB) was found to 0.09 ± SD. Error bars represent standard deviation (n= 3). Statistical comparation between treated and untreated (control) groups were performed using one-way ANOVA (Dunnet * p < 0.05).

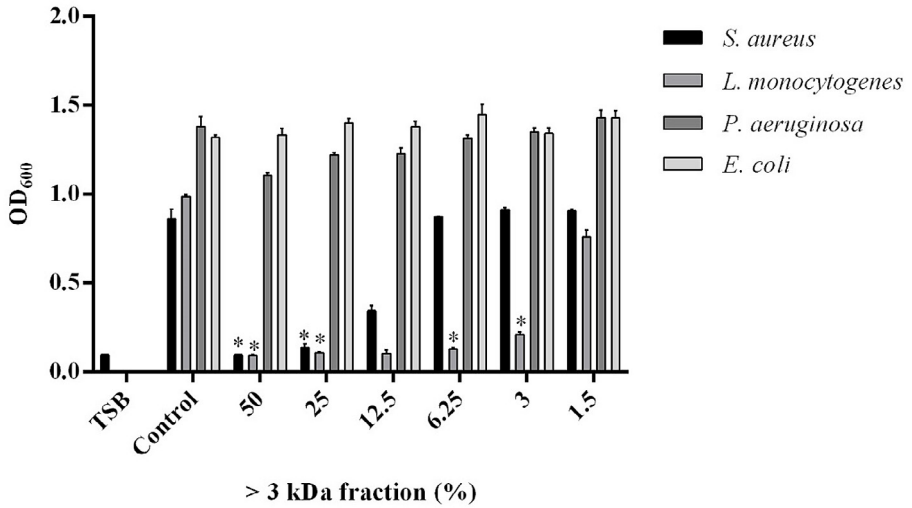
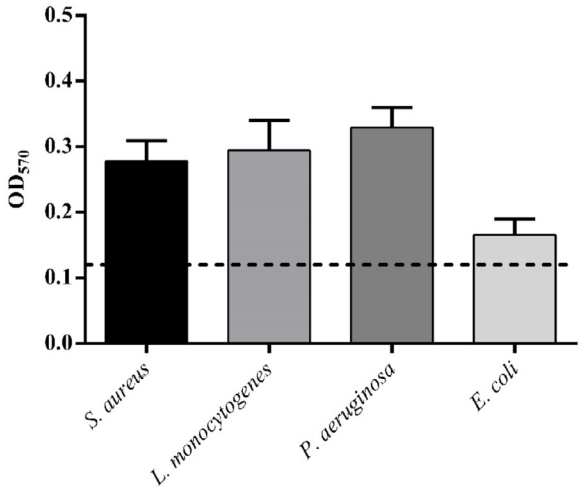


Fig. 4. Biofilm biomass quantitation of *S. aureus* ATCC6538, *L. monocytogenes* ATCC 7644, *P. aeruginosa* ATCC 9027, *E. coli* ATCC 11229, after 24 h. Biofilm formation evaluated by crystal violet light absorbance at 570 nm (optical density, OD570). Dashed line represent the ODc. Negative (OD ≤ ODc), weakly adherent (ODc < OD ≤ 2× ODc), moderately adherent (2 × ODc < OD ≤ 4 × ODc), strongly adherent (4 × ODc < OD). Results display the mean ± SD of three independent experiments.



Prevention and eradication of biofilm formation

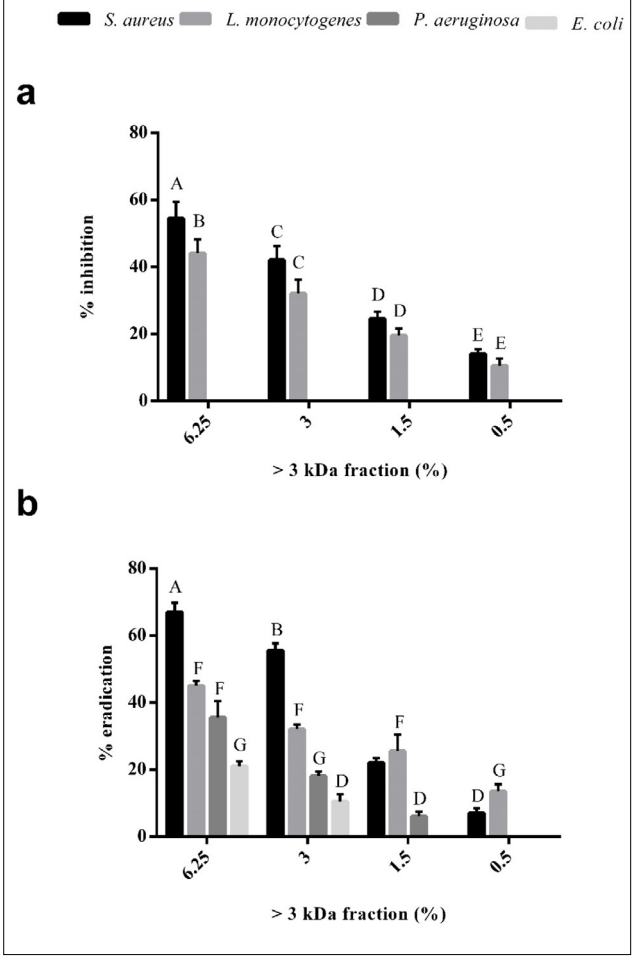
S. aureus, *L. monocytogenes*, *E. coli*, *P. aeruginosa* were tested for biofilm production. Figure 4 shows the total biomass of microbial biofilms after 24 h. The diagram highlights that the microbes form biofilms and they are classified as weakly biofilm-forming (*E. coli*), moderately biofilm-forming (*S. aureus*, *L. monocytogenes*) and strongly biofilm-forming (*P. aeruginosa*).

In Figure 5 (a) the minimal biofilm inhibitory concentration (MBIC) was reported as percentage of effects of different MIC and sub-MIC concentrations (0.75, 1.5, 3 and 6.25%) of the original concentration fraction > 3 kDa on biofilm formation of *S. aureus*, *L. monocytogenes*, *P. aeruginosa* and *E. coli*. The inhibition percentage of biofilm formation is appreciable only for *S. aureus* and *L. monocytogenes*. At MIC (6.25% of the original concentration fraction > 3 kDa) the biofilm formation of *L. monocytogenes* was inhibited by approximately 50%, while biofilm formation of *S. aureus* was inhibited at 58%. From the subsequent dilution the inhibition percentage dropped to values < 50% (45% inhibition biofilm *S. aureus* and 35% biofilm *L. monocytogenes* at ½ MIC), reducing to the greater dilutions gradually.

The inhibition percentage of *S. aureus* biofilm formation is always higher than that of *L. monocytogenes* biofilm.

In Figure 5 (b) the minimal biofilm eradication concentration (MBEC) was reported as percentage of dispersion of established mature biofilm of *S. aureus*, *L. monocytogenes*, *P. aeruginosa*, *E. coli* by MIC and sub-MIC concentrations (0.75, 1.5, 3 and 6.25%) of the original concentration supernatant > 3 kDa. At MIC all formed mature biofilms by the four tested strains were eradicated: the *S. aureus* and *L. monocytogenes* biofilms had higher eradication percentage (65 and 44%, respectively), compared to those of the *P. aeruginosa* and *E. coli* biofilms (32 and 20%, respectively). At ½ MIC only the *S. aureus* mature biofilm had an eradication percentage > 50%. At subsequent dilutions, the *L. monocytogenes* mature biofilm was more eradicated than that of *S. aureus*, although at percentages lower than 30%. The eradication of the *P. aeruginosa* and *E. coli* biofilms was not appreciable at the strongest dilutions.

Fig. 5. (**A**) MBIC reported as percentage of effects of different concentrations of fraction > 3 kDa on biofilm formation of *S. aureus* ATCC6538, *L. monocytogenes* ATCC 7644, *P. aeruginosa* ATCC 9027, *E. coli* ATCC 11229. (**B**) MBEC reported as percentage of dispersion of established mature biofilm of *S. aureus* ATCC6538, *L. monocytogenes* ATCC 7644, *P. aeruginosa* ATCC 9027, *E. coli* ATCC 11229 by various concentrations of supernatant > 3 kDa. Values represent the means ± standard deviations. Data with different letters (A-G) are significantly different (Tukey's, $p < 0.05$).



Discussion

The growing interest in thermophilic microorganisms and their biotechnological applications is demonstrated by numerous studies on extremophilic microorganisms [34-40]. Environmental microbial populations link with one another forming complex, mixed communities. The natural habitats where thermophilic microorganisms are isolated change from terrestrial volcanic sites (including solfatara fields) with temperatures softly

above ambient temperature, to submarine hydrothermal systems (sediments, submarine volcanoes, fumaroles and vents) with temperatures above 300°C. Thermal environments also are inhabited by extremophilic microorganisms, important to check also for the beneficial properties that they will wear the visitors health [41]. Studies that specialize in microbial diversity of mud are increasing in numerous parts of the planet because the environmental microbial populations that interact with one another forming complex, mixed communities, even in extreme conditions, have a giant potential for ecological importance and biotechnological applications in aquaculture, bioremediation, agriculture, and energy production.

Hot springs adjacent to volcanic environments are generally acidic, but the pH is neutral or slightly alkaline in regions near limestone. Thermophiles might also live under harsh conditions involving extreme pH or high salt concentrations [42].

Previous studies have demonstrated that important differences exist in microbial communities among hot springs with various ranges of physicochemical parameters and discrete geographic locations and is strictly temperature that control the composition of sediment communities, mainly varying temperature in geothermal systems with degassing, mineral precipitation, evaporation, autotrophy and oxidation [43].

Microbial mats are found to develop in a very big selection of thermal habitats including hot springs, fumaroles, eruption vents, and on steaming round [44]. These microbial mats are rich, in organic substances with an ubiquitarious communities which are tolerable to extreme conditions.

Hydrothermal systems are the best to know how microbial communities collaborate with different conditions. Hot springs are reported to be microbial-dominated ecosystems, sustaining an upscale microbial diversity and holding different microhabitats that constitute natural niches for thermophilic (> 50°C) and hyperthermophilic (> 80°C) microorganisms. However, characterizing the microorganisms of a natural matrix, like thermal mud, is incredibly difficult because of the vast phenotypic and genotypic heterogeneity. Therefore, a number of them aren't easily isolated by microbiological techniques.

The thermal area mud of Ischia island is widely employed in packs, masks, topical treatments for the body and face. Little is thought about its microbiological aspects. Therefore, this study was directed to extend our knowledge about extremophile bacteria from Ischia thermal mud for potential antimicrobial applications. Thermal mud samples from four thermal springs located within the Ischia island were used to isolate thermophilic microorganisms. These springs differed in temperature that adjust from 50-70°C and pH from 6,4 to 7,5. A complete of 25 thermophilic bacterial strains were chosen supported colony morphology and from a variety of antagonisms effect towards four ATCC strains. Only two isolates showed an antagonistic effect towards *L. monocytogenes*, in order that their molecular identification established as *B. subtilis* GHt1-1. In fact, Bacilli could be a sporogenic, thermophilic bacterium that grows well in acid environments [45, 46] so this result's highly compatible with extreme environmental conditions. *Bacillus* sp. is gram-positive bacteria with a high level of additional cellular enzyme production capacity, which has grown its application in many industries.

To investigate the antimicrobial potential of the *B. subtilis* GHt1-1, previous selected bacteria were used. We found a bioactive metabolite produced during exponential phase of curve growth of *B. subtilis* GHt1-1 that in an exceedingly preliminary study showed maintaining its activity changing temperature and subjecting to enzymatic action. After its slitting up, the foremost active fraction resulted the one amongst > 3 kDa. This fraction exhibited an honest antimicrobial action towards *L. monocytogenes* reaching the worth of 6.25% of the first concentration as minimal inhibition concentration. Surprisingly, this molecule showed a decent antibiofilm action both for inhibition of formation and eradication of mature biofilm on all four bacteria Gram-positive and Gram-negative tested. The best result obtained was on the inhibition, but particularly on the eradication of the mature biofilm of *S. aureus*. This data can be important, especially in fields where the biofilm formation reduces or even cancels the disinfectants and antimcrobials action [47]. Biosurfactants are known to decrease the adhesion of pathogenic microorganisms to solid surfaces [48]. It's been hypothesized that biosurfactants manipulate the interactions between bacteria and surfaces [49]. Due to the capacity of growing in extreme conditions as stress generated in hot outpouring waters and therefore the presence of an antibiotic additive for the prevention of bacterial proliferation, these microorganisms could probably develop some modifications that allow the assembly of efficient protective bioproducts capable to combat opportunistic microorganisms.

Limitations of the study

In this research, the analysis of only one sample per location has been carried out, and this aspect can represent a limit of our study. As there are no similar published studies, we have been prompted to present these preliminary results to give a first information on the potential antimicrobial applications of the extremophilic bacteria of the Ischia thermal muds. However, to study in deep our observations, further studies have been planned in order to increase the number of examined samples and the locations of sampling.

Conclusions

In conclusion, to the most effective of our knowledge, this work presents the primary report on the preliminary

investigation of thermophile microbial diversity and their antimicrobial and antibiofilm activities for future biotechnological interest.
Our results suggest this molecule can be exploited as potential antimicrobial and/or anti-biofilm agents against microbial biofilm formation within new antibiotics production.
Moreover, further studies should be done to know the most metabolite to blame for the antibacterial effect, the composition and also the molecular mechanisms of this bacterial compound.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization, VDO and EG; methodology, VDO and EG; software, FC and RL; validation, MG and ODC; formal analysis, AM; investigation, VDO and EG; resources, MG; data curation, AM; writing, original draft preparation, VDO; writing, review and editing, EG; supervision, EG; project administration, MG. All authors have read and agreed to the published version of the manuscript.

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Researc paper

PER3 polymorphisms and their association with prostate cancer risk in Japanese men

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Keywords

Prostate cancer • *PER3* • Polymorphism • Rs2640908 • VNTR

Summary

Introduction. *Prostate cancer (PCa) is one of the most common cancers affecting men globally. Although PER3 has been suggested as a risk factor for cancer development, there are few reports elucidating the relationship between PER3 and PCa. We investigated the association between PER3 polymorphisms (rs2640908 and VNTR) and susceptibility to PCa in the Japanese population.*
Methods. *Eighty three patients with PCa and 122 controls participated in this study. We analyzed rs2640908 and VNTR polymorphisms by using PCR-Restriction Fragment Length Polymorphism (PCR-RFLP).*
Results. *Compared to the C/C genotype with the rs2640908 polymorphism, the T/T (OR: 0.35, 95% CI: 0.15-0.81, P = 0.02) and C/T + T/T (OR: 0.46, 95% CI: 0.24-0.88, P = 0.02) genotypes had a significantly lower risk of PCa. TT (OR: 0.29, 95% CI: 0.10-0.77, P = 0.02) and CT + TT (OR: 0.47, 95% CI: 0.23-0.97, P = 0.04) also had significant protection against PCa in the smoker group. Significantly, we observed an association between smoking and rs2640908 polymorphism in this study. However, no association between the VNTR polymorphisms and PCa was detected.*
Conclusions. *Our results suggest that PER3 rs2640908 polymorphisms influence an individual's susceptibility to PCa.*

Introduction

Prostate cancer (PCa) is the second most common cancer in men and also ranks fifth among the leading causes of death globally. In 2018, 1.3 million new cases of PCa were diagnosed and 359,000 associated deaths were reported globally [1]. In 2015, PCa also became the most common male cancer in the Japanese population [2]. In 2018, 70,654 new cases of PCa were reported and the age-standardized rate was 35.4 per 100,000 [3]. While the causes of PCa remain to be elucidated, many potential risk factors for PCa have been identified. Age, race, a high fat diet, alcohol abuse, exposure to cadmium or agent orange, and family history are major risk factors associated with PCa [4]. Recently, disruption of circadian rhythm has also been suggested to be a risk factor for carcinogenesis, including development of PCa [5]. The incidence of breast and endometrial cancers was higher in shift workers who experienced disruption of the circadian rhythm [6].

Physiological states such as body temperature, and biochemical processes including hormone secretion, metabolism, and sleep/wake cycle are controlled by circadian rhythms in an approximate 24-hour cycle [7, 8]. The suprachiasmatic nucleus (SCN) in the anterior hypothalamus of the brain is thought as a central part that generate circadian rhythms [9-11]. The circadian rhythms are controlled by the genes, including *circadian locomotor output cycles kaput* (*CLOCK*), *period* (*PER*), and *cryptochrome* (*CRY*) [9-11].

Some previous research indicated the association between various circadian genes and PCa. Wendeu-Foyet et al. reported that pathway of 31 circadian genes including 872 SNPs significantly associated with PCa and this association was mainly supported by the circadian core-genes pathway which were *NPAS2* and *PER1* [12]. Yu et al. also indicated that *NPAS2* as a part of circadian genes significantly associated with disease progression of PCa [13]. Other article showed that some circadian genes (*PER1*, *PER2*, *CRY1*, *CRY2*, *CLOCK*, *NPAS2*) were significantly associated with susceptibility to prostate cancer [14]. On the other hand, circadian genes could play a part of role of carcinogenesis or the tumor suppressor through cell proliferation and apoptosis [15]. These findings indicated there was a potential link between genetic variants in circadian genes and PCa.

PER is one of the main mediators of the circadian rhythm, and has a function in the negative feedback loop where it is translocated from the cytoplasm to the nucleus to regulate their expression by an inhibit transcription [16, 17]. *PER* has three paralogs, *PER1*, *PER2*, and *PER3*. Disruption of the circadian genes, including that of *PER3*, affects carcinogenesis related cellular processes, including proliferation, cell cycle regulation, and apoptosis [18]. *PER3* expression was decreased in chronic myeloid leukemia [19], and expression of *PER3* in colorectal cancer tissue was lower than in healthy mucosa [18, 20]. Polymorphisms of *PER3* have also been associated with various cancers [14, 21, 22].

The rs2640908 polymorphism is a *PER3* single nucleotide polymorphism (SNP) associated with cancer

development [23-25]. The rs2640908 polymorphism has an association with patient overall survival in hepatocellular carcinoma and colorectal carcinoma. Another polymorphism of *PER3* is a variable number tandem repeat (VNTR) consisting of 4-5 repeat 54-bp sequences in exon 18 encoding 18 amino acids [26]. Individuals with a variant of 5 VNTR repeats experience delayed sleep phase syndrome and extreme diurnal preference [27, 28]. A relationship between VNTR polymorphism and elevated levels of serum cytokine IL-6 has also been reported [29]. This suggested that *PER3* polymorphisms could have an influence on the carcinogenesis through cell cycle regulation. However, the relationship between both rs2640908 and VNTR polymorphisms and PCa in the Japanese population is yet to be studied in detail. Thus, the aim of this study was to evaluate the relationship between rs2640908 and VNTR polymorphisms and PCa carcinogenesis within the Japanese population.

Methods

Study subjects

A total of 83 patients with PCa and 122 healthy controls were recruited from the Japanese population. Patients were diagnosed at the University of Occupational and Environmental Health (UOEH) Hospital and University of Miyazaki Hospital in Japan, and all diagnoses were confirmed by histology. The control subjects were recruited from UOEH Hospital, University of Miyazaki Hospital, and a hospital located near UOEH Hospital.

All subjects were surveyed with self–questionnaires that collected information on history of illness, occupation, and smoking status. Participants who had been exposed to carcinogenic agents, heavy metals, and radiation in their occupational history were excluded. The included subjects were classified into two groups according to smoking status. The non-smokers were grouped into the "Never" group, and both current and previous smokers were classified as "Smoker". All participants were briefed about the study, and written informed consent was obtained from each participant. This study was approved by the Ethics Committee of the Faculty of Medicine, University of Miyazaki.

Genotyping

Peripheral blood samples were collected from each subject, and genomic DNA was extracted by proteinase K digestion and phenol/chloroform extraction method [30].

Genotyping of the rs2640908 polymorphism was carried out using PCR-Restriction Fragment Length Polymorphism (PCR-RFLP). The sequence of PCR primers used for amplification were 5'-CTGTTTAACACACGAAGTTGAAGA-3' (forward) and 5'-GTTCTGGATGGGGATTCGCT-3' (reverse). PCR was performed using a KAPATaq EXtra PCR Kit (NIPPON Genetics Co., Ltd., Tokyo, Japan) following manufacturer's instructions. The thermocycler conditions were: initial denaturation at 94˚C for 2 min, followed by 35 cycles of denaturation at 94˚C for 30 s, annealing at 55˚C for 30 s, and extension at 72˚C for 45 s, with final extension at 72˚C for 7 min. PCR products were digested with *AgeI* restriction enzyme (New England Biolabs Inc., Ipswich, MA, USA) and incubated at 37˚C overnight, before being resolved by 2% agarose gel electrophoresis. For genotyping, two digestion products of size 798 and 265 bp were expected for C/C genotype (homozygous wild-type), three products of size 1,063, 798, and 265 bp were expected for C/T genotype, and only a single product sized 1,063 bp was expected for T/T genotype. The electrophoretic image of each genotypes is shown in Figure 1.

PCR genotyping for VNTR polymorphisms was similarly performed with primer sequences:

5'–CAAAATTTTATGACACTACCAGAATGGCTGAC–3' (forward)

and 5'–AACCTTGTACTTCCACATCAGTGCCTGG–3' (reverse).

The thermocycler conditions were: initial denaturation at 94˚C for 2 min, followed by 35 cycles of denaturation at 94 ˚C for 30 s, annealing at 60˚C for 30 s, and extension at 72˚C for 45 s with at final extension at 72˚C for 7 min. A 4/4 genotype (homozygous for 4 repeats) had an expected product size of 581 bp, 4/5 (heterozygotes) had expected product sizes of 635 and 581bp, 5/5 (homozygous for 5 repeats) had an expected product size of 635 bp (Fig. 1). PCR products were resolved and visualized using 2% agarose gel electrophoresis.

Statistical analysis

A t-test was used to compare the continuous variables, and a χ^2 test was used to compare categorical data and to determine probability of allele frequencies being in Hardy–Weinberg equilibrium [31]. Odds ratio (OR) and 95% confidence interval (95% CI) were estimated using a multiple logistic regression analysis with adjustment for age and smoking status. Stratified analysis by smoking status was also performed. The level of statistical significance was set at P value < 0.05. All statistical analyses were performed using R ver. 3.6.1.

Results

Clinical characteristics of patient and control subjects, including age and smoking status, are summarized in Table I. The mean age was 69.2 years (SD: 10.4) for control group and 71.6 years (SD: 8.6) for the patient group. Incidentally, a significantly higher percentage of the control group (83.6%) was classified as "Smoker" compared to the patient group (67.5%, P = 0.01).

Distribution of rs2640908 and VNTR polymorphisms for patient and control groups are shown in Table II. Allele frequencies for rs2640908 and VNTR polymorphisms in the control group were in Hardy-Weinberg equilibrium (P = 0.86 and 0.76, respectively). For rs2640908

Tab. I. Characteristics of the controls and cases.

Variable	Controls (n = 122)	Cases (n = 83)	P-value
Age			
Mean (SD)	69.2 (10.4)	71.6 (8.6)	0.08
Smoking status (%)			
Never	20 (16.4)	27 (32.5)	0.01
Smoker	102 (83.6)	56 (67.5)	

t-test and χ^2 test were used for age and smoking status, respectively.

Tab. II. Associations between the PER3 genotype (rs2640908 and VNTR) and PCa.

Genotype	Controls (n = 122)	Cases (n = 83)	Crude OR (95% CI)	Adjusted OR (95% CI)
rs2640908				
C/C (%)	26 (21.3)	29 (34.9)	Ref	Ref
C/T (%)	63 (51.6)	40 (48.2)	0.57 (0.29-1.10)	0.52 (0.26-1.03)
T/T (%)	33 (27.0)	14 (16.9)	0.38 (0.16-0.85)*	0.35 (0.15-0.81)*
C/T + T/T (%)	96 (78.7)	54 (65.1)	0.50 (0.27-0.94)*	0.46 (0.24-0.88)*
VNTR				
4/4 (%)	82 (67.2)	56 (67.5)	Ref	Ref
4/5 (%)	37 (30.3)	25 (30.1)	0.99 (0.53-1.82)	0.94 (0.50-1.76)
5/5 (%)	3 (2.5)	2 (2.4)	0.98 (0.13-6.07)	1.28 (0.16-8.69)
4/5 + 5/5 (%)	40 (32.8)	27 (32.5)	0.99 (0.54-1.79)	0.96 (0.52-1.77)

χ^2 test and multiple logistic regression were used for crude OR and adjusted OR for age and smoking status, respectively. 95% CI: 95% confidence interval; OR: odds ratio; Ref: reference; *: P < 0.05.

Tab. III. Associations between the PER3 genotype (rs2640908 and VNTR) and PCa when stratified by smoking status.

Genotype	Controls (n = 122)	Cases (n = 83)	Crude OR (95% CI)	Adjusted OR (95% CI)
Never				
rs2640908				
C/C (%)	3 (15.0)	8 (29.6)	Ref	Ref
C/T (%)	11 (55.0)	12 (44.4)	0.41 (0.07-1.83)	0.39 (0.07-1.76)
T/T (%)	6 (30.0)	7 (25.9)	0.44 (0.07-2.34)	0.53 (0.08-3.02)
C/T + T/T (%)	17 (85.0)	19 (70.4)	0.42 (0.08-1.72)	0.43 (0.08-1.79)
VNTR				
4/4 (%)	12 (60.0)	20 (74.1)	Ref	Ref
4/5 (%)	8 (40.0)	6 (22.2)	0.45 (0.12-1.60)	0.40 (0.10-1.46)
5/5 (%)	0 (0)	1 (3.7)	-	-
4/5 + 5/5 (%)	8 (40.0)	7 (25.9)	0.53 (0.15-1.81)	0.48 (0.13-1.70)
Smoker				
rs2640908				
C/C (%)	23 (22.5)	21 (37.5)	Ref	Ref
C/T (%)	52 (51.0)	28 (50.0)	0.59 (0.28-1.25)	0.57 (0.27-1.21)
T/T (%)	27 (26.5)	7 (12.5)	0.28 (0.10-0.76)*	0.29 (0.10-0.77)*
C/T + T/T (%)	79 (77.5)	35 (62.5)	0.49 (0.24-0.99)*	0.47 (0.23-0.97)*
VNTR				
4/4 (%)	70 (68.6)	36 (64.3)	Ref	Ref
4/5 (%)	29 (28.4)	19 (33.9)	1.27 (0.62-2.57)	1.22 (0.60-2.48)
5/5 (%)	3 (2.9)	1 (1.8)	0.65 (0.03-5.27)	0.81 (0.04-6.97)
4/5 + 5/5 (%)	32 (31.4)	20 (35.7)	1.22 (0.61-2.41)	1.19 (0.59-2.37)

χ^2 test and multiple logistic regression were used for crude OR and adjusted OR for age, respectively. 95% CI: 95% confidence interval; OR: odds ratio; Ref: reference; *: P < 0.05.

genetic variants, risk for PCa was significantly lower for T/T genotype (adjusted OR: 0.35, 95% CI: 0.15-0.81, P = 0.02), and C/T + T/T genotype (adjusted OR: 0.46, 95% CI: 0.24-0.88, P = 0.02) relative to the C/C genotype, with no significant difference observed for C/T genotype (adjusted OR: 0.52, 95% CI: 0.26-1.03, P = 0.06). In contrast, no significant association was observed between any of the VNTR variants and PCa.

Table III shows the analysis stratified by smoking status. For rs2640908 polymorphisms in the "Smoker" group, there was a significantly lower risk of PCa in T/T genotype (adjusted OR: 0.29, 95% CI: 0.10-0.77, P = 0.02) and C/T + T/T (adjusted OR: 0.47, 95%

CI: 0.23-0.97, P = 0.04) compared to the C/C genotype. Again, no relationship was observed between VNTR genotypes and PCa.

Discussion

In this study, we studied the relationship between the *PER3* polymorphisms, rs2640908 and VNTR, and risk of PCa in the Japanese population. We demonstrated that for the rs2640908 polymorphism, the T/T and C/T + T/T genotypes are associated with a lower risk of PCa. However, we were unable to find a significant association between VNTR variants and PCa.

Disruption of the circadian rhythm is linked to an increased risk of several diseases, including cancer [18-20, 32]. Disruption can arise from different factors, such as shift work and exposure to light at night (LAN exposure) [33]. Shift work influences body temperature, energy allocation, and disrupts circadian rhythm, resulting in damage to health. The circadian rhythm is a physiological fluctuation that takes place in approximately 24-hour cycles, and is involved in the health and survival of most living organisms. Some reports have described auto–regulatory transcriptional and translational feedback loop mechanisms for circadian genes, with both positive and negative regulators [34]. Circadian genes have also been linked to carcinogenesis through DNA repair, apoptosis, and cell proliferation [15, 35, 36].

PER is a circadian gene, with 3 subtypes (*PER1*, *PER2*, and *PER3*) [14]. A previous study has suggested that heterozygosity of a *PER3* polymorphism could be a risk factor for breast cancer among premenopausal women [26]. *PER3* also plays an important role in regulating cell proliferation and apoptosis [37]. Deletion and reduced expression of *PER3* results in upregulation of the estrogen receptors, and is associated with an increased recurrence of breast cancer [38], suggesting that the *PER3* may also play a role in homeostasis for reproductive hormones.

There are two polymorphisms described for *PER3*, rs2640908 and VNTR. At least one variant allele of the rs2640908 polymorphism is associated with a significantly lower risk of death among patients with hepatocellular carcinoma when compared to homozygous wild-type patients [24]. The T/T genotype of the rs2640908 polymorphism also has a protective effect in colorectal cancer compared to the C/C genotype [25]. We found a similar effect for PCa. However, the biological mechanisms that underlie this protection against carcinogenesis remain to be elucidated. The rs2640908 polymorphism is found in the exonic splicing enhancer (ESE) region, which can affect or alter translation initiation sites and translation efficiencies through mRNA splicing, and destabilize the binding of the serine/arginine-rich (SR) protein [39]. The rs2640908 polymorphism may therefore reduce exon recognition and define an alternative splice site [40]. This would affect cell proliferation, cell cycle regulation, and apoptosis, potentially leading to cancer [25].

In our study, no correlation was observed between VNTR polymorphisms and PCa. Varying relationships between VNTR polymorphism and carcinogenesis have been reported previously. The VNTR variant with 5 repeats is associated with increased risk of prostate cancer in men with high levels of insulin resistance [41] and with colorectal adenoma [21]. In contrast, a meta-analysis could not identify any significant relationships between VNTR polymorphisms and breast, prostate, and colon cancers [42]. The 5 repeats sequence of the VNTR polymorphism play an essential role as it is a phosphorylation site, and the 5/5 genotype plays a crucial role in the circadian process compared to the 4/4 genotype [43]. Heritable chronotypes may be polygenic, and variants of several genes may be required for full phenotypic expression [43]. That may explain why no association was observed between VNTR polymorphism and PCa in this study.

There relation between circadian genes and PCa was inconsistent. Markt et al. did not find the consistent association between 96 SNPs across 12 circadian-related genes and fatal prostate cancer risk using three patient cohorts [44]. On the other hand, the study on EPICAP study showed the evidence supporting hypothesis of a link between circadian genes and PCa [12]. Since circadian rhythms were produced by multiple molecular interactions of protein, and PCa was a complex polygenic trait, a single-SNP approach may not be sufficient to investigate the association between circadian genes and PCa [12]. Therefore, further investigation will be need to evaluate the relation between circadian genes and carcinogenesis of PCa with more samples and various genes including *PER3* gene, especially for Japanese population.

We also evaluated the association between rs2640908 polymorphisms and susceptibility to PCa in smokers. We found that the T/T and C/T + T/T genotypes conferred lower risk of PCa compared to the C/C genotype within the "Smoker" group, but not the "Never" group. This result suggests that there is an association between smoking and *PER3* polymorphisms, as previously observed in colon cancer [25]. Cigarette exposure changes DNA binding by modulating the redox potential of cells and tissues [45], and therefore affects transcriptional activity. Binding of transcriptional circadian genes, including *BMAL1*, *CLOCK*, and *NPAS2,* is dependent on the redox ratio [46]. Circadian genes and smoking may therefore interact in a synergistic manner. However, the possibility of association between gene polymorphisms and smoking remains controversial. Jin et al has advocated that genetic differences in risk tend to be smaller at high doses of carcinogens, including tobacco, when the environmental effect may overpower any genetic predisposition [47]. However, this was disputed by Kuroda et al, who reported that the Pro/Pro genotype of a *TP53* polymorphism in smokers was significantly higher in patients with urothelial cancer compared with that in the control [48]. Polymorphisms for the metabolic genes *GSTT1*, *GSTM1*, and *CYP1A1* are not associated with the smoking status in onco-hematological diseases [49].

Considering these contradictory findings, further studies are warranted to clearly elucidate the relationships between gene polymorphisms and smoking.
There were some limitations to this study. First, our small sample may have induced a sampling bias and affected the results of the stratified analysis. Secondly, we had no information regarding the history of shift work, alcohol consumption, BMI, sleep time, clinical characteristics, smoking period and number of cigarettes. The lack of these data also induced information bias, and introduced the influence to our results. Especially, since circadian genes polymorphism could influence sleep condition and shift work tolerance [50], the interaction with circadian genes and sleep condition (sleep duration and sleep quality) could influence the carcinogenesis of PCa. Therefore, additional study will be needed to evaluate the relation between *PER3* gene polymorphisms and carcinogenesis of PCa with considering sleep condition. We could not use smoking condition (smoking period and number of cigarettes), but used the status of smoking. We found that the rate of smoking was higher in the control than in the patient group. We estimated the interaction with smoking and *PER3* polymorphism (rs2640908) by multiple logistic regression analysis. Therefore, smoking condition (smoking period and number of cigarettes) could be important factor. It would be necessary to evaluate the relation between smoking condition and *PER3* polymorphism stratified by smoking condition. Despite these limitations, we believe our findings provide a basis for future studies investigating the association between prostate cancer and circadian gene polymorphisms.

Conclusions

In conclusion, this is the first study that focused on associations between *PER3* polymorphisms (rs2640908 and VNTR) and PCa risk. For rs2640908, the T/T and C/T + T/T genotypes had a significant protective effect against PCa in the Japanese population. However, no relationship between VNTR polymorphisms and PCa could be detected. Our finding suggests that the rs2640908 polymorphism may be a useful marker for prostate cancer and contributes to further understanding of the molecular mechanisms underlying PCa pathogenesis.

List of abbreviations

PCa: Prostate cancer.
SNP: Single Nucleotide Polymorphism.
VNTR: Variable Number Tandem Repeat.
PCR: Polymerase Chain Reaction.
PCR-RFLP: Polymerase Chain Reaction - Restriction Fragment Length Polymorphism.
CLOCK: Circadian Locomotor Output Cycles Kaput Gene.
PER: Period Gene.
CRY: Cryptochrome Gene.
PER1: Period 1.
PER2: Period 2.
PER3: Period 3.
IL-6: Interleukin-6.
UOEH: University of Occupational and Environmental Health.
AgeI: Restriction Enzyme.
χ^2 test: Chi-square test.
OR: Odds Ratio.
95% CI: 95% Confidence Interval.
SD: Standard Deviation.
LAN exposure: Light at Night Exposure.
IARC: The Agency for Research on Cancer.
DNA: Deoxyribonucleic Acid.
ESE: Exonic Splicing Enhancer.
mRNA: Messenger Ribonucleic Acid.
SR: Serine/Arginine-Rich.
BMAL1: Brain and Muscle Arnt - Like 1.
NPAS2: Neuronal PAS domain 2.
TP53: Tumor Protein 53.
GSTT1: Glutathione S - transferase theta 1.
GSTM1: Glutathione S - transferase Mu 1.
CYP1A1: Cytochrome P450 Family 1 Subfamily A Member 1.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

TH contributed to experimental work and designed the experiments and analyzed the results. SM and TK contributed in the data collection. YK contributed on interpreted, reviewed the experiment design, and critically reviewed the manuscript. All authors reviewed the manuscript and approved the final draft.

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RESEARCH PAPER

Establishment of brucellosis relapse and complications registry: a study protocol

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Keywords

Brucellosis • Relapse • Complication • Registry • Developing countries

Summary

Brucellosis is an endemic bacterial zoonotic disease in developing countries; that is a serious public health problem in Iran. Brucellosis is a life-threatening multi-system disease in human with different clinical manifestations, complications and relapse. The incidence of brucellosis in Hamadan province, west of Iran is high. In addition, there is few reliable and population-based studies regarding relapse and complications of brucellosis in developing countries, therefore establishment of the registry system in areas with adequate occurrence of cases is needed to better understand the predictors of brucellosis relapse and complications and management of the disease. Detecting occurrence of relapse and complications over time and by geographical area provide information for further investigations and identification of health system deficiencies in the management of patients.

IMPACTS

- There is limited data on brucellosis patients with history of relapse or complications in endemic countries of brucellosis.
- Diseases registries like Brucellosis Relapse and Complications Registry can be used to perform epidemiological studies to identify the main risk factors as well as clinical research.
- Registration the occurrence of relapse and complication among brucellosis patients provides information for better management of patients.

Introduction

Brucellosis is a zoonotic bacterial disease, which can cause of significant economic losses due to the livestock abortion, and also because of its burden and complications in human, especially in developing countries, considered as a big concern for public health and international trade [1].

True incidence of brucellosis in livestock may be 10-20 times higher than the reported figures [2]. Brucellosis in humans can cause a wide range of clinical manifestations (fever, chillness, myalgia, arthralgia, night sweating, fatigue, weight loss, etc) with various organ involvements. Brucellosis can present in acute, subacute and chronic forms and it causes serious complications such as endocarditis or neurobrucellosis. The disease has the ability to relapse, and in 5 to 15% of cases, even with treatment, relapse is seen. Mortality is reported less than 1% of patients with brucellosis (Harrison 2019 and Mandell 2020) [2, 3].

Nearly half of the countries with the highest incidence rate for human brucellosis including Iran are located in the Middle East region [4]. Despite the preventive efforts by the health authorities, Iran is still one of the endemic countries for the disease. Results of the meta-analysis study showed that the highest incidences of brucellosis are occurred in west and northwest parts of Iran [5].

Hamadan province is located in the west of Iran. This province is known as one of the hubs of animal husbandry in the country, so that the production of livestock during 2016 in Hamadan was 598,000 tons, the province is ranked the first in the Western part and 9th throughout the country in terms of animal husbandry and livestock [6]. Hamadan has always been one of the provinces with high incidence of brucellosis in the country [7] with 7,318 brucellosis cases from 2009 to 2015 [8].

Despite the introduce and use of standard therapeutic options for brucellosis [9] a proportion of patients are encountered with failure in treatment, relapses and complications [10]. Results of a local study in Hamadan province declared that the rate of relapse among brucellosis patients was 6.45% [8]. The evidence regarding risk factors for relapse are rare. Host characteristics like advanced age, immunity status, severity of infection, and treatment delays are mentioned as the potential risk factors of relapse [8, 10].

Until now no data have been published on the epidemiology of relapse and complications of brucellosis in Iran with a valid and reliable data. A

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published similar study in west of Iran has used data from national notification brucellosis surveillance system to address baseline characteristics of brucellosis patients with potential complications [8]. Therefore, robust longitudinal data are needed to better understand the predictors of brucellosis relapse and complications and management of disease. This study aims to describe the protocol of Brucellosis Relapse and Complications Registry in Hamadan province, west of Iran

The objectives of the registry

Identification of the potential risk factors for relapse and complications of brucellosis is essential to provide a comprehensive understanding of the nature of the disease. Considering the limited conducted studies regarding brucellosis relapse and complications as an endemic country for brucellosis and paucity of information, the need to achieve a valid and reliable data with considerable sample size is necessary. The registry will provide enough motivation for researchers to do multiple researches across the fields of medical, nursing and public health.

Methodology of the registry

Study design

Brucellosis Relapse and Complications Registry is an observational and prospective study enrolling relapse and complicated cases of brucellosis. Approval from the Ethical Committee of Hamadan University of Medical Sciences was obtained (Ref. No. 16.35.1.4218). Enrollment and registration of eligible brucellosis relapse and complication cases were started from September 2015. The recruitment process in primary phase was ended in December 2019. All patients must provide written informed consent to participate in the registry.

Case definition

A case of brucellosis is define as "a patient with clinical manifestations compatible with brucellosis (fever, chillness, myalgia, weakness, night sweating, arthralgia) and Standard Tube Agglutination Test (STA) ≥ 1:80, and 2-mercaptoethanol (2ME) agglutination ≥ 40 or a positive blood culture for Brucella" [11].

Case classification

- *Confirmed case*: a clinically compatible illness with definitive laboratory evidence of Brucella infection.
- *Probable case*: a clinically compatible illness with at least one of the following: Epidemiologically linked to a confirmed human or animal brucellosis case or presumptive laboratory evidence, but without definitive laboratory evidence, of Brucella infection.
- *Suspected case*: lab results only without clinical information.
- *Relapse*: is defined as the recurrence of characteristic signs and symptoms (with positive culture or serology of brucellosis) occurring at some time after the completion of a course of treatment. Patients with relapse characteristically have objective signs of infection, such as fever, and persistently elevated titers of IgG antibodies in their serum. Most relapses occur within six months after therapy is discontinued, and relapse is not usually due to the emergence of antibiotic resistant strains, although this has been seen after monotherapy with rifampicin or streptomycin [12].
- *Complicated case* defines as a patient with symptoms of brucellosis who has at least one involved organ and has a positive serology or culture simultaneously.

Eligibility criteria

The new cases of brucellosis without any complications as well as non-native patients will be excluded from study.

Data collection procedure

The data collection procedure obviously showed in Figure 1. As shown, identified cases of relapse brucellosis or patients with complications related to brucellosis by physicians in rural or urban health centers, private clinics and hospitals in Hamadan province, using a referral form is referred to a trained infectious specialist present at Sina Hospital in official hours and Imam Khomeini Clinic in other times for final diagnosis and examination of documents.

After confirmation and meets the eligibility criteria by focal-point, completed the questionnaire for patients and finally data is entered in the software by the trained expert.

Recorded data is refined and reviewed monthly to fixing defects and avoid duplication of records. Repetitive case will be recorded as a new item in the software if they have relapse criteria or complications. Patients are actively re-examined every three months by mentioned trained infectious specialist and record the results. The incomplete questionnaires will be followed up by the relevant expert to correct the deficiencies.

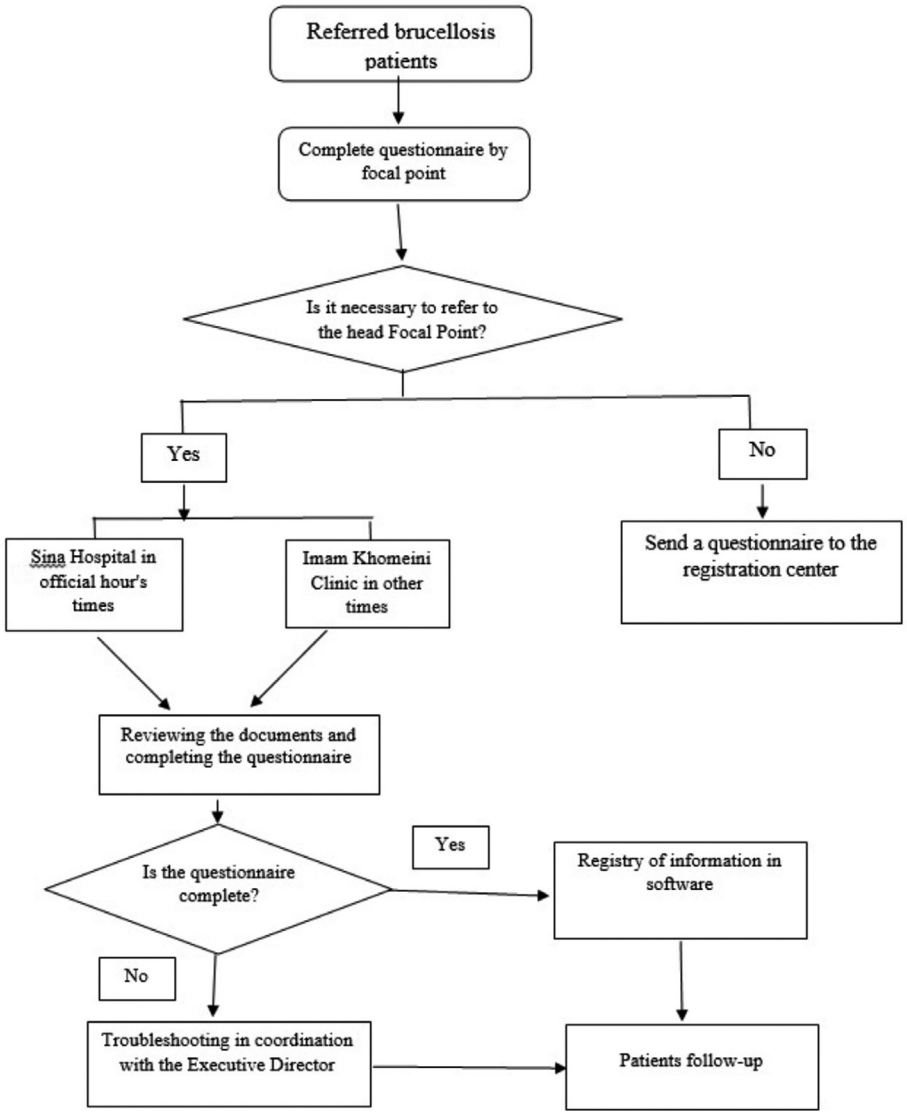
Measurement tool

A researcher- developed questionnaire is used to collect data. To ensure the validity of questionnaire, it was designed by three of researchers. Subsequently, the questionnaire is reviewed and validated by a multidisciplinary panel of experts including: principal investigator, microbiologist, health professional, epidemiologist and four infectious disease specialists. For comparability of results, we used ICD-10 codes for coding of relapse and complications. To ensure uniformity in the register by the executive director, a dictionary was provided for the questionnaire.

This questionnaire including:

1. demographic characteristics (age, sex, pregnancy status, residency, place of residency, job);

Fig. 1. Flowchart of brucellosis relapse and complications registry.



2. information regarding disease (history of disease, date of infection, treatment status);
3. risk factors of disease (Contact with domesticated animals, history of unpasteurized dairy consumption),
4. clinical symptoms (e.g. fever, chillness, weakness, fatigue, sweating, sleep disorders, weight loss, anorexia, headache, generalized body pain, lumbar pain, back pain, joint pain, abdominal pain, testicular pain, constipation, diarrhea, cough, behavioral disorders);
5. clinical signs (e.g. joint swelling, splenomegaly, vertebral tenderness, orchitis, rash, lymphadenopathy, hepatomegaly, nuchal rigidity, heart murmur);
6. complications of brucellosis including:
   - osteoarticular complications - e.g. sacroiliitis, spondylitis, peripheral arthritis, osteomyelitis, bursitis, and tenosynovitis,
   - gastrointestinal complications - e.g. nausea, vomiting, and abdominal discomfort. Rare cases of ileitis, colitis and spontaneous bacterial peritonitis have been reported,
   - hepatobiliary complications - e.g. Hepatic abscesses and chronic suppurative lesions, acute and chronic cholecystitis,
   - respiratory tract complications - e.g. hilar and paratracheal lymphadenopathy, interstitial pneumonitis, bronchopneumonia, lung nodules, pleural effusions, and empyema,
   - genitourinary complications - e.g. orchitis and epididymitis, pelvic abscesses and salpingitis,
   - pregnancy - e.g. brucellosis during the course of pregnancy carries the risk of spontaneous abortion or intrauterine transmission to the infant,
   - cardiovascular complications - e.g. infective endocarditis,
   - neurological complications - e.g. neurobrucellosis, cerebral vasculitis, mycotic aneurysms, brain and epidural abscesses, infarcts, hemorrhage, and cerebellar ataxia,

Tab. I. Steps of assessing the quality of data.

Stage	Comparability	Completeness
Questionnaire design	Using ICD-10 codes for coding of relapse and complications	Focus group discussion with infectious specialists
Questionnaire completion	Increase Kappa agreement between interviewers by holding workshop and sharing standard procedures	Holding briefings and workshops, choosing focal-point for each county, drawing patients registry software

- peripheral nerve complications include neuropathy/ radiculopathy, Guillain-Barré syndrome, and a poliomyelitis-like syndrom,
- cutaneous complications - e.g. rashes, nodules, papules, erythema nodosum, petechiae, and purpura,
- ophthalmic complications - e.g. uveitis. It can present as chronic iridocyclitis, nummular keratitis, multifocal choroiditis or optic neuritis;

7. para laboratory and imaging findings [Wright, 2ME, Coomb's Wright, Blood culture, Bone marrow aspiration culture, ESR (mm/h), CRP (qualitative), WBC (mm^3) and Hb (g/dl) , Whole body bone scan with TC 99, MRI of vertebra , Testis sonography, Abdominal sonography)].

Quality assessment

Quality assurance

In order to ensure the quality of the data, several steps were considered. Table I shows these steps.

Quality control

During the registration process, all completed questionnaires will be reviewed by the program manager. In the case of a defect, a questionnaire will be sent to the relevant physician for correction, and the repeated questionnaires will be deleted.

To ensure proper diagnosis, the program manager will randomly review some of the referral patients' questions.

In order to ensure that data entry is adapted to the software and the questionnaire, randomly each week, a number of patients' questionnaires registered by the registration expert will be reviewed by the executive director of the program.

Coverage of registration of eligible cases will be estimated using completeness percent. Moreover, frequency distribution of registered cases among a variety of characteristics includes sex, age groups and residency areas will be estimated.

In regard of representativeness of the study population, given that the Sina Hospital is referral hospital, and because of the presence of infectious specialists in Imam Khomeini Clinic simultaneously, it seems that the registered patients in this system represent all patients with relapse and complications of brucellosis in Hamadan province.

Ethical considerations

The study protocol has been approved by Ethics Committee of Hamadan University of Medical Sciences was obtained (Ref. No: 16.35.1.4218). Entry to the study will be voluntary. Prior to registration, about the confidentiality of information, planning the registry, the purpose of the project, the non-interference of the registration process with the treatment process will be explained for patients.

Discussion

Registries are powerful instruments to support health care and research, and usually made on data collected from events or outcomes interested for specialists in daily healthcare and cannot be achieved in another way [13].

Brucellosis Relapse and Complications Registry is the first registry regarding brucellosis relapse and complications in Iran. The aim of this registry is providing better understanding of the nature of the disease and effectiveness of treatments by identification of potential risk factors for relapse and complications of brucellosis. As we know brucellosis a rare disease in advanced countries with eradication programs [14]. For example in France, from 2004 to 2013 according human brucellosis surveillance a total of 250 brucellosis cases was notified (0.3 cases per million) [15]. But in Iran, the situation is different, so that in Hamadan province (2.4% of the country's population) the number of 7,318 brucellosis cases was notified in a seven year period [8].

Vast majority of studies in the field of brucellosis in developed countries is restricted to case reports or case series studies, because the number of patients in these countries is not considerable, in other words, brucellosis is not the problem of those countries. In limited studies conducted in the country [8 16], the results are based national modifiable surveillance system data, which are not collected for research purposes and are based on the passive surveillance. The generalizability results of other studies because of their low sample size or restricted study area are also low [2, 3, 17]. Given the same situation in other endemic brucellosis countries, establishment of relapse and complications of brucellosis registry is essential in endemic areas.

Conclusions

Developing Brucellosis Relapse and Complications Registry in endemic countries with adequate occurrence of relapse and complications is essential. Outputs of these registries can be used to perform epidemiological studies to identify the main risk factors as well as clinical research. Detecting occurrence of relapse and complication over time and by geographical area provide information for further investigations and identification of health system deficiencies in the management of patients.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

FK, MM, MA and MK developed the original idea and the protocol, abstracted, and prepared the manuscript. All authors participated in the study design and read and approved the final manuscript.

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Research paper

Infection prevention and control standards and associated factors: Case study of the level of knowledge and practices among nurses in a Saudi Arabian hospital

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Keywords

Infection prevention and control • Nurses • Saudi hospital • Knowledge • Practices

Summary

Introduction. *Healthcare-associated infection is a significant public health issue in both developed and developing countries. This study was performed to assess the knowledge and practices of infection prevention and control (IPC) of nurses working in a Saudi hospital, and to examine their associations with the nurses' sociodemographic characteristics and work/training experience.*

Methods. *A self-administered questionnaire survey was conducted with participation of male and female nurses of all nationalities who had direct contact with patients while providing healthcare services at King Abdulaziz Medical City-Riyadh (KAMC-R). Sociodemographic characteristics, and work/training experience were reported; IPC knowledge and practices were assessed by questionnaire. Data of 308 valid responses were analyzed. Percentage of correct responses to nine IPC knowledge questions and frequent adherence to 11 IPC practices were calculated. IPC knowledge and practice scores were developed by using principal component analyses; individual scores were classified into high/low level of knowledge or practices by the median of the scores. Logistic regression analysis was performed to evaluate associations between IPC knowledge or practice scores and sociodemographic or work/training variables.*

Results. *Majority of the participants were females (89.3%). Significant associations between high education level and high level of IPC knowledge (AOR = 2.72, 95% CI = 1.45-5.10) and practices (AOR = 3.66, 95% CI = 1.90-7.05) were observed, after controlling the influence of sociodemographic and work/training variables.*

Conclusion. *High scores for IPC knowledge and IPC practices were independently associated with nurses' high level of education, regardless of their nationality or previous working experience. Further studies to develop effective programs for IPC regardless of the nurses' educational attainment are recommended.*

Introduction

Healthcare-associated infection (HAI) is a significant public health issue around the world [1]. It affects both developed and developing countries [2]. About 5% to 10% of hospitalized patients in developed countries, and about 20% of patients in developing countries are affected by HAI [3]. Treatment of HAIs draws a lot from countries' budgets for healthcare; in the U.S., it costs 5 to 10 billion dollars annually to manage HAIs [4].

The World Health Organization (WHO) has created the term Infection Prevention and Control (IPC), for encouraging a scientific approach and practical solutions to prevent the harm accruing from HAI to patients and healthcare workers (HCWs) [5]. The Centers for Disease Control (CDC) established the concept of universal precautions (UPs) in 1987, and then, changed to standard precautions (SPs) in 1996 [6]. SPs are used when dealing with any patient, regardless of the diagnosis [7].

Studies have discussed IPC from different points of view. According to one reported study, assessment of the current levels of knowledge and practices of HCWs is the first step towards establishment of a successful IPC program [2]. Another study suggested that in order to increase the compliance level of HCWs towards IPC standards, the barriers need to be known and removed [8]. Another study has recommended periodic assessment of the knowledge levels for filling any gaps [9].

As a background to this study, Saudi Arabia has a total population of 34,218,169 persons, and is a high-income country [10]. The Saudi healthcare system has been ranked by the WHO as 26th from the top, out of 191 countries [11]. The nursing workforce in Saudi Arabia depends mainly on expatriate workers, who account for 62.6% of the entire workforce, and there are workers of over 44 nationalities in the Saudi health sector [10]. Saudi IPC is a young and rapidly growing speciality [12]. The most common types of HAIs in Saudi Arabia are pneumonia, urinary tract infection (UTI), and bloodstream infection. Approximately, 19.2% of HAIs in Saudi Arabia are reported to be device-associated [13]. WHO recently reported an outbreak of the Middle

East Respiratory Syndrome Coronavirus (MERS-CoV) in Saudi Arabia from October 1 to 30, 2019, which caused six deaths [14].

The Saudi Ministry of Health (MOH), at the current time, follows the healthcare 2020 vision, aimed at achieving the best possible health condition or health status for Saudi inhabitants [15]. This vision involves the establishment of an effective system by following appropriate and effective methods to estimate the risks and benefits of the methods employed [15].

This study was performed to assess the IPC knowledge and practices of nurses working in a Saudi hospital, and to examine their associations with the nurses' sociodemographic characteristics and work/training experience.

Methods

Study design and sampling

A cross-sectional self-reported questionnaire survey was conducted at King Abdulaziz Medical City-Riyadh (KAMC-R) between August 2 to September 5, 2019. The hospital follows the Joint Commission International (JCI) standards as the unifying standard for healthcare and practice [16]. According to the assumption of proportion of high level of IPC knowledge as 50%, degree of precision as 0.05, sample size for the study was calculated as 384. Nurses working at the following units of the hospital were invited to participate in the study, regardless of their gender and nationalities: medical unit, surgical unit, cardiac unit, emergency unit, labor and delivery unit, hemodialysis unit, intensive care unit, and ambulatory care center. Nurses who provided healthcare services and had direct contact with patients were included in the study sample. During the study period, 820 nurses participated in the survey; data of 803 valid responses were analyzed.

Data collection and instrument

The questionnaire was developed in English based on the WHO guidelines [17] and CDC guidelines [18]. Nurses in Saudi Arabia use English as a working language. By using multiple choice questions and a Likert scale for responses, sociodemographic characteristics, work/training experiences, knowledge about IPC, and IPC practices of participated nurses were evaluated. To develop a questionnaire, a pilot questionnaire form was sent to two nurses and their views on the questionnaires were reflected to formulate words in the questionnaire.

The sociodemographic information included the gender, age, education, and nationality. Questions on work/training experiences included years of service, previous work experiences, experience in KAMC-R, and experience outside KAMC-R.

Nine questions were used to evaluate the subjects' knowledge on IPC, and 11 questions were used to evaluate the adherence to IPC practices by referencing WHO guidelines [17], CDC guidelines [18] and surveys conducted in other countries.

The survey instrument was pre-tested in a preliminary survey with 30 nurses from the same hospital prior to the start of the actual data collection process. Those nurses were excluded in the actual main data collection.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 22 software was used for the statistical analyses. The responses to nine individual questions about IPC knowledge were divided into correct or in-correct responses. The percentages of correct responses to individual questions were calculated. Adherence to IPC practices were evaluated based on self-reported responses on a Likert scale for frequencies (Always = 3; Sometimes = 2; Seldom = 1; Never = 0) to perform 11 practices. The percentages of the response of "always" for IPC practices and the means of the score for 11 practices were calculated.

To develop composite scores for IPC knowledge and IPC practices, individually, principal component analyses (PCA) were performed by using correct or in-correct answers to nine questions on IPC knowledge and self-reported frequencies of adherence to 11 IPC practices. The factor scores of the first component of IPC knowledge questions and the first component of IPC practices questions were used as the composite IPC knowledge score and the composite IPC practice score.

For further analysis to evaluate the associations between IPC knowledge or practices and the sociodemographic or work/training variables, the composite scores for IPC knowledge and practices were classified into high/low level of knowledge or practice by the median of individual composite scores.

The associations between IPC knowledge or practice scores and sociodemographic characteristics or work/training variables were evaluated by logistic regression analysis. Composite IPC knowledge score, high/low, was used as a dependent variable and its association with independent variables (sociodemographic characteristics and work/training experiences) were analyzed. Similar analysis using composite IPC practice score, high/low, as a dependent variable was also performed.

Ethical considerations

The study was conducted with the approval of the Tokyo Medical and Dental University Ethics Committee (M2018-310), and King Abdullah International Medical Research Center (SP19/406/R). The survey followed the principle of voluntary participation and informed consent for participation was obtained before answering to questions. They were informed that they were free to withdraw from the study at any time without any disadvantages accruing to them. Nurses who refused to participate in the survey were not included in the study. Those who were not directly involved in providing healthcare services to patients, such as nurse managers, were excluded from the study.

Table I. Infection prevention and control (IPC) knowledge and practices towards IPC of nurses working in a Saudi hospital (n = 308).

IPC knowledge		
Topics of questions	% of correct answers	
Hand hygiene	93.2	
Definition of standard precautions	54.5	
Rubbing of hands	84.4	
Five moments of hand hygiene	40.9	
Handling of personal protective equipment	71.1	
Handling of sharp objects	76.3	
Immunization for healthcare providers	41.2	
Respiratory hygiene	95.1	
Contact infection	95.5	
IPC practices		
Questions	% always practicing	IPC practices score* (Mean)
Performing hand hygiene before touching patients	95.8	2.96
Performing hand hygiene after touching patients	98.1	2.98
Performing hand hygiene before clean/aseptic procedure	97.1	2.97
Performing hand hygiene after touching the patient's surroundings	92.2	2.92
Performing hand hygiene after dealing with body fluids	98.7	2.99
Following the recommended time when hands washing	73.4	2.70
Following the recommended time when rubbing one's hands	81.5	2.80
Discarding sharp items into sharps containers immediately after use	98.4	2.98
Using suitable personal protective equipment before entering the patient's room	90.6	2.89
Looking up the required IPC information by oneself (using available resources)	64.6	2.58
Asking IPC team about the required IPC information, if needed	56.8	2.41
Overall Mean		2.83

* The score was calculated as: Always 3; Sometimes 2; Seldom 1; Never 0.

Results

Majority of the participated nurses were females (89.3%), and bachelor's/master's degree holders (81.2%). Most participants were 20 to 40 years of age (68.8%). Regarding working units and years of work at the hospitals, 22.4% were working in the medical unit; 76.6% served for less than 10 years in KAMC-R. Non-Saudi Arabian participants accounted for 78.3%; the nationalities were as follows: 55.5% Filipino, 14.3% Malaysian, 4.9% South African, 1.3% British, 0.6% Jordanian, 0.3% Slovakian, 0.3% Greek, 0.3% Korean, 0.3% Irish, and 0.3% Lebanese. 76.1% had prior work experience; 90.3% had received training about IPC at KAMC-R, and 89.6% were satisfied with the training they had received.

Table I shows the summary statistics of answers to individual questions pertaining to IPC knowledge and practices. The percentage of correct answers to individual IPC knowledge questions ranged from 40.9% to 95.5%, depending on the questions. For example, 40.9% of participants correctly chose the recommended 5 moments for hand hygiene, 71.1% of the participants chose correct answers for appropriate handling of personal protective equipment, and 95.1% of the participants chose correct answer for practices related to respiratory hygiene. The percentage of participants that answered "always" for the 11 individual questions pertaining to adherence to IPC practices ranged from 56.8% to 98.7%. 95.8% and 98.1% of the participants reported that they always ensure hand hygiene before and after touching patients, respectively; 98.4% always discarded sharp items into the containers for sharps immediately after use, and 64.6% always looked up information on IPC by themselves instead of contacting IPC department, when they need to seek information.

Table II shows the factor loading of the first factor based on PCA using IPC knowledge and practices. The results of PCA on IPC knowledge showed that even the first component, R^2, was 15.5% and representativeness of this component for overall IPC knowledge was limited. The results of PCA on IPC practices showed that the first component represented 29.1% of all variance, with a Cronbach alpha for the 11 items of 0.702.

Table III shows the distribution of high scores for IPC knowledge by the sociodemographic characteristics and work/training experiences of the nurses, and the results of logistic regression analysis showing the associations of high scores for IPC knowledge with the sociodemographic characteristics and work/training experiences of the nurses. Among the participants holding bachelor's or master's degrees, 55.2% had high scores for IPC knowledge, while only 34.5% of participants below a bachelor degree showed high scores for IPC knowledge. The percentages of high scores for IPC knowledge among those with and without previous work experience were 55.6% and 37.9%, respectively.

The unadjusted odds ratio (OR) showed that a high score

Table II. Factor loadings of principal component analysis of infection prevention and control (IPC) knowledge and practices.

IPC knowledge		
Item	**Factor loading**	**Commonalities (R^2)**
Hand hygiene	0.506	0.256
Definition of standard precautions	0.344	0.118
Rubbing of hands	0.132	0.017
Five moments of hand hygiene	0.443	0.197
Handling of personal protective equipment	0.253	0.063
Handling of sharp objects	0.540	0.291
Immunization for healthcare providers	0.425	0.181
Respiratory hygiene	0.521	0.272
Contact infection	-0.028	0.001

R^2 for component/factor: 15.5%; Cronbach alpha = 0.242.

IPC practices		
Item	**Factor loading**	**Commonalities (R^2)**
Performing hand hygiene before touching patients	0.597	0.356
Performing hand hygiene after touching patients	0.493	0.243
Performing hand hygiene before clean/aseptic procedure	0.483	0.233
Performing hand hygiene after touching the patient's surroundings	0.454	0.206
Performing hand hygiene after dealing with body fluids	0.459	0.211
Following the recommended time when hands washing	0.744	0.554
Following the recommended time when rubbing one's hands	0.671	0.450
Discarding sharp items into sharps containers immediately after use	0.356	0.127
Using suitable personal protective equipment before entering the patient's room	0.529	0.280
Looking up the required IPC information by oneself (using available resources)	0.497	0.247
Asking IPC team about the required IPC information, if needed	0.547	0.299

R^2 for component/factor: 29.1%; Cronbach alpha = 0.702.

for IPC knowledge was significantly associated with a high education level [OR = 2.34, 95% CI = 1.29-4.25], and previous work experience [OR = 2.05, 95% CI = 1.20-3.51], and negatively associated with the nurse being of Saudi Arabian nationality [OR = 0.57, 95% CI = 0.33-0.98]. After adjustments for all independent variables, only the variable of education level showed significant independent association with high IPC knowledge score: adjusted odds ratio (AOR) for high education level was (AOR = 2.72, 95% CI = 1.45-5.10).

Table IV shows the distribution of high scores for IPC practices by the sociodemographic characteristics and work/training experiences of the nurses, and the results of logistic regression analysis showing the association of high scores for IPC practices with the sociodemographic characteristics and work/training experiences of the nurses. Among the participants holding bachelor's or master's degrees, 51.6% showed high scores for IPC practices, while only 29.3% of participants below a bachelor degree showed high scores for IPC practices. The percentages of high scores for IPC practices among those with and without previous work experiences were 54.3% and 25.7%, respectively.

The unadjusted OR showed that a high score for IPC practices was significantly associated with a high age [OR = 2.16, 95% CI = 1.25-3.75], high education levels [OR = 2.57, 95% CI = 1.39-4.77], and previous work experience [OR = 3.44, 95% CI = 1.92-6.15], and negatively associated with the nurse being of Saudi Arabian nationality [OR = 0.27, 95% CI = 0.14-0.5]. After adjustments for all independent variables, only the variable of education level showed significant independent association with high IPC practice score: AOR for high education level was [AOR = 3.66, 95% CI = 1.9-7.05].

Discussion

The high percentage of female nurses among the study participants was consistent with the reported percentage of female workers in the Saudi nursing workforce (80.7%) [10]. The percentage of expatriate workers in the current study of 78.2% was higher than reported percentage of foreign workers in the Saudi nursing workforce (62.6%) [10].

More than half of the participants were Filipinos (55.5%). This reflects a report in 2011 by Kanchanachitra et al., which reported large number of international migration of Filipino nurses to Saudi Arabia, UAE, UK and USA, and referred the Philippines as one of the major countries for export of nurses [18].

The current study showed that nurses participated in the study had a high level of knowledge on hand hygiene, respiratory hygiene, contact infection, and rubbing of hands procedure, handling of personal protective equipment and handling of sharp objects; an intermediate

Table III. Distribution of high infection prevention and control (IPC) knowledge score and its association with sociodemographic characteristics and working/training experiences of nurses working in a Saudi hospital (n = 308).

Characteristics		High IPC knowledge score					
	n	%	P*	OR (CI 95%)	P**	AOR (CI 95%)	P**
Sociodemographic characteristics							
Gender							
Female	275	49.5	0.062	Ref.		Ref.	
Male	33	66.7		2.04 (0.95-4.38)	0.066	1.65 (0.72-3.77)	0.237
Age (years)							
20-30	106	49.1	0.881	Ref.		Ref.	
31-40	106	50.9		1.08 (0.63-1.85)	0.784	0.77 (0.41-1.45)	0.426
41-50	80	55.0		1.27 (0.71-2.27)	0.422	0.66 (0.29-1.53)	0.335
>50	16	50.0		1.04 (0.36-2.97)	0.944	0.58 (0.15-2.19)	0.419
Highest completed education							
Below a bachelor degree	58	34.5	0.004	Ref.		Ref.	
Bachelor or Master degree	250	55.2		2.34 (1.29-4.25)	0.005	2.72 (1.45-5.10)	0.002
Nationality							
Non-Saudi Arabian	241	54.4	0.042	Ref.		Ref.	
Saudi Arabian	67	40.3		0.57 (0.33-0.98)	0.043	0.83 (0.30-2.24)	0.708
Working/training experience							
Participation in services (years)							
<10	236	49.2	0.172	Ref.		Ref.	
≥10	72	58.3		1.45 (0.85-2.47)	0.174	1.67 (0.80-3.49)	0.173
Previous working experience							
No	74	37.9	0.008	Ref.		Ref.	
Yes	234	55.6		2.05 (1.20-3.51)	0.008	2.0 (0.81-4.95)	0.133
Experience of training inside KAMC-R							
No	30	50.0	0.881	Ref.		Ref.	
Yes	278	51.4		1.06 (0.50-2.25)	0.881	1.06 (0.47-2.35)	0.895
Experience of training outside of KAMC-R							
No	190	53.2	0.407	Ref.		Ref.	
Yes	118	48.3		0.82 (0.52-1.30)	0.408	0.80 (0.48-1.33)	0.390

* Chi-square test; ** Logistic regression analysis; IPC: Infection prevention and control; KAMC-R: King Abdulaziz Medical City-Riyadh; OR: Odds Ratio; AOR: Adjusted Odds Ratio; Ref.: Reference

level of knowledge on SP; knowledge below the average on the 5 moments of hand hygiene and immunization schedule or healthcare providers.

HAI is central to the provision of safe and high-quality healthcare, therefore, the related IPC policies and procedures should be adhered when dealing with patients as well as equipment. The IPC methods should ideally be applied to ensure that a sterile environment is provided.

With regards to the scores for IPC knowledge and practices developed by PCA, the score for IPC practices explained 29.1% of variance for the 11 variables and showed reasonable representation and consistencies; on the other hand, the IPC knowledge score only explained 15.5% of the variance for the 9 variables. Further studies are needed to develop a good indicator to reflect level of knowledge among HCWs in the context of Saudi Arabia.

The results identified education level of the nurses as a significant independent factor related to high scores for both IPC knowledge and IPC practices. No significant associations of the scores were observed with previous work experience or experience of receiving training on IPC. These findings suggest that for nurses below a bachelor degree education, effective interventions to improve their knowledge of IPC and IPC practices are critically important.

The hospital had experienced an outbreak of MERS-CoV in 2015, and a special IPC program called "right care, right now" was implemented [16], however, the current results did not show any association of the scores for IPC knowledge or practices with experience of IPC training inside KAMC-R. Therefore, the impacts of in-hospital training programs need further investigation.

Saudi Arabia has announced the Saudi Vision 2030 for improving the delivery of services in all fields and sectors, including the health sector. The vision is aimed at improving the efficiency and effectiveness of the healthcare sector through the use of information technology and digital transformation [19]. Thus, for provision of training on IPC or IPC education sessions, use of modern information technology and digital sources is highly recommended.

Table IV. Distribution of high infection prevention and control (IPC) practices score and its association with sociodemographic characteristics and working/training experiences of nurses working in a Saudi hospital (n = 308).

Characteristics		High IPC practices score					
	n	%	p*	OR (CI 95%)	p**	AOR (CI 95%)	p**
Sociodemographic characteristics							
Gender							
Female	275	46.2	0.215	Ref.		Ref.	
Male	33	57.6		1.58 (0.76-3.28)	0.218	0.96 (0.43-2.16)	0.921
Age (years)							
20-30	106	35.8	0.032	Ref.		Ref.	
31-40	106	54.7		2.16 (1.25-3.75)	0.006	1.5 (0.78-2.85)	0.221
41-50	80	52.5		1.98 (1.09-3.57)	0.024	1.13 (0.49-2.64)	0.773
> 50	16	50.0		1.79 (0.62-5.15)	0.281	1.43 (0.37-5.56)	0.604
Highest completed education							
Below a bachelor degree	58	29.3	0.002	Ref.		Ref.	
Bachelor or Master degree	250	51.6		2.57 (1.39-4.77)	0.003	3.66 (1.90-7.05)	<0.001
Nationality							
Non-Saudi Arabian	241	53.9	< 0.001	Ref.		Ref.	
Saudi Arabian	67	23.9		0.27 (0.14-0.50)	<0.001	0.36 (0.13-1.03)	0.056
Working/training experience							
Participation in services (years)							
< 10	236	46.2	0.439	Ref.		Ref.	
> 10	72	51.4		1.23 (0.73-2.09)	0.439	1.02 (0.48-2.16)	0.954
Previous working experience							
No	74	25.7	< 0.001	Ref.		Ref.	
Yes	234	54.3		3.44 (1.92-6.15)	<0.001	1.79 (0.70-4.57)	0.223
Experience of training inside KAMC-R							
No	30	50.0	0.764	Ref.		Ref.	
Yes	278	47.1		0.89 (0.42-1.89)	0.764	1.04 (0.46-2.36)	0.918
Experience of training outside of KAMC-R							
No	190	47.4	0.988	Ref.		Ref.	
Yes	118	47.5		1.00 (0.63-1.59)	0.988	1.33 (0.79-2.26)	0.286

* Chi-square test; ** logistic regression analysis; IPC: Infection prevention and control; KAMC-R: King Abdulaziz Medical City-Riyadh; OR: Odds Ratio; AOR: Adjusted Odds Ratio; Ref.: Reference

Limitations

The study was designed as a cross-sectional study, which is not adequate to address causation. There could be potential reporting bias due to self-reporting of practices by the HCWs rather than observational or objective evaluation. Furthermore, there could have been potential sampling bias, as this survey was conducted at a single hospital run under unique system by the Ministry of National Guard Health Affairs, while Saudi Arabia is a big country with 13 administrative regions.

Conclusion

The study reported IPC knowledge and IPC practices of nurses working in a Saudi hospital. High scores for IPC knowledge and IPC practices were independently associated with a high level of education completed by the nurses, regardless of their nationality or previous working experiences. It is important to develop effective programs to improve IPC knowledge and compliance to recommended IPC practices, regardless of the level of education of nurses in the current workforce. Periodic conduct of an IPC awareness program for HCWs is also recommended.

Ethical approval

The study protocol was approved by the Tokyo Medical and Dental University Ethics Committee (M2018-310), and King Abdullah International Medical Research Center (SP19/406/R).

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Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

RSA and KN conceptualized and designed the study, RSA coordinated and managed the implementation of the survey and obtained data, RSA, KN, and SA analyzed and interpreted the results, and KS reviewed the analysis. RSA developed initial manuscript, and KN, SA, YT, NW and KS reviewed and revised the manuscript.

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Research paper

Implementation of control measures against an outbreak due to *Clostridioides difficile* producing toxin B in a tertiary hospital in Mexico

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Keywords

Hospital outbreak • Infection control • *Clostridioides difficile* • Toxin B

Summary

Introduction. *To describe the outbreak of Clostridioides difficile infection (CDI), and the impact of the prevention and control measures that were implemented in the "Hospital Juárez de México" (HJM) for its control.*
Methods. *A cross-sectional, descriptive, observational, and retrospective study was designed. All information on the hospital outbreak and on health care-associated infections (HCAI) was obtained from the files of the Hospital Epidemiological Surveillance Unit (HESU) of the HJM.*
Results. *A total of 15 cases of CDI were detected from February 20th to May 22nd, 2018, which represented 55.6% and 44.4% for the male and female gender, respectively, with an average age of 56 years and a range of 24 to 86 years old. It was possible to identify six failures and deficiencies that involved health personnel and hospital logistics through analyses based on the situational diagnosis in the services involved and through the construction of cause-effect diagrams. Additionally, through the detection of the outbreak by means of laboratory tests and timeline, the HESU team implemented measures and prospective surveillance to control and prevent the emergence of new cases.*
Conclusions. *The implementation of basic quality tools, control measures, and the prospective epidemiological surveillance had a positive impact on the control against the outbreak of C. difficile producing toxin B.*

Introduction

Clostridioides difficile (*C. difficile*) is a Gram-positive bacillus, spore-forming and toxin producer that in recent years has represented a great challenge in terms of infection control within health institutions in the world, being one of the main etiological agents of the health care-associated infections (HCAI) [1]. *C. difficile* infection (CDI) is the most common cause of diarrhea associated with health care and long-term use of antimicrobials [1]. The transmission of this pathogen mainly occurs in hospital facilities, where exposure to antimicrobials and contamination of the environment by *C. difficile* spores is common [1]. *C. difficile* produces toxins that cause damage to the epithelial cells, these toxins are known as toxin A and toxin B [1]. Toxin A, called enterotoxin, which is more potent, increases secretion, causes more mucosal damage and inflammation, however, in cell cultures, toxin B has been shown to have greater cytotoxic activity, and in subsequent studies it has been shown that it is more toxic in the human colonic epithelium than toxin A [1, 2]. Worldwide, it is estimated that between 20 and 30% of cases of diarrhea associated with antibiotics are caused by *C. difficile.* In Canada, a rate between 3.8 to 9.5 cases per 10,000 patient days is calculated between 1997 and 2005. As of 2002, more severe and recurrent outbreaks have been observed, the great majority associated with the use of antimicrobials, mainly fluoroquinolones, with an attributable mortality of 6.9 to 7.5% [3, 4].
In some hospitals in Mexico, the presence of *C. difficile* has been detected as one of the main infectious agents, showing a higher prevalence in hospital services such as Internal Medicine, General Surgery, and Intensive Care Units [5].
According to the literature, the main risk factor for *C. difficile* infection is the indiscriminate use of antimicrobials, mainly from the family of carbapenems and cephalosporins [6, 7]. The outbreaks that have occurred in our country have shown difficulties in their control and prevention, even remaining constant with an endemic behavior [8, 9].
The aim of this work was to describe the hospital outbreak of *C. difficile* infection and the impact of the prevention and control measures that were implemented in the "Hospital Juárez de México" (HJM).

Methods

Study design

A cross-sectional, descriptive, observational, and retrospective study was designed. All information was obtained from the hospital outbreak and from the

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health care-associated infections (HCAI) from the Hospital Epidemiological Surveillance Unit (HESU) of the HJM.

Period of analysis and case definition of CDI

The period of the outbreak study was from February 20th to May 22nd, 2018. For the identification of cases, operational definitions were made and inclusion criteria was included such as patient of any age who had been hospitalized for at least 48 hours and who had presented more than three diarrheic stools in 12 hours, accompanied by one or more of the following symptoms: fever, abdominal distension and/or abdominal pain was considered as a suspected case of CDI. For a confirmed case of CDI, we had to meet the operational definition of a suspected case and have a positive result on any of the following tests:

- commercial immunochromatographic qualitative test against glutamate dehydrogenase (GDH) (CERTEST *Clostridium difficile* antigen GDH, Certest Biotec S.L.);
- real-time PCR amplification of a fragment of the gene coding for *C. difficile* toxin B was performed by using the automated BD MAX technology (Becton Dickinson) according to the supplier's instructions.

Collection and analysis data

The outbreak information was handled in Microsoft Excel package (Microsoft Corporation; Redmond, WA). The variables and risk factors described and analyzed were age, gender, hospital service, use of antimicrobials before CDI diagnosis, use of proton pump inhibitors, and type of diagnosis. Frequencies and percentages are used for data description.

Results

A total of 15 cases of CDI were detected during February 20th to May 22nd, 2018. The index case was a patient who had a history of having been previously hospitalized in the HJM during December 2017 and January 2018 in General Surgery. One week after his hospital discharge, his start with characteristic symptomatology in his home (diarrheic discharge, abdominal pain and fever). Since the clinical picture began at home, the health personnel who valued his readmission did not suspect that the etiologic agent was *C. difficile*. For this reason, there was a delay in the diagnosis and in the implementation of preventive measures, which generated exposure to patients and health personnel.

The epidemiological investigation and case analysis showed that 66.6 and 34.4% of patients corresponded to the male and female gender, respectively, with an average age of 56 years and a range of 24 to 86 years of age. According to the hospital services, where the cases were detected, 40% were in Internal Medicine, 26.7% in General Surgery, 13.3% in Neurosurgery, 13.3% in Hematology, and 6.7% in Thoracic Surgery. According to the timeline, 13.3% was detected in February 40% in March, and 46.7% in April. Figure 1 shows the distribution of cases in the epidemic curve.

Three deaths were recorded, of which only one was related to CDI, therefore, the fatality rate was 5.6%. The index case began with diarrheic discharge in February; however, when reviewing the epidemiological background, he was hospitalized at the HJM in December; despite identifying this data, it could not be determined whether if it was the primary case or the source of the outbreak. Among the risk factors detected, 88.9% of the cases had some antimicrobial scheme, the most commonly used being carbapenems, quinolones,

Fig. 1. Epidemic curve of outbreak due to *Clostridioides difficile* infection.

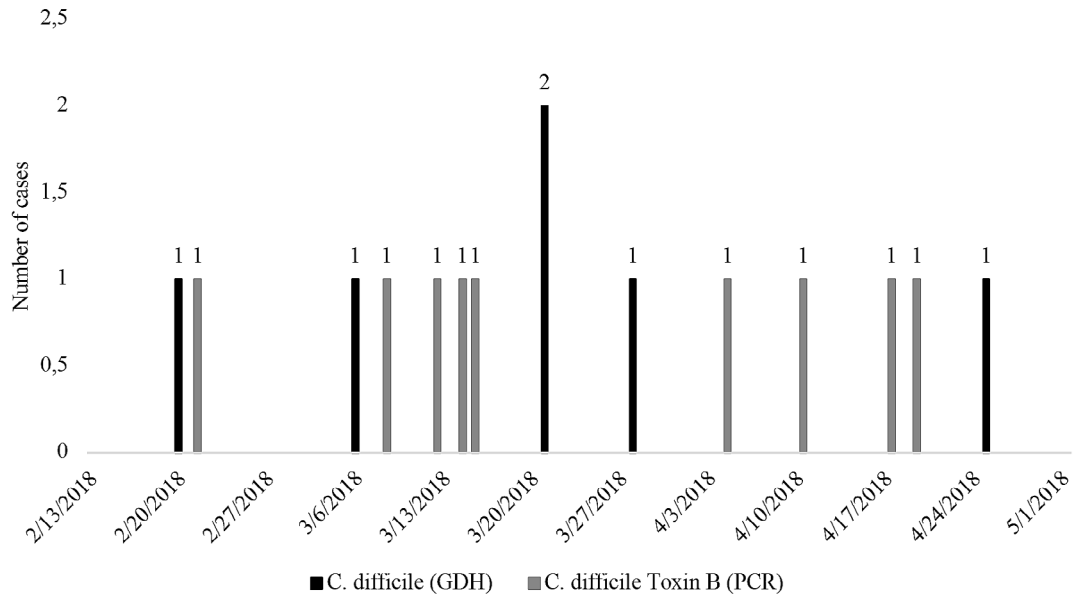
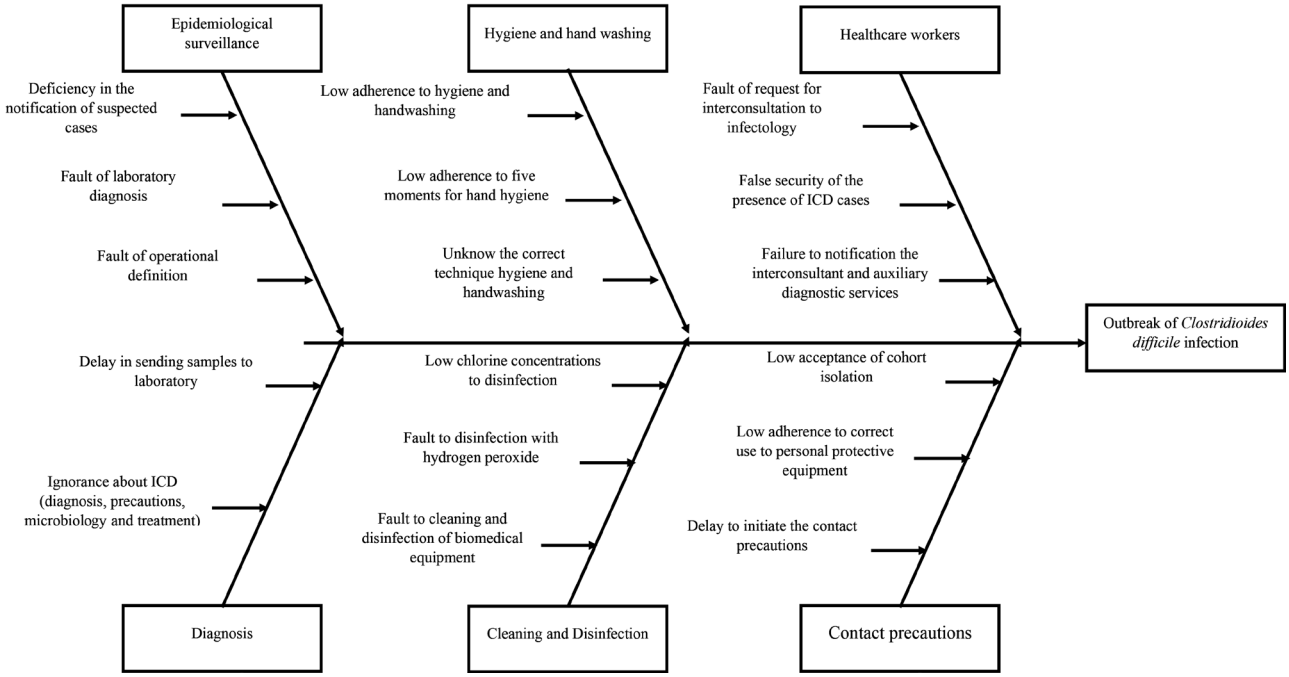


Fig. 2. Ishikawa diagram of outbreak due to *Clostridioides difficile* infection.



and cephalosporins. In all cases, the use of proton pump inhibitors was detected. When determining that it was a hospital outbreak due to *C. difficile*, the HESU team began with the prospective epidemiological surveillance, the implementation of control measures for the outbreak, and the prevention of the appearance of new cases, based on the situational diagnosis carried out in the services involved, where faults and deficiencies were identified and outlined in the cause-effect diagram (Fig. 2).

Implementation of outbreak control measures

Hygiene and hand washing, and contact precautions

During the outbreak, a low percentage of adherence to hygiene and hand washing was detected in the services involved, the above was determinate by personalized questioning. Therefore, training for the personnel of the involved areas on the correct technique of hygiene and hand washing, as well as, the five moments for hand hygiene was carried out. A total of 118 health workers from the hospital wards involved were trained, of which 75% were nurses, 13% cleaning staff, 9.2% doctors, and 2.7% were support staff. 0.1% corresponded to administrative staff, family members, and patients. These measures were applied to patients who met the operational definition of a suspected case of CDI. In addition, family members, patients, and health personnel were trained in the matter of the correct use of personal protective equipment.

Hospital cleaning and disinfection

A diagnosis of the situation was performed, where it was identified that the hospital cleaning and disinfection process was not standardized, and it had errors in the sequence of steps. Consequently, it was decided to use two concentrations of sodium hypochlorite, 1,600 ppm for routine cleaning, and 5,000 ppm for final cleaning at patient discharge.

The cleaning of the biomedical equipment and objects that were found inside the patient's room or environment, was carried out daily and at the time of the patient's discharge with towels impregnated with peroxide. This step was complementary to disinfection with the chlorine concentrations mentioned above, before and after, but always together. As a last step in the sequence of disinfection, in the suspected or confirmed cases, the nebulization with hydrogen peroxide with silver particles was used, where it was requested by the services and authorized by the staff of the HESU, and after this step a patient could be allowed to enter the room.

Laboratory diagnosis

When a suspect case was detected, the sample of diarrheic stools was collected and submitted for emergency diagnosis to the Genetics and Molecular Diagnostic Laboratory of the HJM for their corresponding study. One of the weaknesses detected during the study process of the outbreak was that the medical and nursing staff did not have sufficient knowledge to perform a differential diagnosis of CDI. Therefore, the necessary training was initiated to identify CDI and the operational definition of the case. The second problem was that even when the personnel that identified a suspected case of CDI, they did not notify it, the case was detected through active epidemiological surveillance. The third and final problem was that samples were occasionally sent to the laboratory for CDI diagnosis.

Cohort isolation

One of the obstacles for the isolation of CDI cases was the structural characteristic of the HJM, since it limited the correct application of precautions contact measures, thus, relocation of beds and/or rooms was carried out in order to be able to shape specific and unique areas for suspected and confirmed cases. These measures were carried out until the discharge of the patient. In the same period of the outbreak, a total of three positive cases of *C. difficile* coming from other hospital units were identified, along with eight cases of gastroenteritis associated with health care with negative results to *C. difficile*.

Intervention with health workers

During training on hygiene and hand washing, the matter of identification, notification, diagnosis and treatment of suspected or confirmed cases of CDI was also addressed. The training covered the following points:

- operational definition of suspected case of CDI to improve detection;
- sample submission to the central or research laboratory for the timely diagnosis of CDI cases;
- application and registration in clinical file and medical indications of contact precautions in suspected and confirmed cases of CDI;
- effective communication of the suspicion or confirmation of the CDI to the interconsultant, surgical, and auxiliary diagnostic services (imaging);
- correct cleaning and disinfection of biomedical equipment in contact with suspected or confirmed CDI patients;
- interconsultation to the infectology service when detecting a suspected case of CDI for the timely initiation of antimicrobial treatment.

Discussion

To our knowledge, this is the first study of a hospital outbreak of diarrhea caused by *C. difficile* producing toxin B in Mexico, although there are previous reports in our country of the presence of this toxin, they only focus on isolates of clinical origin [10].

It is known that the identification of the source of dissemination in a *C. difficile* outbreak is very complex, which is why it is necessary to take into account that the hospital environment is probably the main source of contamination. This is due to poor cleaning and disinfection processes, combined with a low adherence to hygiene and hand washing of health workers [10]. The constant training and supervision of health personnel on hygiene and hand washing, and on cleaning and disinfection is a task of great importance, since it is easy to lose habits in the application of these measures. Previous studies have shown that hygiene and hand washing are the most important measures for the prevention and control of HCAI [11, 12].

One of the points to improve, is the importance of having an effective cleaning and disinfection process, with the appropriate products, of the areas involved in the circulation of *C. difficile*. Hospital environments should be evaluated, since there are different surfaces and biomedical equipment that can be difficult to disinfect, such as mattress surfaces, beds, and toilets [13]. The disinfectants that are used should be evaluated, as well as the concentrations to achieve a significant reduction of the spores [11]. Wong et al., 2018, concluded that the use of disinfectants with sporicidal activity in the hospital environment after discharge of the patient with CDI helps to reduce the risk of cross-transmission of *C. difficile* [14]. The effectiveness of cleaning and disinfecting with impregnated towels or with nebulization with hydrogen peroxide, complemented with silver particles has been demonstrated [15-17].

To obtain positive results with this type of products, it must be considered that they will always have to be complementary to the use of suitable concentrations of chlorine, either before or after the cleaning and disinfection step [18, 19]. They must be used strategically to optimize this input, and always with good communication with the technical team in charge of the application and with the hospital services involved [20, 21].

Although *C. difficile* is an infectious agent that is difficult to control, and that in a large number of hospitals its presence has an endemic behavior, efforts to make effective prevention and control measures of the outbreak must be constant with the trainings and supervisions in the hospital services involved. It is important to mention that hospital epidemiological surveillance actions work in a similar way to field epidemiology, having the structure based on the surveillance of morbidity, mortality, and by laboratory. It is necessary to establish the operational definition of CDI cases, both of suspected and confirmed cases, the technique in collecting and submitting samples for laboratory diagnosis, and the assessment by endoscopy and pathology services, if required. The establishment of these parameters will allow to carry out a proper epidemiological surveillance of cases of CDI. Furthermore, it is important to integrate indicators such as the incidence rate [22, 23]. One factor to take into account of the CDI cases is the increase in the costs derived from medical care, van Buerden et al, 2017, calculated the costs attributable to the care and control of an outbreak of *C. difficile* ribotype 027, and it was of approximately € 1,222,376, the factor that increased the cost was the increase in hospital stay and the closing of rooms to implement contact precautions [24]. The impact on the economy of the institutions is important, without considering the cost that it generates to the family members of the infected patients. One of the characteristics of the HJM, which represents a barrier for infection control, is the deficient number of rooms for the isolation of cases, these limits and impacts the adherence to precautions based on the transmission of diseases, in this case contact precautions. Ideally when making plans on the construction of new hospitals or the remodeling of existing institutions, the team of the HESU should consider aspects related to the prevention and control of infections. Without a doubt, the effective communication with the

staff of the diagnostic laboratories was the key to contain the outbreak, since there is a coordinated notification with the HESU team, which strengthens the timely detection activities. It is important to permanently assemble a system for the notification and detection of suspected cases of CDI to identify a case in a timely manner, initiate contact precautions and antimicrobial treatment, and effective measures of cleaning and disinfection. The importance of communicating this report is to raise awareness about the importance of prevention and control measures, which must be well executed and supervised, since the success or failure of the risk of infection to patients, family members, and health workers depends on this.

Conclusions

The implementation of effective and adequate measures of prevention and control of *C. difficile* are a constant challenge for hospital epidemiology, for which strategies should be designed for hospital structures, so that the results are as favorable as possible. The use of basic quality tools to carry out the analysis with a risk approach for the study of outbreaks is a methodology that we must explore, since they can give a wider perspective to face the barriers that are detected. Additionally, we must not forget that epidemiological surveillance is based on morbidity, mortality, and the laboratory, the latter was a strength for our HESU group, because having results in a timely manner allowed us to implement prevention and control measures in a short time.

Ethical considerations

There are no ethical implications, since the information used was obtained as part of the routine activities of the HESU. The collection and presentation of the information was carried out under the observation of the principles of confidentiality and discretion according to the Federal Law of Responsibility and Access to Public Information.

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None

Conflict of interest statement

None

Authors' contributions

O.S.H and J.M.B.L.: Original idea, article writing, critical review and discussion of data and data analysis, B.M.T., J.G.M., R.J.V., N.E.G.G., A.E.H. and M.R.S.: Collection data, critical review, J.C.B.A.: Laboratory tests.

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Research paper

Clostridium difficile outbreak: epidemiological surveillance, infection prevention and control

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Keywords

Clostridium difficile outbreak • Infection prevention • Epidemiological surveillance • Joinpoint regression • *Clostridioides difficile* infection

Summary

Introduction. *Clostridium difficile infection (CDI) is currently considered the most common cause of health care-associated infections. The aim is to describe the trend of CDI in an Italian hospital and to assess the efficacy of the measures adopted to manage the burden.*
Methods. *Data were retrieved in the San Salvatore Hospital of L'Aquila, from 1 January 2016 to 31 December 2018. Incidence rate of CDIs was calculated as the number of new infected persons per 10,000 patient-days. Changes in the CDI rate during the period considered were analysed using a Joinpoint regression model and related to the preventive strategies adopted. The strategies adopted focused mainly on patient isolation, reinforcement of proper hand hygiene techniques, antimicrobial stewardship and environmental disinfection.*
Results. *CDI/10,000 patient-days was 6.27 in 2016 and increased to 7.71 in 2017, then drastically decreased to 2.76 during 2018. The Joinpoint regression analysis identified three Joinpoints: Sep-2016, Jan-2017, and Sep-2017. There was a reduction from 2016/01 to 2016/09 (slope = -1.44; p = 0.67), then there was an increase from September 2016 to February 2017 (slope = 30.01; p = 0.29), both statistically not significant. Therefore, there was an important decrement from February 2017 to September 2017, statistically significant (slope = -15.84; p = 0.012).*
Conclusions. *Reports based on routine laboratory data can accurately measure population burden of CDI with limited surveillance resources. The adoption of multi-pronged strategies has proven effective in reducing CDI. It's important to keep attention high regarding preventive measures of CDI, also a continuous joint effort by all health professionals, caregivers and patients is needed.*

Introduction

Clostridium difficile (CD) is a Gram-positive anaerobic bacterium. This spore-forming bacillus can be found in a wide range of habitats, from soil and water to the intestines of animals, including humans (3-5% of human adults) and it is transmitted along the fecal-oral route. The principal virulence factors of the microorganism are exotoxin proteins, toxin A and toxin B, produced by the pathogenic strains of CD. Diseases caused by CD can range in severity from mild diarrhea to fulminant pseudomembranous colitis and, without suitable treatment, toxic megacolon and death. It has been associated mainly with hospitals, where it occurs both endemically and epidemically. *Clostridium difficile* infection (CDI) is one of the most important healthcare-associated infections in industrialized countries. In particular, it is considered the most common etiology of nosocomial diarrhea [1].
During the last few years, social and health changes led to an increase in this type of infection: over the past 20-years, hospital-acquired CDI has become more frequent, more severe, and more likely to recur or relapse after standard therapy. This increased severity has been attributed to the emergence of hypervirulent strains such as ribotype 027 or NAP1 or ribotype 078 which have been documented worldwide [2]. A recent systematic review and meta-analysis found a CDI incidence of 2.24 per 1,000 admissions per year and 3.54 per 10,000 patient-days per year; the rate of cases in the general population, for all ages, is 41.94 per 100,000 population per year [3]. The cases of CDI have led to an increase in mortality and morbidity, especially in older adults. Mortality is at least 6% within 3 months of diagnosis and 13% in patients > 80 years old. In addition, CDI has a significant economic impact on the healthcare system and is a cause of burden on healthcare institutions. The average length of hospitalization is increased by 14 days and the attributable cost per adult patient was about €10,000, with the majority of the cost being due to hospitalization [4]. Nosocomial transmission is the most frequent for this type of infection, in this context, practical measures for reducing infection are crucial to prevent and control the spread of CDI [5]. Thus, epidemiological surveillance and control measures take a central role in countering CDI.
The present study aimed to describe the trend of CDI in an Italian hospital, by investigating an outbreak which

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occurred between October 2016 and April 2017, and assessing the efficacy of the control measures adopted to manage the burden.

Methods

Data collection

Data were retrieved in the San Salvatore Hospital of L'Aquila, in Abruzzo, a region in the center of Italy, from January 1st 2016 to December 31st 2018. The study was authorized by the Hospital Management of San Salvatore Hospital, and the data were treated anonymously.

We analyzed the laboratory database to identify CDIs in patients over 18 years of age: we defined a "case" of CDI as a positive *Clostridium difficile* toxin assay from a stool specimen.

Data related to tests from outpatient facilities, extra-hospital facilities, and inappropriate tests were excluded. The latter were selected according to the European surveillance protocol for CD [6]: tests were repeated within 2 weeks of the first positive test. Therefore, positive tests during the 2-8 weeks after the first positivity were considered "recurrences".

Preventive protocol

On January 1st 2017 the Hospital Management of San Salvatore Hospital adopted preventive strategies to face the increasing cases of CDI. Strategies were categorized as: (1) diagnosis and surveillance; (2) hand hygiene; (3) patient isolation and personal equipment; (4) glove and protective clothing use; (5) reception, transport, transfer, and discharge of patients; (6) environmental cleaning; (7) management of medical devices, linen, dishes and waste; (8) antibiotic stewardship; and (9) education and information for staff, patients and caregivers. The indications contained allow for the prompt identification CDI cases and to guarantee correct management during hospitalization until discharge.

Diarrheal fecal samples from patients with suspected infection by CD were tested using an Intermedical CLOSTRIDIUM TRIO TOSSINA A/B/GDH kit, which detects both the presence of the glutamate dehydrogenase (GDH) antigen, and the presence of the A and B toxins. A positive test for the GDH antigen and one of the two toxins is sufficient to confirm the diagnosis of CDI.

Once the positive isolates were identified, the following interventions were implemented to reduce the incidence of CD colonization and infection:

- placing patients in contact isolation;
- soap and water hand hygiene;
- report the isolation to Hospital Management;
- development of an educational tool for patients and visitors;
- formulary restriction to prevent overuse of offending antibiotics.

The protocol provides that the room cleaning procedure be carried out by personnel equipped with adequate personal protection twice a day using chlorinated at 1,000 ppm. The cleaning procedure includes all lateral environmental surfaces frequently in contact with the patient and reusable medical equipment. Moreover, a patient who is suspected of CD infection is placed in contact isolation where there is room cleaned, and stool specimens are collected to determine if they are CD antigen positive.

Training courses and flyers were used to educate direct patient care staff regarding cross-contamination via the environment as a real possibility in this type of patient. In addition, patients and visitors are kept up to date with all the information regarding the transmission of the pathogen.

Statistical analysis

The incidence rate of CDIs was calculated as the number of newly infected persons for each month by the overall length of stay (incidence per 10,000 patient-days). In addition, positivity rates on the tested samples were calculated. The denominators were obtained through the SISWeb, a suite of interacting programs that allow for the management of the entire course of treatment of both outpatients and inpatients, and the collection of data from each health event, data for the clinical dossier. Changes in the CDI rate during the period considered were analyzed using a joinpoint regression model. Joinpoint regression model analyses rates, proportions, and any other measure that can be considered (e.g., counts), to study statistically significant changes in the trend and their locations within the model time [7]. We performed two models: in the first, the dependent variable was the CDI rate per 10,000 patient-days without log transformation and the independent variable was the time (months); in the second, the dependent variable was "crude rate x 100" (CDI/requests x 100) without log transformation and the independent variable was the time (months). We assumed that the random errors in the regression model were Poisson, and we estimated the regression coefficients by weighted least squares for the model $y = xb$, using the Joinpoint Regression Program (version 4.7.0.0 *https://surveillance.cancer.gov/joinpoint*).

Results

From January 2016 to December 2018, 1994 stool samples were tested for CD and 248 (12.4%) were positive. Positive tests corresponded to 186 CDI episodes, regarding 149 persons. Patient characteristics are summarized in Table I.

The number of stool samples tested increased from 597 in 2016 to 846 in 2017, then decreased to 551 in 2018. The numbers of infections were 70 in 2016, 85 in 2017, and 31 in 2018. The proportion of these samples tested as positive was stable in 2016 (11.7%) and 2017 (10.1%), then it was halved in 2018 (5.6%). The highest proportion of CDI episodes on tested samples was observed in surgical wards (10%), closely followed by medical wards (9.4%), whereas Intensive Care Units showed the lowest proportion (4.5%). However, the

Tab. I. Patient characteristics.

	2016, n(%)	2017, n(%)	2018, n(%)	Total, n(%)
Sex				
Male	25 (43.1%)	28 (37.9%)	16 (64%)	69 (46.3%)
Female	33 (56.9%)	38 (62.1%)	9 (36%)	80 (53.7%)
Average length of stay (days)	25.0	23.8	30.4	25.4
Ward				
Surgical	10 (17.2%)	14 (21.2%)	0	24 (16.1%)
Medical	48 (82.8%)	50 (75.8%)	24 (96%)	122 (81.9%)
Intensive care	0	2 (3%)	1 (94%)	3 (2%)
Age				
< 60 years	10 (17.2%)	4 (6.1%)	3 (12%)	17 (11.4%)
60 -75 years	18 (31.1%)	16 (24.2%)	6 (24%)	40 (26.8%)
> 75 years	30 (51.7%)	46 (69.7%)	16 (64%)	92 (61.8%)

raw number of cases in medical wards far outpaced others with a total of 157 CDI cases (84%). 84% of CDI occurred in medical ward, followed by Surgical (14%) and by Intensive Care Unit (2%).

The incidence during the considered period was 5.53/10,000 patient-days (95% CI: 4.73-6.32). During 2016, CDI/10,000 patient-days was 6.27 and increased to 7.71 in 2017, then drastically decreased to 2.76 in 2018, as shown in Figure 1.

The Joinpoint regression analysis identified three Joinpoints in the first model: sep-2016, jan-2017, and sep-2017 (Fig. 2). These points divided the trend line into four linear segments, each with a different slope. There was a moderate reduction during the time range 2016/01-2016/09 (slope = -1.44; p = 0.67), then there was an increase from September 2016 to February 2017 (slope = 30.01; p = 0.29), both statistically not significant. Therefore, there was an important decrement from February 2017 to September 2017, statistically significant (slope = -15.84; p = 0.012). Finally, in the last segment, the trend was fairly stationary with a not significant slope = 0.16 (p = 0.78).

In the second model, the Joinpoint regression analysis identified two Joinpoints: feb-17 and oct-17 (Fig. 3). These points divided the trend line into three linear segments, each with a different slope. There was an increment during the time range January 2016 - February 2017 (slope = 0.86; p = 0.043), then there was a decrement from February 2017 to October 2017 (slope = -1.54; p = 0.039), both statistically significant. Finally, in the last segment, the trend was fairly stationary with a not significant slope = 0.10 (p = 0.57).

Discussion

Several studies reported that the incidence and severity of CDI have been increasing in recent years across the United States, Canada, and Europe. It is now considered the most common cause of healthcare-associated infection: therefore, it requires continuous active surveillance. Public health surveillance is the ongoing systematic collection, analysis, and interpretation of data, closely integrated with the timely dissemination of these data to those responsible

Fig. 1. Incidence CDI/10,000 patient-days by month.

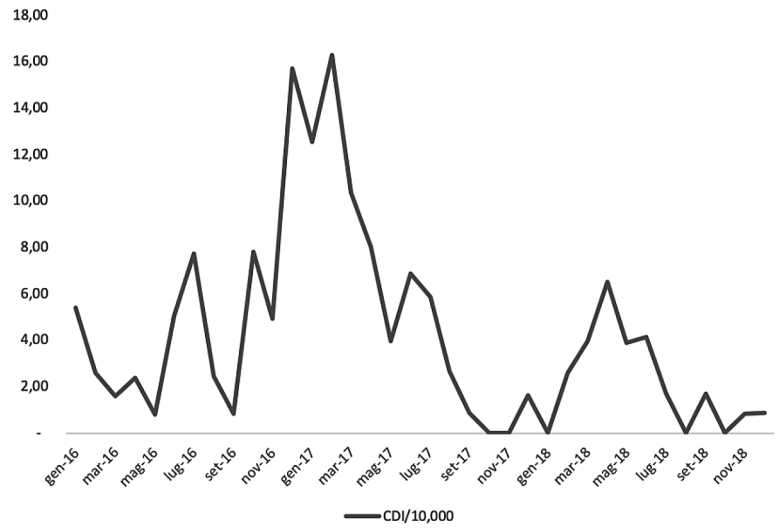


Fig. 2. Distribution of CDI/10,000 patient-days by month.

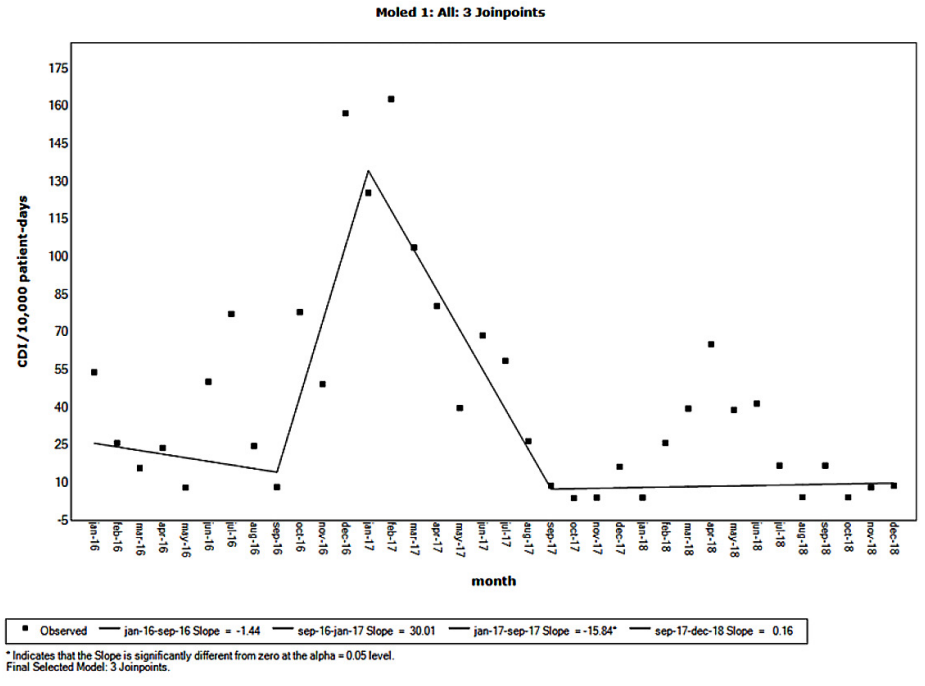
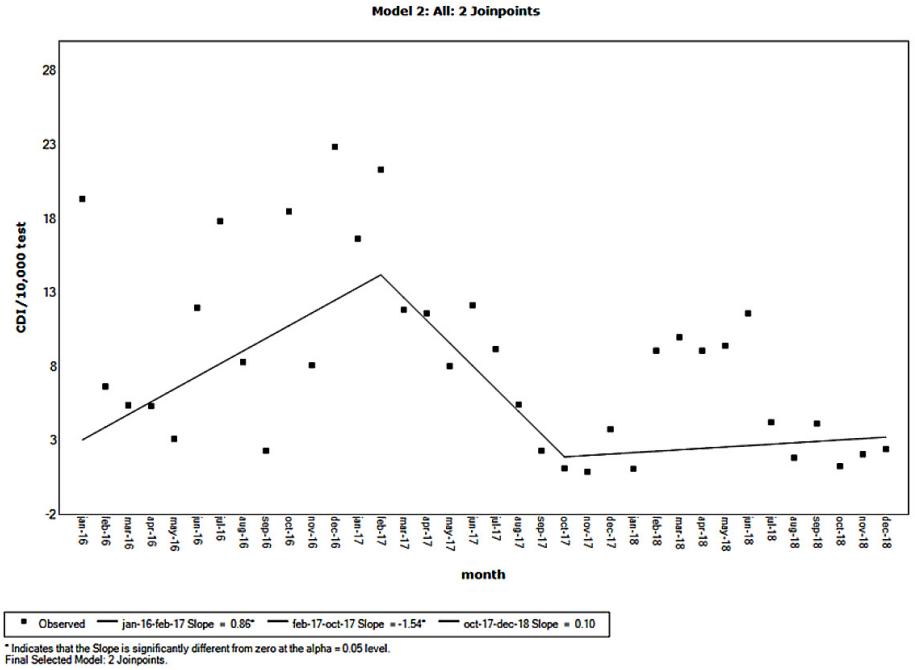


Fig. 3. Distribution of CDI/request x 100 by month.



for preventing and controlling disease and injury.[9] In particular, a laboratory-based surveillance system is an important cornerstone in the control of CDI: it allows for the detection of changes in local epidemiology and to provides information to guide decisions. Thanks to the surveillance activity it was possible to manage the outbreak that occurred between October 2016 and April 2017 by implementing new preventive strategies.

In particular, during 2016 and 2017 we reported an incidence of CDI episodes per 10,000 patient-days equal to 6.27 (CI 95%: 4.81-7.74) and 7.71 (CI 95%: 6.06-9.34) respectively. The increase in 2017 is mainly due to the high number of cases observed in the first three months of the year. These data are greater than those reported in the ECDC report, both for Europe and Italy, 3.98 (CI 95%: 3.45-4.51) and 2.76 respectively [8]. However,

the comparison with the reported Italian mean is not significant due to the poor adherence of Italian hospitals to the ECDC project (only two participants). Regardless, the episodes of CDI in San Salvatore Hospital were higher than the European average not only during the outbreak but also in the previous period. This situation has made it necessary to reaffirm the importance of prevention as a means of combating the spread of CDI and the need for a multidisciplinary approach in the management of CDI in hospitals. A previous study by Weiss et al. [9] showed that a multi-pronged intervention strategy is most effective in reducing the rate of healthcare CDI. Implementation of behavioral protocols, environmental sanitation, and antibiotic stewardship is considered the most effective strategies for the prevention and control of *C. difficile* infections. These interventions are aimed at identifying, isolating, and efficaciously treating patients affected by CDI to prevent the spread of infection [10]. The transmission of *C. difficile* and other pathogens particularly depends in particular, on the presence of other patients with infections, contaminated surfaces and hand carriage transmission by medical staff, that are the major route of the transmission of the infection [11-14]. An infected patient occupying the room can disseminate microorganisms and rapidly contaminate frequently touched surfaces in near-patient areas and these surfaces may remain contaminated for extended periods [15]. Consequently, *C. difficile* can be found on bedrails, bedsheets, commodes, call buttons, toilets, windowsills, blood pressure cuffs, electronic thermometers, floors, and any other surface that comes into contact with contaminated hands [16]. Indeed, there is a close correlation between hand contamination and the degree of environmental contamination, for this reason, proper hand hygiene is a crucial point in the prevention of nosocomial infections. Therefore, the use of hospital decontamination protocols and the correct disinfection of the contaminated surfaces and medical devices is essential to prevent the transmission of nosocomial infections [17].

According to a multi-pronged intervention scheme, the Hospital Management drew the attention of health professionals implementing behavioral protocols including hand hygiene, glove, and protective clothing use, and management of medical devices, linen, dishes, and waste. Moreover, particular attention has been paid to environmental cleaning, instructing cleaning staff, and strengthening communication between them and nursing staff. Those visiting infected patients were also taught to wash their hands and to limit contact only to the patient being visited. Indeed, the training of healthcare personnel, visitors, caregivers, and patients represents the best way to get adherence to the guidelines. Through this approach, numerous sessions of instruction/training for nursing staff and healthcare providers were developed. By modifying risk behaviors, these interventions certainly helped to control the outbreak: they were introduced on 1 January 2017 and both Joinpoint models show a statistically significant decrease in CDI since February. Such reduction remained constant until the last trimester of 2017. Both Joinpoint regression models suggest that the strategies implemented achieved good results, as shown by the trend of the last segment in the regressions: the regressions showed steady maintenance of the rates in the last segment with lower levels than the first segment for more than a year. The success of these measures has also led the company management to draft a new protocol to be adopted in all hospital facilities of the Local Health Unit 1 of Abruzzo. It is necessary to monitor the progress of these good practices and to implement new preventive techniques [18].

Moreover, our study indicates that reports based on routine laboratory data can accurately measure the population burden of CDI with limited surveillance resources. This activity can help target prevention programs and evaluate their effectiveness. Healthcare professionals assisting patients with CDI face the risk of infection in their facilities. In addition, we will use surveillance data to evaluate antibiotic stewardship and CDI prevention.

Conclusions

In conclusion, epidemiological surveillance for infection control is a very useful tool to identify sudden outbreak. However, in order to combat the spread of CDI, a continuous joint effort by all health professionals, caregivers and patients is needed. Our study shows not only the importance of a good surveillance system, but also the importance of keeping high attention on preventive measures of this type of infection.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MM and CV contributed to the design, to the statistical data analysis and to the writing of the manuscript. GA and LM contribuited to data collection. LAR and MG carried out the preparation and implementation of preventive protocol. Necozione S planned and supervised the work, interpreting the results and working on the manuscript.

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Research paper

Breast cancer screening during the Syrian crisis: A cross-sectional study

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Keywords

Breast cancer, Syria, breast cancer screening, breast self-examination, healthcare inaccessibility

Summary

Introduction. *Although breast cancer has a lower incidence in developing countries, mortality rates are higher, mainly due to delay in diagnosis and the poor diagnostic and therapeutic capacities. Although screening tests have been available for quite a long time, delayed and advanced presentation is still common, especially in developing countries. The decade-long Syrian crisis has severely crippled the healthcare system and depleted the already-limited capacities of the healthcare services, which under prioritized the care provided to unurgent cases like breast cancer. This study aimed to investigate the practices of breast cancer screening among breast cancer patients.*

Methods. *A cross-sectional study conducted in Al-Beiruni Hospital at Damascus University in 2019, through personal interviews using a structured questionnaire.*

Results. *The sample consisted of 519 patients with breast cancer. One-hundred twenty (23.2%) of them reported undergoing one or more of the different screening methods at least once every six months prior to diagnosis. Several factors had a statistically significant association with the probability of undergoing or performing screening methods including living in large cities, having fewer children, having a full-time or part-time job, and the level of education. Patients who reported having a relative diagnosed previously with breast cancer or any other malignancies were also more likely to screen themselves. Inaccessibility to healthcare services, which was exaggerated by the armed conflicts, had a significant association with less practicing of the screening methods too (OR: 0.4 [0.3-0.7]).*

Conclusion. *The Syrian war and its direct and indirect consequences negatively affected screening practices of breast cancer.*

Introduction

Breast cancer (BC) is the leading cause of cancer mortality in women and the main cause of cancer-related death in developing countries [1, 2]. BC incidence is slightly lower in developing countries compared with the western world, which can be attributed in part to the lower prevalence of known risk factors [2], more common protective factors (i.e. breastfeeding) [3, 4], as well as the inability to afford the costly screening programs [5]. Many factors are responsible for the bad course of BC in developing countries such as late presentation, lack of homogenous screening density around the country and the difference in quality of medical services between rural and urban areas [6-8].

Although breast cancer screening (BCS) methods have apparently increased the incidence of BC in developed countries, they helped to reduce mortality and improve the quality of life [9-11]. Nevertheless, many BC patients still present with an advanced disease rather than through screening programs worldwide [12, 13], and more frequently in developing countries [14]. In addition, controversy continues due to the lack of evidence supporting the extension of the valid screening recommendations from the rich countries to poorer ones [5]. Therefore, early detection has been an active area of research in developed countries and an area of urgent need for investigation in low-income countries like Syria [8].

The decade-long Syrian crisis has severely crippled the healthcare system and depleted the already-limited capacities of the healthcare services. Over half of the healthcare facilities became out of service before 2016 [15], and the situation became even worse over time due to tools evacuation and programmed destruction. Therefore, the war caused prioritization of the most urgent cases like war-related injuries and decreased the investment in improving the management and screening programs of unurgent cases like malignancies and chronic diseases [15,16]. However, cancer centers in the main cities continued to offer services despite drugs shortage and the reducing number of oncologists and healthcare personnel. A recent survey-based study on doctors, unveiled the disrupted oncology care especially

* These authors contributed equally to the work and share first authorship.

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in conflict zones, and suggested an important role for the awareness of patients and their screening practices to mitigate the lack of healthcare accessibility [16]. The aim of this study is to investigate the practices of BCS among Syrian patients and to discover their association with different demographic factors.

Methods

Patients

This cross-sectional study was conducted in Al-Beiruni Hospital, the leading Syrian cancer center affiliated with Damascus University. Data collection took place in the period between August and December 2019, and only patients with a diagnosis of BC were recruited. Patients with neurological or psychiatric illnesses that hinder the data collecting process were excluded. Patients were approached in the waiting area of the BC clinic or department and were interviewed by one of four senior medical students at Damascus University. Data collectors were all trained on the tool of measurement and frequent meetings were held to discuss difficulties confronted during data collection. Interviews lasted for 10-20 minutes and a paper survey was filled out during the interview by the interviewer.

Questionnaire

The questionnaire consisted of three sections. The first asked about demographic information including: age, address, occupation, educational qualification, and healthcare services accessibility. The second inquired about BCS methods such as breast self-examination (BSE), clinical breast examination (CBE), and mammography as well as the frequency of applying these methods. In this section, patients were also asked about the source of information about BCS. The third section included questions about patients' medical and family history such as personal history of BC or benign breast diseases, and family history of malignancies. The questionnaire was in Arabic, which is the mother language for all participants. The final version of the questionnaire was first piloted by different data collaborators on 25 patients from different social, educational, and financial backgrounds to confirm that they can tolerate the time required and answer the questions free of interrater variability and without concern regarding consistency and structure.

Informed Consent and Ethical Approval

Data collaborators explained to the patients about the study and its measures and aims before the interviews, and participation in the interviews was voluntary. Assurance of the confidentiality of the data was also conveyed to the patients and a verbal informed consent was taken from them for the aim of publishing the anonymous data. The interviews were done in a private room near the waiting area of the BC clinic. This study was approved by the local ethical committee of the hospital and the Syrian Association of Medical Oncology.

Data analysis

Data collaborators entered survey data from the paper questionnaires into an electronic Google form. Data were later imported into Microsoft Excel 365 version 2011 (Build 13426.20404; year 2020) and analyzed using the Statistical Package for the Social Sciences version 23.0 (SPSS Inc., Chicago, IL, United States). Medians and interquartile ranges were used to represent continuous data, while counts and percentages were used for categorical data. Chi-square and Fisher's exact tests were used to assess the association between practicing BCS and demographic and history data. An alpha value of 0.05 was used to determine the threshold of statistical significance. Additionally, a binary logistic regression model was created to investigate the independently associated predictors of BCS performance.

Results

Demographic data

We interviewed 519 female BC patients, who were diagnosed between 2011 and 2019, but the median was 2018. Their ages at diagnoses ranged from 25 to 87, however, the ages at the point of data collection were between 27 and 88. Three-hundred-eighty-five (74.2%) patients were married, 411 (79.2%) lived in private apartments with their children, and 222 (42.8%) of them resided in the seven major cities (referred to as urban in this study). About a third (33.5%) of the participants had more than four children, while less than a fifth (17.5%) had no children at all. The most common work type was domestic work (74.4%), and only 105 (20.3%) patients had full- or part-time jobs. Smokers constituted 73 (14.1%) of the sample but negative smoking was the most common (44.5%). Almost a third (35.6%) of the patients did not have enough income to cover their needs, and only 7 (1.3%) could earn enough money for savings (Table I).

BCS practices

Most of the patients in our sample (76.9%) had not performed BCS by the time of the diagnosis. BSE was the most frequent screening method, and it was practiced by 120 patients (23.2%). Whereas imaging and CBE were rarely performed. The most reported source of information was different media outlets including social media (81.7%; Table II).

Factors affecting BCS

Patients who reported possible healthcare accessibility had a higher percentage of screening practice (25.4%) than their counterparts (11%; $P = 0.004$). Similarly, patients from urban areas (28.4%) performed screening more than those who lived in rural areas (19.2%; $P = 0.016$). Although, age groups, body mass index (BMI), marital and financial status did not reach a statistically significant association with BCS, patients with one to three children (29.2%) were more likely to

Tab. I. Demographic Data.

	Count	Percentage		Count	Percentage
Gender			**Education level of the patient**		
Female	519	100	Illiterate	99	19.1
Year of diagnosis	2018*	2017-2019†	Primary education (6-9 years)	239	46
Age at diagnosis	48*	41-55†	Secondary education (12 years)	63	12.1
Age at the time of the study	50*	43-57†	Higher education (university or higher education institutes)	118	22.7
Weight (n = 231)	72*	64-82†	**Work status**		
Height (n = 214)	160.5*	158-165†	Part-time job (< 5 hours/day)	47	9.1
BSA (n = 214)	1.76*	1.67-1.88†	Full-time job	58	11.2
BMI (n = 212)			Housewife	367	70.7
Normal Weight	59	27.8	Unable to work	11	2.1
Obese	77	36.3	Retired	36	6.9
Overweight	71	33.5	**Work type**		
Underweight	5	2.4	Educational	42	8.1
Housing unit			Physical	42	8.1
Shelter (internally displaced)	3	0.6	Office work	49	9.4
Private house (living alone)	13	2.5	Domestic	386	74.4
Private house (with children)	411	79.2	**Smoking**		
Private house (grand family)	60	11.6	Smoker	73	14.1
Shared house	32	6.2	Smoked earlier	31	6.0
Residency			Negative smoker	231	44.5
Urban (living in the seven major Syrian cities§)	222	42.8	Smoking period (n = 104)	11*	5-25†
Rural (living in smaller cities or rural areas)	297	57.2	**Financial status**		
Marital status			Enough for needs and savings	7	1.3
Widow	70	13.5	Enough for basic needs	327	63.0
Single	48	9.2	Not enough for basic needs	185	35.6
Married	385	74.2	**Consanguinity among parent**		
Divorced	16	3.1	Found	174	33.5
Number of children			**Diagnosed psychiatric diseases**		
None	91	17.5	Depression	18	3.5
One	19	3.7	Anxiety	3	0.6
Two	47	9.1	Schizophrenia	2	0.4
Three	95	18.3	Other diseases	2	0.4
Four	93	17.9	**Psychiatric drugs**		
More than four	174	33.5	Chronic drugs	20	3.9

* Median; † Interquartile range; § Damascus, Damascus suburbs, Aleppo, Homs, Latakia, Hama, and Tartus.

Tab. II. Breast cancer screening methods.

	Count	Percentage
Frequency of BSE screening		
Once per week	58	11.2
Once per month	39	7.5
Once every six months	23	4.4
Never	399	76.9
Type of screening		
Self-examination	120	23.2
Clinical Breast examination	4	0.8
Mammogram or Ultrasound	15	2.9
Source of advice about screening (n = 120)		
Medical professionals	10	8.3
Parents, neighbors, or friends	12	10
Social networks and media	98	81.7

undergo screening in comparison to patients who have more (19.5%; P = 0.025). On the other hand, patients who have a full- or part-time job (40%) had a higher percentage of BCS than housewives and retired patients (18.8%; P < 0.001). The level of education of patients (P < 0.001), their spouses (P < 0.001) and fathers (P = 0.001) had statistically significant associations with screening performance as well (Table III).

BCS practices happened more frequently in the group of patients who reported a family history of malignancy (28.9%; P = 0.011), and the same held true for patients with a family history of BC in particular (31.3%; P = 0.002). On the contrary, personal medical histories did not have any significant association with BCS (Table IV).

A binary logistic regression model was created

Tab. III. Breast cancer screening practice and its association with different demographic factors.

	Total	Practicing BCS	Percentage	Odds ratio	CI (95%)	P value
Age at the time of the study						
27-42	126	21	16.7	-	-	0.120*
43-50	142	41	28.9			
51-57	127	31	24.4			
58-88	124	27	21.8			
BMI (n = 212)						
Normal range	59	16	27.1	1.1	0.6-2.1	0.862†
Over- or under-weight	153	39	25.5			
Residency						
Urban	222	63	28.4	1.7	1.1-2.5	0.016†‡
Rural	297	57	19.2			
Healthcare services accessibility						
Difficult	82	9	11	0.4	0.2-0.7	0.004†‡
Possible	437	111	25.4			
Housing unit						
Private with children	411	96	23.4	1.1	0.6-1.8	0.898†
Other accommodation options	108	24	22.2			
Financial status						
Not enough for the basic needs	185	35	18.9	0.7	0.4-1.1	0.103
Enough for the basic needs with/without savings	334	85	25.4			
Marital status						
Married	385	88	22.9	0.9	0.6-1.5	0.813†
Other options	134	32	23.9			
Children (n = 428)						
One to three	161	47	29.2	1.7	1.1-2.7	0.025†‡
More than three	267	52	19.5			
Work						
Full-time or part-time job	105	42	40	2.9	1.8-4.6	< 0.001†‡
Housewife or retired	414	78	18.8			
Education level (patient)						
Illiterate	99	11	11.1			< 0.001*‡
Primary education	239	33	13.8			
Secondary and higher education	181	76	42	4.8§	3.1-7.7§	
Education level (husband)						
Illiterate	116	17	14.7			< 0.001*‡
Primary education	236	43	18.2			
Secondary and higher education	167	60	35.9	2.7§	1.8-4.2§	
Education level (father)						
Illiterate	284	50	17.6			0.001*‡
Primary education	191	52	27.2			
Secondary and higher education	44	18	40.9	2.5§	1.3-4.8§	
Education level (mother)						
Illiterate	378	79	20.9			0.144*
Primary education	131	38	29			
Secondary and higher education	10	3	30	1.4§	0.4-5.6§	
Smoking						
Never smoked / negative smoking	415	88	21.2	0.6	0.4-1.0	0.050*
Smoker (currently or previously)	104	32	30.8			

* Chi square test; † Fisher exact test; ‡ Significant at the level of 0.05; §These odds ratios were calculated against the other two classes of the question (illiterate and primary education) combined.

for the significantly associated variables, namely, residence, work, number of children, smoking habits, healthcare accessibility, financial status, family history of malignancies and education of the patient, her husband and father. This model had a Nagelkerke R square of (20%; $P < 0.001$), a sensitivity of (23.3%), and a specificity of (94.2%). The model revealed that receiving secondary or higher education and having

Tab. IV. Breast cancer screening practice and its association with different personal and familial histories.

	Total	Practicing BCS	Percentage	Odds ratio	CI (95%)	P value*
Personal history of benign breast disease						
Yes	74	21	28.4	1.4	0.8-2.4	0.297
No	445	99	22.2			
Personal history of breast malignancies						
Yes	18	4	22.2	0.9	0.3-2.9	1.000
No	501	116	23.2			
Personal history of other malignancies						
Yes	1	0	0	-	-	1.000
No	518	120	23.2			
Family history of benign breast disease						
Yes	46	12	26.1	1.2	0.6-2.4	0.587
No	473	108	22.8			
Family history of breast malignancies						
Yes	179	56	31.3	2.0	1.3-3.0	0.002†
No	340	64	18.8			
Family history of malignancies						
Yes	211	61	28.9	1.7	1.1-2.6	0.011†
No	308	59	19.2			

* Fisher's exact test; † Significant at the level of 0.05l

Tab. V. A binary logistic regression model of demographic and medical history predictors of BCS performance.

	B	S.E.*	Wald	P value	OR†	CI (95%)
Residing in urban areas	0.26	0.23	1.32	0.251	1.3	0.8-2.0
Having less than four children	0.05	0.24	0.04	0.849	1.0	0.6-1.7
Secondary or higher education (patient)	1.11	0.3	14.23	< 0.001§	3.0	1.7-5.4
Secondary or higher education (husband)	0.19	0.26	0.51	0.475	1.2	0.7-2.0
Secondary or higher education (father)	0.31	0.36	0.71	0.400	1.4	0.7-2.8
Having a full-time or part-time job	0.42	0.28	2.25	0.134	1.5	0.9-2.7
Smoking currently or previously	0.44	0.27	2.63	0.105	1.6	0.9-2.6
Sufficient financial status	0.07	0.26	0.06	0.801	1.1	0.6-1.8
Possible healthcare accessibility	0.59	0.4	2.19	0.139	1.8	0.8-3.9
Family history of malignancies	0.37	0.23	2.52	0.113	1.4	0.9-2.3
Family history of breast cancer	0.5	0.23	4.62	0.032§	1.6	1.0-2.6

* Standard error; † (exp(B)); § Significant at the level of 0.05l

a family history of breast cancer had a significant association with BCS practices independently from the other predictors (Table V).

Discussion

To our knowledge, this is the first study to investigate BCS performance by BC patients in Syria. It was found that the rate of screening performance was low, and multiple factors that are thought to be related to the Syrian crisis (i.e., education and healthcare accessibility) had a significant impact on the practice of BCS.

Regarding the demographics of the sample, only seven patients (1.3%) had enough income for savings, and this is in line with the recent report, which showed that more than 83% of the population live below the upper poverty line due to the detrimental effects of the crisis on the Syrian economy [17]. Illiteracy on the other hand was reported by 19.1% of the sample, which is not surprisingly about 10% lower than the illiteracy rate of Syrian adult females in the latest nationwide statistics published in 2004 [18]. Participants of this study also reported a slightly higher percentage of employment than the rate of the whole population [19]. Lastly, the sample was nearly equally distributed between urban and rural areas. Hence, it could be stated that the sample is relatively representative of the Syrian BC patients.

Rates of BCS reported by the interviewed patients were lower than in other developing countries like Ghana, Jordan and Iran [20-22]. Rates of BSE in particular

were lower than what was reported in Iraq, where the comparable healthcare system had also been crippled by war to some extent [20], but higher than reported in Qatar [23], where there is apparently more dependence on CBE and mammography most likely due to affluence and availability of resources. Regarding the source of information about BCS, a Jordanian study reported that 65% of its participants received information regarding BSE from Health-care workers [24]. In contrast, less than a tenth of the patients who perform screening in this study reported getting information about it from physicians. This was probably a result of the deterioration of the healthcare system and the inaccessibility of medical services in some Syrian regions during the crisis. In that regard, a study reported that the scarcity of physicians, hence, the hard access to them, put the media at the top of health-related information resources [22]. In Iran, where health care facilities were more accessible without current conflicts, a systematic review concluded that healthcare professionals were the most reported provider of information regarding BCS followed by media outlets [25].

In terms of healthcare accessibility, the decade-long war in Syria had disastrous ramifications on the healthcare system. The destruction of medical facilities, killings of healthcare providers and the severe shortage of drugs and medical equipment caused a dramatic decline in the quality of medical services [26]. Moreover, almost half the physicians in Syria escaped the country which exaggerated the deficiency of medical services [26, 27]. As a result, only half the hospitals in some areas are properly working. Meanwhile the rest are either partly working, not working or cannot be reached, which led to the negligence and delay of treatment for noncritical cases [28]. Consequently, several besieged areas were left with no accredited oncologist or access to oncology treatment modalities, causing referral of patients to other areas or even towards other countries [16]. Many patients were also exposed to medical errors due to the treatment by an underqualified doctor [16]. The results of the current study were in line with these reports because patients who reported having possible access to healthcare applied BCS twice the rate of those who reported lack of healthcare accessibility. Wu et al. also confirmed these findings when they concluded that the BCS rises with the availability of specialized healthcare providers and medical tools for checkups [29].

On another level, this study found that urban areas have significantly higher rates of BCS, a result shared by other studies [29,30]. Wu et al. attributed this result to disparities in the financial status [29]. Secondly, patients in rural areas in Syria had to face dangerous and unreliable commute to access hardly reachable healthcare facilities [28]. Furthermore, prophylactic screening modalities were only reported in the capital Damascus [16]. In addition to that, the religious and conservative climate that prevails in rural regions could restrain BCS, where some women, especially in Muslim communities, might refuse to be examined by a male doctor to avoid any embarrassment or stigma of being diagnosed with BC, which could lead in some cases to divorce or being estranged by their families [31]. The unavailability of female healthcare workers and the embarrassment of the examination were reported as obstacles to BCS in Egypt by almost 40% of the participants [32]. Saudi women also renounced the idea of being screened by a male doctor and were more inclined to undergo screening if female professionals were available [33]. Lastly, it was found that women living in rural areas were more likely to lack awareness regarding BC [34,35], and that their information on BSE practice was more likely to be inadequate [36] in comparison to those who lived in urban areas. So, since the most powerful factor of BSE performance was possessing awareness about it [37], then the lack of information could justify the low performance of BCS and especially BSE in this study.

This study found that patients' level of education, as well as the one of their spouses and fathers all had significant positive associations with performing BCS. Other studies also emphasized this positive association with the performance of BCS [23], and BSE [20, 35]. However, financial status did not affect the probability of performing BCS in our sample, which might be due to the fact that screening tests are available for free in community hospitals in Syria. This is in contrast with previous research in Saudi Arabia and Qatar that found high income to be a significant predictor of BCS performance despite the availability of free medical services in the country [23, 33]. However, the high income might have coincided with high education in these studies. A study in Egypt reported that high medical expenses were found as a considerable hindrance to seeking screening, in addition to difficulties in commute towards healthcare facilities [32]. Hence, even when medical care is available for free, people in developing countries still face other economic difficulties that need to be considered.

This study is in agreement with the outcomes of other studies which found that employed women have higher rates of BSE practice than their counterparts [20, 38, 39]. A possible explanation could be that most occupations require an educational certificate, hence, most job holders were educated. It might also be attributed to the fact that employment increased participants' chances of getting informed about screening. However, reports also indicate that time shortage is an important obstacle that hinders performing BCS [33] and BSE [40], which means that employment could also play a negative role in screening.

Having a family history of BC specifically and other malignancies generally were found to be significant indicators for performing BCS in this study. This could be caused by the emotional impact of witnessing the agony of a relative, or because this brought awareness and knowledge about the disease into the family. Other studies report the same findings for BSE [20, 39, 41, 42]. However, Abdel-Aziz et al. did not reach statistical significance in the association between a family history of BC and BCS performance. This is

most likely due to the cultural suppression of such topics in Saudi Arabia [33]. A remarkable observation was also found by Mamdouh et al. who found that the presence of breast cancer in the family affected the perspective of participants who stated fewer barriers to BCS [32].

In light of what was discussed in this paper, it was found that the most effective measures in the direction of promoting BCS among women in Syria are to implement multilayered interventions that aim to increase the knowledge and practice of BCS in Syrian women, especially the inexpensive personal methods that do not necessitate improving healthcare facilities [16]. Population-based campaigns should be launched with the aim of raising women's knowledge regarding BC [6], and the method of BSE as an easy and costless way of screening. These campaigns should focus on illiterate and unemployed women especially in the rural areas, who might be the most vulnerable. Secondly, increasing the numbers of female physicians might mitigate the factor of shyness, making it more comfortable for women to raise concerns and accept BCS programs [31, 33]. Interestingly, mammography campaigns could result in over-diagnosis of BC, which in turn will reduce the resources distributed for treatment in a developing country where shortage of resources already exists [5], and will result in imposing unjustified economic and emotional strain on an exhausted population. Therefore, to make a real change in the BC death rates in these countries, it is better to start with promoting a healthier lifestyle and enhancing management modalities [5]. This could be specifically true for a war-torn country like Syria, which is left with a drained healthcare system and a critical need for resources. Lastly, with the impaired healthcare system it might be more efficient to make use of the different media outlets to spread knowledge about BC and BCS. Although the sample of this study included patients who reported lack of access to healthcare services, this might not be representative of the true lack of accessibility nation-wide, because refugees and internally displaced populations in shelters are less likely to present to our center. However, since Al-Beiruni is a community hospital that provides oncology care for free, the sample should be representative of the Syrian BC patients excluding these two categories. On the other hand, this is a retrospective study that might be susceptible to recall bias due to the time gap between the diagnosis and the time of the interview. However, self-reported BCS practices are more likely to be overreported, which might reflect even a lower prevalence of these screening practices.

Conclusion

Screening practices of breast cancer in the Syrian population are less common in comparison to countries with comparable populations and healthcare systems. The lack of healthcare accessibility, residing in rural areas, illiteracy, being unemployed, having more children, bad financial status and not having any family history of malignancies were associated with fewer breast cancer screening practices.

Availability of data and materials

The dataset supporting the conclusions of this article is available and can be shared upon request.

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Conflict of interest statement

Authors have no competing interests to declare.

Authors' contributions

SH and IH planned for the project and obtained the ethical approval. MB, ZB, and YA collected the data. IH did the data analysis. SH, IH, and DAS wrote the manuscript. MS critically revised the article. All authors revised and approved the final version of the article.

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Research paper

A cross-sectional study of the knowledge and screening practices of diabetes among adults in a south western Nigerian city

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Keywords

Diabetes • Knowledge • Screening Practices

Summary

Introduction. *The control of diabetes depends largely on preventive actions often influenced by knowledge and awareness of the condition, its risk factors, complication, and management. This study assessed the awareness, knowledge, and practices regarding diabetes among adults in two communities in Ibadan, Nigeria.*
Methods. *A community-based cross-sectional study was conducted among five hundred randomly selected non-diabetic respondents, aged 18 to 65 years. Data was collected using the pretested, modified version of the WHO STEPS instrument translated into Yoruba language. Data collected were analysed using descriptive and inferential analysis and the level of significance was set at $p < 0.05$.*
Results. *Majority of the respondents (89.6%) had previously heard about diabetes. Of these (n = 448), 31.8% were knowledgeable about diabetes and only 28% have ever had their blood glucose level measured by a doctor or other health professionals. Sex and monthly income were statistically associated with respondents' diabetes knowledge while age, religion, monthly income, employment status, marital status, ethnicity and level of education were statistically associated with screening practices ($p < 0.05$). Monthly income was found to be a significant predictor of the level of knowledge adjusted by sex. Earning N20,000 ($ 52.60) or less had higher odds of being knowledgeable compared to earning no income (OR 0.54, CI 0.35, 0.83).*
Conclusion. *Though Diabetes awareness is high, knowledge gaps and poor screening practices is of concern. This calls for tailored multi-component, community-based, health education interventions.*

Introduction

Diabetes is a fast-rising non-communicable disease of global public health importance. In Africa, it is projected to be the 7th leading cause of death by 2030 [1]. As of 2013, Nigeria had the highest number of diabetes cases at 3.9 million cases with a national prevalence of 4.9%. This prevalence with its attributed death of 1.3 million in 2019 is projected to reach 41 million cases by 2045 [1-3].
The control of diabetes majorly depends on early diagnosis, prevention and self-management often influenced by the awareness and knowledge of the condition, its risk factors and complications [4-10]. Assessing diabetes mellitus knowledge and preventive behaviours in the general public would aid the identification of knowledge gaps and guide the development of tailored and appropriate interventions [11]. However, studies conducted in Nigeria have been limited to healthcare providers and related communities [12-14]. Therefore, this study assessed the diabetes knowledge, screening practices and associated factors among community members.

Methods and Subjects

Description of the study area

This study was a part of a larger community-based, cross-sectional study which explored the knowledge, risk factors and preventive practices on non-communicable diseases in Nigeria. This paper report results from two urban communities in Ibadan North Local Government Area (one of the five [5] Local Government Areas in Ibadan Metropolis) with an estimated size of 27,249 square kilometers of Oyo State, Nigeria. The local government is divided into twelve [12] wards with a population size of 432,900 [15]. The people are mainly of the Yoruba tribe, although other ethnic groups in Nigeria are well represented but constitute the minority. Data for the study were collected between November 14th and December 3rd, 2018.

Sampling procedure

The study with a sample size of 500 included 147 males and 353 females within the ages of 18 and 65 years randomly selected from both communities. The calculated sample size was allocated proportionally to the size of the population in each community after getting the number of households in each community. The first household was chosen by lottery method and systematic sampling technique was used in selecting the subsequent households. One respondent was then selected by ballot method from each randomly selected household who after giving consent to participate was interviewed. In the absence of such, the next household was chosen.

Data collection and management

This study was approved by the University of Ibadan/University College Hospital Ethical Review Committee, Nigeria and the assigned reference number is UI/EC/17/0410. Informed and voluntary consents were given by all the participants. Data were collected through an electronic data capture tool (ODK Collect) using a pretested KAP questionnaire on diabetes and the modified WHO STEPS instrument [16] which was translated into the local language, Yoruba. Nine data collectors and two supervisors collected the data by moving from house to house after a two-day training on research ethics, data collection procedures and tool contents to increase the quality of data obtained. Supportive supervision was daily carried out by the supervisor during the period of data collection.

Data analysis

The data collected was exported into the Statistical Package for Social Science (SPSS) version 21.0; frequency distribution was computed for all items and the variables were computed for further inferential analysis such as Chi-square test and regression. Analysis of the dependent variable, knowledge about diabetes, and the independent variables, demographic characteristics (age, sex, religion, level of education, ethnicity, marital status, employment status, household size, monthly income and years of residence) and previous awareness and practice towards diabetes were reported. The data was explored using descriptive statistics. All individual answers to knowledge about diabetes were computed to obtain total scores and calculated for the mean. We then classified the level of knowledge of respondents into two groups (knowledgeable and not knowledgeable) using the mean score as the cut-off. In calculating the mean score for awareness, all respondents who answered yes to previous awareness about diabetes were considered to be previously aware of diabetes. Then binary logistic regression was done using the Hosmer and Lemeshow test to see the independent effect of predictors on the dependent variable while the amount of variation in the dependent variable was indicated using the Nagelkerke R Square values. Odds ratio and adjusted odds ratio were respectively calculated and all statistical tests were considered statistically significant at $p < 0.05$ and 95% CI.

Result

Socio-demographic characteristics of respondents

Majority of the respondents, 70.6% were females 54.2% were adults and 54.8% lived in households with 2 to 4 members. The overall respondents' median age was 33 years. Majority of the respondents (88.8%) were of Yoruba ethnicity, had lived in the community for at least 10 years (65.8%) and with 8.4% having no formal education. Most of the respondents were self-employed (72.6%) and earned an average monthly income of 20,000 or less (54.8%) (Tab. I).

Table I. Sociodemographic characteristics of respondents (n = 500).

Participants' characteristics	Statistics
Sex	
Male, n (%)	147 (29.4)
Female, n (%)	353 (70.6)
Age group	
Youth, n (%)	119 (23.8)
Adult, n (%)	271 (54.2)
Middle age, n (%)	110 (22.0)
Religion	
Christianity, n (%)	255 (51.0)
Islam, n (%)	245 (49.0)
Years of residence	
10 years or less, n (%)	329 (65.8)
11 to 20 years, n (%)	75 (15.0)
21 to 30 years, n (%)	60 (12.0)
More than 30 years, n (%)	36 (7.2)
Monthly income	
No income, n (%)	34 (6.8)
20,000 or less, n (%)	336 (67.2)
More than 20,000, n (%)	130 (26)
Household size	
1 member, n (%)	41 (8.2)
2 to 4 members, n (%)	274 (54.8)
5 and more members, n (%)	185 (37.0)
Employment status	
Employed, n (%)	64 (12.8)
Self-employed, n (%)	363 (72.6)
Non-paid employment, n (%)	5 (1.0)
Unemployed, n (%)	61 (12.2)
Retired, n (%)	7 (1.4)
Marital status	
Never married, n (%)	136 (27.2)
Currently married, n (%)	320 (64.0)
Separated, n (%)	4 (0.8)
Divorced, n (%)	3 (0.6)
Widowed, n (%)	31 (6.2)
Cohabitating, n (%)	6 (1.2)
Ethnic group	
Yoruba, n (%)	444 (88.8)
Igbo, n (%)	26 (5.2)
Hausa, n (%)	4 (0.8)
Other tribes, n (%)	26 (5.2)
Level of education	
No formal schooling, n (%)	42 (8.4)
Primary school not completed, n (%)	7 (1.4)
Primary school completed, n (%)	78 (15.6)
Secondary school not completed, n (%)	37 (7.4)
Secondary school completed, n (%)	226 (45.2)
College/University completed, n (%)	105 (21.0)
Postgraduate degree, n (%)	5 (1.0)

Table II. Level of knowledge of participant about diabetes (n = 448).

	Frequency	%	Maximum score	(SE)	±SD
Not Knowledgeable	289	57.8	36.0	13.7(0.35)	7.3
Knowledgeable	159	31.8			

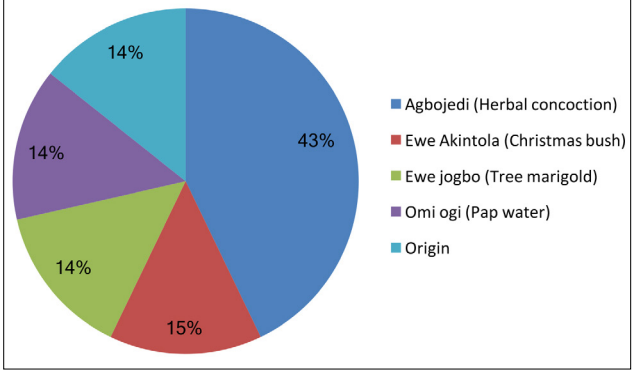
Table III. Frequency distribution of participants' responses to knowledge **on diabetes** (n = 448).

Variables	Response (%)	
	Yes	No
Risk factors for diabetes		
Family history of diabetes	37.9	62.1
Age over 40 years	35.0	65.0
Lack of exercise	33.3	66.7
Tobacco use	41.1	58.9
Alcohol use	61.6	38.4
Eating too much sugar	87.7	12.3
Old age	37.3	62.7
Overeating	30.6	69.4
Stress	29.7	70.3
Eating too much fat	28.1	71.9
Overweight	32.1	67.9
Early symptoms of diabetes		
Passing lots of urine	76.1	23.9
Excess thirst	46.0	54.0
Tiredness/Lethargy	51.3	48.7
Loss of appetite	33.3	66.7
Weight loss	51.1	48.9
Vision problems	31.7	68.3
Skin and genital infections	24.1	75.9
Methods of Prevention		
No action	9.4	90.6
Weight control	42.2	57.8
Exercise	49.3	50.7
Eat lots of fruits and vegetables	73.0	27.0
Limit sugar	87.3	12.7
Limit fatty foods	42.4	57.6
Health checks/screening	81.0	19.0
Avoid stress	40.2	59.8

Awareness and knowledge of respondents about diabetes

Majority of the respondents (89.6%; n = 500) had previously heard about diabetes, however, overall, 57% were not knowledgeable about the disease causation symptoms, and prevention (n = 448) (Tab. II);76.1% and 46.0% of the respondents knew that frequent urination and excessive thirst are early symptoms of the disease (Tab. III) while 87.7% of the respondents agreed that excessive sugar consumption is a risk factor for developing diabetes and 87.3% agreed that limiting sugar intake is a measure to reduce the likelihood of developing diabetes (Tab. III). However, majority disagreed to family history (62.1%), lack of exercise (66.7%) and overweight (67.9%) as risk factors for diabetes (Tab. III). Although , the aggregated mean score for knowledge on diabetes was 13 ± 7.3 (Tab. II) all the respondents indicated a willingness to have more information about the problems associated with diabetes.

Fig. 1. Herbal drugs used for diabetes, n = 18.



Screening practices for diabetes among respondents

Only 31% (139) of the respondents (n=448) had ever had their blood glucose level measured by a doctor or other health professionals. Of this proportion, 13% reported being diagnosed with diabetes. All 13% also reportedly use medications as prescribed by the health professional with herbal drugs (Fig. 1).

Factors associated with diabetes awareness, knowledge and screening practices

Age group, religion and years of residence in the community, monthly income, employment status, and level of education are statistically associated with the level of awareness ($p < 0.05$) (Tab. IV). Adults age group (93.4%) was the most aware group while the middle age (15.5%) was the most unaware group. Respondents with unpaid employment (60.0%), and no formal schooling (33.3%) were mostly unaware compared with those with post-graduate degrees (100%) (Tab. IV).

Only monthly income was statistically associated with respondents' level of knowledge about diabetes ($p < 0.05$). Respondents' earning more than 20,000 NGN monthly (48.8%) were more knowledgeable than the other groups while the least knowledgeable (8.3%) were those without a source of income (Tab. V). Respondents who had lived in the community for more than 10 years (11-30 years) were more un-aware compared to those who had lived 10 years or less (92.4%).

Similarly, age group, religion and marital status, monthly income, employment status, and level of education are statistically associated with screening practices ($p < 0.05$) (Tab. VI). Most of the respondents had never been screened for diabetes. Of these, 84.0% are youths, 71.6% are adults while 60.0% are middle age. Respondents with no source of income (91.2%)

Table IV. Chi-square test for association between respondents' socio-demographic characteristics and awareness about diabetes (n = 500).

Participants' characteristics	Aware	Un-aware	Chi²-test
Sex			
Male, n (%)	136 (92.5)	11 (7.5)	0.17
Female, n (%)	312 (88.4)	41 (11.6)	
Age group			
Youth, n (%)	102 (85.7)	17 (14.3)	0.01
Adult, n (%)	253 (93.4)	18 (6.6)	
Middle age, n (%)	93 (84.5)	17 (15.5)	
Religion			
Christianity, n (%)	237 (92.9)	18 (7.1)	0.01
Islam, n (%)	211 (86.1)	34 (13.9)	
Years of residence			
10 years or less, n (%)	304 (92.4)	25 (7.6)	0.03
11 to 20 years, n (%)	62 (82.7)	13 (17.3)	
21 to 30 years, n (%)	50 (83.3)	10 (16.7)	
More than 30 years, n (%)	32 (88.9)	4 (11.1)	
Monthly income			
No income, n (%)	24 (70.6)	10 (29.4)	0.00
20,000 or less, n (%)	297 (88.4)	39 (11.6)	
More than 20,000, n (%)	127 (97.7)	3 (2.3)	
Household size			
1 member, n (%)	37 (90.2)	4 (9.8)	0.87
2 to 4 members, n (%)	247 (90.1)	27 (9.9)	
5 and more members, n (%)	164 (88.6)	21 (11.4)	
Employment status			
Employed, n (%)	60 (93.8)	4 (6.3)	0.00
Self-employed, n (%)	330 (90.9)	33 (9.1)	
Non-paid employment, n (%)	2 (40.0)	3 (60.0)	
Unemployed, n (%)	7 (100.0)	0 (0.0)	
Retired, n (%)			
Marital status			
Never married, n (%)	125 (91.9)	11 (8.1)	0.56
Currently married, n (%)	285 (89.1)	35 (10.9)	
Separated, n (%)	3 (75.0)	1 (25.0)	
Divorced, n (%)	3 (100.0)	0 (0.0)	
Widowed, n (%)	26 (83.9)	5 (16.1)	
Cohabitating, n (%)	6 (100.0)	0 (0.0)	
Ethnic group			
Yoruba, n (%)	398 (89.6)	46 (10.4)	0.05
Igbo, n (%)	25 (96.2)	1 (3.8)	
Hausa, n (%)	2 (50.0)	2 (50.0)	
Other tribes, n (%)	23 (88.5)	3 (11.5)	
Level of education			
No formal schooling, n (%)	28 (66.7)	14 (33.3)	0.00
Primary school not completed, n (%)	6 (85.7)	1 (14.3)	
Primary school completed, n (%)	65 (83.3)	13 (16.7)	
Secondary school not completed, n (%)	31 (83.8)	6 (16.2)	
Secondary school completed, n (%)	209 (92.5)	17 (7.5)	
College/University completed, n (%)	104 (99.0)	1 (1.0)	
Postgraduate degree, n (%)	5 (100.0)	0 (0.0)	

non-paid employment (100%) had never been screened for diabetes. Only 16.2% of single respondents and 9.5% of those with no formal education (9.5%) had ever been screened (Tab. VI).

Predictors of awareness, knowledge and screening practices of diabetes

The logistic regression performed to ascertain the effect of socio-demographic characteristics on the awareness

Table V. Chi-square test for association between respondents' socio-demographic characteristics and levels of knowledge (n = 448).

Participants' characteristics	Not-Knowledgeable	Knowledgeable	Chi²-test
Sex			
Male, n (%)	76 (55.9)	60 (44.1)	0.012
Female, n (%)	213 (68.3)	99 (31.7)	
Age group			
Youth, n (%)	67 (65.7)	35 (34.3)	0.947
Adult, n (%)	163 (64.4)	90 (35.6)	
Middle age, n (%)	59 (63.4)	34 (36.6)	
Religion			
Christianity, n (%)	149 (62.9)	88 (37.1)	0.44
Islam, n (%)	140 (66.4)	71 (33.6)	
Years of residence			
10 years or less, n (%)	197 (64.8)	107 (35.2)	0.98
11 to 20 years, n (%)	40 (64.5)	22 (35.5)	
21 to 30 years, n (%)	31 (62.0)	19 (38.0)	
More than 30 years, n (%)	21 (65.6)	11 (34.4)	
Monthly income			
No income, n (%)	22 (91.7)	2 (8.3)	0.00
20,000 or less, n (%)	202 (68.0)	95 (32.0)	
More than 20,000, n (%)	65 (51.2)	62 (48.8)	
Household size			
1 member, n (%)	24 (64.9)	13 (35.1)	0.85
2 to 4 members, n (%)	162 (65.6)	85 34.4(	
5 and more members, n (%)	103 (62.8)	61 (37.2)	
Employment status			
Employed, n (%)	36 (60.0)	24 (40.0)	0.63
Self-employed, n (%)	217 (65.8)	113 (34.2)	
Non-paid employment, n (%)	2 (100.0)	0 (0.0)	
Unemployed, n (%)	29 (59.2)	20 (40.8)	
Retired, n (%)	5 (71.4)	2 (28.6)	
Marital status			
Never married, n (%)	76 (60.8)	49 (39.2)	0.36
Currently married, n (%)	185 (64.9)	100 (35.1)	
Separated, n (%)	1 (33.3)	2 (66.7)	
Divorced, n (%)	3 (100.0)	0 (0.0)	
Widowed, n (%)	20 (76.9)	6 (23.1)	
Cohabitating, n (%)	4 (66.7)	2 (33.3)	
Ethnic group			
Yoruba, n (%)	261 (65.6)	137 (34.4)	0.34
Igbo, n (%)	12 (48.0)	13 (52.0)	
Hausa, n (%)	1 (50.0)	1 (50.0)	
Other tribes, n (%)	15 (65.2)	8 (34.8)	
Level of education			
No formal schooling, n (%)	24 (85.7)	4 (14.3)	0.08
Primary school not completed, n (%)	6 (100)	0 (0.0)	
Primary school completed, n (%)	42 (64.6)	23 (35.4)	
Secondary school not completed, n (%)	22 (71.0)	9 (29.0)	
Secondary school completed, n (%)	131 (62.7)	78 (37.3)	
College/University completed, n (%)	61 (58.7)	43 (41.3)	
Postgraduate degree, n (%)	3 (60.0)	2 (40.0)	

level was statistically significant (X^2 16.26, p = 0.04). The model explained 29% (Nagelkerke R^2) of the variance in awareness and correctly classified 90.4% of the cases (Tab. VII). Only monthly income was found to be a significant predictor of the level of awareness adjusted by other covariates. Earning N20,000 or lesser had double odds of awareness compared to earing no income (OR 0.28, CI 0.08, 0.99).

The logistic regression performed to ascertain the effect of socio-demographic characteristics on the level of

Table VI. Chi-square test for association between respondents' socio-demographic **characteristics** and screening practices (n = 500).

Participants' characteristics	Screened	Never screened	Chi²-test
Sex			
Male, n (%)	42 (28.6)	105 (71.4)	0.85
Female, n (%)	98 (27.8)	255 (72.2)	
Age group			
Youth, n (%)	19 (16.0)	100 (84.0)	0.00
Adult, n (%)	77 (28.4)	194 (71.6)	
Middle age, n (%)	44 (40.0)	66 (60.0)	
Religion			
Christianity, n (%)	84 (32.9)	171 (67.1)	0.01
Islam, n (%)	56 (22.9)	189 (77.1)	
Years of residence			
10 years or less, n (%)	94 (28.6)	235 (71.4)	0.92
11 to 20 years, n (%)	19 (25.3)	56 (74.7)	
21 to 30 years, n (%)	16 (26.7)	44 (73.3)	
More than 30 years, n (%)	11 (30.6)	25 (69.4)	
Monthly income			
No income, n (%)	3 (8.8)	31 (91.2)	0.00
20,000 or less, n (%)	88 (26.2)	248 (73.8)	
More than 20,000, n (%)	49 (37.7)	81 (62.3)	
Household size			
1 member, n (%)	10 (24.4)	31 (75.6)	0.12
2 to 4 members, n (%)	87 (31.8)	187 (68.2)	
5 and more members, n (%)	43 (23.2)	142 (76.8)	
Employment status			
Employed, n (%)	23 (35.9)	41 (64.1)	0.00
Self-employed, n (%)	106 (29.2)	257 (70.8)	
Non-paid employment, n (%)	0 (0.0)	5 (100.0)	
Unemployed, n (%)	7 (11.5)	54 (88.5)	
Retired, n (%)	4 (57.1)	3 (42.9)	
Marital status			
Never married, n (%)	22 (16.2)	114 (83.8)	0.00
Currently married, n (%)	102 (31.9)	218 (68.1)	
Separated, n (%)	0 (0.0)	4 (100.0)	
Divorced, n (%)	0 (0.0)	3 (100.0)	
Widowed, n (%)	12 (38.7)	19 (61.3)	
Cohabitating, n (%)	4 (66.7)	2 (33.3)	
Ethnic group			
Yoruba, n (%)	120 (27.0)	324 (73.0)	0.05
Igbo, n (%)	7 (26.9)	19 (73.1)	
Hausa, n (%)	0 (0.0)	4 (100.0)	
Other tribes, n (%)	13 (50.0)	13 (50.0)	
Level of education			
No formal schooling, n (%)	4 (9.5)	38 (90.5)	0.02
Primary school not completed, n (%)	2 (28.6)	5 (71.4)	
Primary school completed, n (%)	25 (32.1)	53 (67.9)	
Secondary school not completed, n (%)	9 (24.3)	28 (75.7)	
Secondary school completed, n (%)	58 (25.7)	168 (74.3)	
College/University completed, n (%)	39 (37.1)	66 (62.9)	
Postgraduate degree, n (%)	3 (60.0)	2 (40.0)	

knowledge was not statistically significant (X^2 0.91, $p > 0.05$). The model explained 7% (Nagelkerke R^2) of the variance in the level of knowledge and correctly classified 64.5% of the cases. However, monthly income was found to be a significant predictor of the level of knowledge adjusted by another covariate (sex). Earning 20000 NGN or less had higher odds of knowledge compared to earning no income (OR 0.54, CI 0.35, 0.83) (Tab. VIII).

However, the logistic regression performed to ascertain

Table VII. Logistic regression **analysis** for the **predictors of** level of awareness **of diabetes** (n = 500).

Independent variable	Regression coefficient	Sig.	EXP (B)	95% Confidence Interval EXP(B)	
				Lower	Upper
Age group (Ref Middle age)					
Youth	-0.54	0.31	0.58	0.21	1.64
Adult	0.30	0.49	1.35	0.58	3.16
Religion (Ref. Islam)					
Christianity	0.40	0.26	1.50	0.74	3.02
Years of residence (Ref. more than 30 years)					
10 years or less	0.30	0.65	1.35	0.37	5.02
11 to 20 years	-0.57	0.42	0.57	0.14	2.24
21 to 30 years	-0.46	0.51	0.63	0.16	2.51
Monthly income (Ref. More than 20,000)					
No income	-1.98	0.01	0.14	0.03	0.67
20,000 or less	-1.27	0.05	0.28	0.08	0.99
Employment status (Ref. Retired)					
Employed	-20.51	0.99	0.00	0.00	0.00
Self-employed	-19.61	0.99	0.00	0.00	0.00
Non-paid employment	-22.57	0.99	0.00	0.00	0.00
Unemployed	-20.03	0.99	0.00	0.00	0.00
Ethnic Group (Ref Other tribes)					
Yoruba	0.45	0.54	1.58	0.37	6.68
Igbo	1.19	0.38	3.29	0.23	47.38
Hausa	-0.35	0.80	0.71	0.05	9.94
Level of Education (Ref Postgraduate degree)					
No formal schooling	-19.16	0.99	0.00	0.00	0.00
Primary school not completed	-17.89	0.99	0.00	0.00	0.00
Primary school completed	-18.53	0.99	0.00	0.00	0.00
Secondary school not completed	-18.41	0.99	0.00	0.00	0.00
Secondary school completed	-17.25	0.99	0.00	0.00	0.00
College/University completed	-15.55	0.99	0.00	0.00	0.00
Constant	40.34	0.99	3.36E+17		
Hosmer and Lemeshow test = Chi-square 16.26, sig 0.04					
-2 Log Likelihood = 256.729					
Nagelkerke R^2 = 0.29					

the effect of socio-demographic characteristics on the screening practice was not statistically significant (X^2 3.78, $p > 0.05$).

The model explained 21% (Nagelkerke R^2) of the variance in screening practice and correctly classified 75.2% of the cases (Tab. IX).

Discussion

In this study, we assessed the level of awareness, knowledge and screening practices towards diabetes in selected communities in Ibadan, Nigeria. The main findings of this research indicate an 89.6% awareness level about diabetes but a 28% positive practice towards diabetes screening and a 31.8% (13.7 ± 7.3) level of knowledge on diabetes in the communities. We also found only income was significantly associated with respondent's level of knowledge about diabetes while sex, household size and marital status were the only socio-demographic features not statistically associated with the level of awareness ($p > 0.05$).

These findings are consistent with studies from low- and middle-income countries such as Pakistan and Zimbabwe which found poor knowledge, attitude and practices regarding diabetes in a community population and among patients attending an outpatient diabetic clinic [7,8]. However, studies within Nigeria show a high level of awareness about diabetes [17,18]. These studies revealed good knowledge of the diseases compared to other NCDs assessed in their study and among diabetic patients receiving treatments, but we assessed the knowledge of a larger population with no discrimination to whether or not they have the disease.

Although this study revealed a high level of awareness about diabetes in the studied population, poor level of knowledge and poor screening practices were of concern. These findings were similar to those reported in other studies with relatively poor knowledge and attitude towards diabetes among a relatively similar population of Nigerian youths [19-21]. Though knowledge is known to contribute significantly to early prevention and detection of diseases, given the consistency of the poor level of knowledge and screening reported in this study

Table VIII. Logistic regression estimate for the level of knowledge (n = 448).

Independent variable	Regression coefficient	Sig.	EXP (B)	95% Confidence Interval EXP(B)	
				Lower	Upper
Sex (Ref. Female)					
Male	0.32	0.16	1.38	0.89	2.13
Monthly income (Ref. More than 20,000)					
No income	-2.23	0.00	0.11	0.02	0.48
20,000 or less	-0.62	0.01	0.54	0.35	0.83
Constant	-0.21	0.32	0.81		
Hosmer and Lemeshow test = Chi-square 0.91, sig 0.82					
-2 Log Likelihood = 559.974					
Nagelkerke R^2 =0.07					

Table IX. Logistic regression estimate for screening practices (n = 500).

Independent variable	Regression coefficient	Sig.	EXP (B)	95% Confidence Interval EXP(B)	
				Lower	Upper
Age group (Ref Middle age)					
Youth	-1.07	0.02	0.34	0.15	0.82
Adult	-0.71	0.02	0.49	0.28	0.89
Religion (Ref. Islam)					
Christianity	0.14	0.55	1.15	0.72	1.85
Monthly income (Ref. More than 20,000)					
No income	-1.28	0.07	0.28	0.07	1.12
N20,000 or less	-0.29	0.25	0.75	0.46	1.23
Employment status (Ref. Retired)					
Employed	-0.46	0.63	0.63	0.10	4.12
Self-employed	-0.61	0.51	0.54	0.09	3.29
Non-paid employment	-19.95	0.99	0.00	0.00	0.00
Unemployed	-0.83	0.42	0.44	0.06	3.19
Marital status (Ref. Cohabitating)					
Never married	-3.03	0.00	0.05	0.01	0.35
Currently married	-2.31	0.02	0.10	0.01	0.70
Separated	-22.62	0.99	0.00	0.00	0.00
Divorced	-22.84	0.99	0.00	0.00	0.00
Widowed	-1.43	0.21	0.24	0.03	2.20
Ethnic Group (Ref Other tribes)					
Yoruba	-1.08	0.03	0.34	0.13	0.89
Igbo	-1.21	0.08	0.30	0.08	1.13
Hausa	-19.47	0.99	0.00	0.00	0.00
Level of Education (Ref Postgraduate degree)					
No formal schooling	-3.04	0.01	0.05	0.01	0.48
Primary school not completed	-1.16	0.40	0.31	0.02	4.58
Primary school completed	-1.15	0.26	0.32	0.04	2.36
Secondary school not completed	-1.61	0.14	0.20	0.02	1.69
Secondary school completed	-0.95	0.35	0.39	0.05	2.77
College/University completed	-0.49	0.62	0.61	0.09	4.20
Constant	4.93	0.00	137.69		
Hosmer and Lemeshow test = Chi-square 3.78, sig 0.88					
-2 Log Likelihood = 513.459					
Nagelkerke R^2 = 0.21					

and previous studies, it is crucial that a multi-sectorial or multifaceted intervention which will address these features for effective change result be implemented. Multifaceted interventions have been proven to improve behaviour change while enhancing knowledge, skills, health-seeking behaviour and personal empowerment for non-communicable diseases such as hypertension [22,23]. This study did not consider community centered policies

and strategies that may aid the screening practices of diabetes. We, however, argue that though there are operational policies, strategies and action plans for diabetes in Nigeria and other low-and middle-income countries, there is a need to be more intentional in the intervention approach. People are aware of diabetes but have poor knowledge about the condition and this in turn affects their practices about it. However notably, majority of the respondents in this study are willing to have more information about problems associated with diabetes.

Conclusion

Though Diabetes awareness is high, knowledge gaps and poor screening practices is of concern. This calls for tailored multi-component, community-based, health education interventions. With respect to the study's findings, including the willingness of the population to have more information about the problems associated with diabetes, we recommend a socio-ecological approach for community health education intervention on the knowledge of diabetes in Nigeria.

Ethical approval

This study was approved by the University of Ibadan/ University College Hospital Ethical Review Committee, Nigeria and the assigned reference number is UI/ EC/17/0410.

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Conflict of interest statement

The authors declare that they have no competing interests.

Authors' contributions

AAO, MMO, MO and YJ were involved in the conceptualized of the research idea, planning, data collection and analysis led by OO. AAO wrote the first draft; MMO, MO, YJ and OO performed extensive edits and all authors approved the final version of the manuscript.

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Research paper

Awareness, knowledge and training gaps regarding asbestos among General Practitioners: a pilot study

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Keywords

Asbestos exposure • Central Italy • Continuing medicine education • General practitioners • Occupational diseases

Summary

General Practitioners (GPs) have good knowledge of health status and sociocultural backgrounds of their patients, thus could be decisive in early detection of cases of asbestos-related diseases (ARDs). In this cross-sectional pilot study, we investigated perception and knowledge on asbestos risk amongst a sample of GPs practicing in Molise region, central Italy, who have anonymously completed a 29-items questionnaire specifically developed for this research. Based on GPs' answers, we obtained scores and classified awareness and knowledge into four percentage quartile classes including inadequate (0-24%), poor (25-49%), moderate (50-74%) and high (75-100%), and scarce (0-24%), sufficient (25-49%), good (50-74%) and optimal (75-100%), respectively. Twenty-eight GPs (median age 63 years; 82% male) participated. Perception and knowledge among participants varied from 62 to 84% and from 18 to 42%, respectively, with 65 and 42% showing an adequate level, respectively. Our survey revealed a satisfactory perception and knowledge of general features about this topic, while a poor awareness of detailed aspects, underlining the need of continuing medical education in the field of occupational medicine. The study remarks that criteria for ARDs diagnosis should be better specified, introducing a detailed list to harmonize medical protocols for symptoms identification and patients' examination. Hence, increasing awareness of asbestos risk and ARDs among GPs represents a crucial opportunity, because of their prominent position to promptly take care of patients and provide targeted information.

Introduction

Asbestos-related diseases (ARDs) represent a public health challenge, due to their silent clinical evolution and associated medical and social costs [1]. Multiple studies have reported the risk of developing cancers due to occupational and non-occupational asbestos exposure [2, 3]. The International Agency for Research on Cancer stated that asbestos fibres are carcinogenic for humans [4], with sufficient evidence for cancer of the larynx, lung, malignant mesothelioma and ovary, and limited evidence for cancer of the stomach, colon rectum and pharynx. Malignant pleural mesothelioma represents the foremost pathology characterized by a long latency before onset [5].

In Italy, physicians with occupational expertise realize the surveillance activities in the workplaces, although General Practitioners (GPs) must report any diagnosed or suspected case. Because GPs have good knowledge of health status and familiar/sociocultural backgrounds of their patients, could be decisive in detecting early cases [6].

Therefore, increasing their awareness of asbestos risk and ARDs represent a crucial opportunity, because of the prominent position to inform and promptly take care of patients. In a previous survey [7], we found that only 70 and 50% of GPs had knowledge of patients' occupational history and environmental exposure, respectively, suggesting the need to study level of awareness and experiences in ARDs diagnosis and management.

In this pilot study, we examined asbestos risk perception, knowledge and experiences in diagnosing ARDs among a sample of GPs practicing in Molise region, central Italy.

Methods

This pilot survey addressed a sample of GPs in Molise region, central Italy. In our study, a formal institutional review board was not required, since no experimental/clinical/diagnostic procedures were applied to GPs after being informed on the survey aims. A trained person went to clinics of GPs, obtained a signed consent and collected the questionnaires that were anonymously self-completed.

We developed a 29-items questionnaire for addressing the study aims, which consisted of three parts. The first section comprised 7 questions about GPs' sociodemographic characteristics, education and practiced patients. The second section included 12 questions, 4 single-choice and eight as 10-items Likert-scale to evaluate degree of an opinion from "Strongly disagree" to "Strongly agree" (questions Q1-Q6 and Q8; Tab. I). The third section comprised 10 questions exploring knowledge on epidemiological/clinical aspects, and responsibilities in diagnosis of asbestosis (Q9-Q18; Tab. II). We customised some questions from previous studies, including those on asbestos risk for human health [8], certificates for occupational

diseases in the past years [9], and patients' occupational activities [10].

A validation step was carried out by administering the questionnaire to a restricted number of GPs, to obtain critical comments, evaluate comprehension of the content, verify the correct reading of the questions, and highlight the degree of reliability.

We carried out data analysis using Statistical Package for the Social Sciences (SPSS®) Ver.25. Results were reported as absolute and relative frequencies, and calculated mean, median and standard deviation for quantitative variables.

In the section on perception, for Likert-scale question 16 and 160-points as minimum and maximum score, were assigned respectively: results were aggregated to allow classification into quartiles as inadequate (16-39 points), poor, moderate or high (120-160).

In the section on knowledge, questions included 22 correct and 34 wrong options, assigning 1-point for question correctly answered, while 0 and -0.25-points for the missing and wrong answers, respectively. To calculate level of knowledge we applied the following formula: [number of correct options + (-0.25*number of wrong options)/22 correct options]*100, which allowed classification into scarce (0-24%), sufficient, good or optimal (75-100%). For the statistical analysis, T-test for independent samples and one-way ANOVA were used to separately assess the association of perception/knowledge score with each question. Furthermore, the association between perception/knowledge score and GPs demographic and education characteristics was also evaluated using Chi-square or Fisher's Exact test. Statistical significance for each test was established at $p < 0.05$.

Results

For this pilot study, we initially identified thirty GPs, who were asked to complete the questionnaire; however, two questionnaires were discarded because were not fully completed (response rate 93.3%). Therefore, the final analysis was carried out on 28 GPs (median age 63 years; 82% males). Sixty-one percent of GPs had working experience ≥ 30 years, 65% had a medical specialization, and 75% practiced more than 1,000 patients. Fifty percent of GPs reported to be familiar to patients' work activities, 57% issued a certificate for occupational diseases in the last 5 years, and 10% visited patients affected by ARDs in the previous 12 months. Only 64% known that protection measures against asbestos were available, and the use of protective devices and wearing specific clothing were identified by 36 and 11%, respectively.

We found that 46% of GPs recognized the role of the secondary or familial exposure due to living with exposed workers as a risk factor for mesothelioma development (Tab. I). Only 69% reported that issuing of certificates for occupational diseases was included among their responsibilities, and poor knowledge of governmental procedures and lack of time was identified as the greatest and the least limiting factor for the reporting. Other

Tab. I. Awareness on asbestos risk and ARDs.

Item	Yes N (%)	No N (%)	Association with perception score
Q1 Is asbestos exposure harmful for human health?	28 (100)	0 (0)	0.30
Q2 Does asbestos exposure in living and workplace environments increase risk of mesothelioma development?	28 (100)	0 (0)	0.20
Q3 Which among the following GPs competences are related to occupational diseases?			
(a) Diagnosis	21 (75.0)	7 (25.0)	0.10
(b) Reporting	22 (78.6)	6 (21.4)	0.40
(c) Issuing medical certificates	19 (67.8)	9 (32.2)	0.20
Q4 Which types of exposure can induce mesothelioma development?			
(a) Occupational exposure	28 (100)	0 (0)	0.20
(b) Living with an asbestos exposed worker	13 (46.4)	15 (53.6)	0.60
(c) Environmental exposure	23 (82.1)	5 (17.9)	0.10
Q5 Which are the limiting factors for occupational diseases reporting?			
(a) Lack of knowledge of governmental procedures	23 (82.1)	5 (17.9)	0.08
(b) Lack of knowledge of diagnostic criteria	14 (50.0)	14 (50.0)	0.30
(c) Lack of time	6 (21.4)	22 (78.6)	**0.008***
(d) Inadequate professional update	15 (53.6)	13 (46.4)	0.04*
(e) Complexity of the list of occupational diseases for which reporting is mandatory	20 (71.4)	8 (28.6)	0.60
Q6 Is the professional updating in occupational diseases adequate to address patients' questions on ARDs?	11 (39.3)	17 (60.7)	0.40
Q7 Is the quality of regional Continuing Medical Education on this topic appropriate?	4 (14.3)	24 (85.7)	0.10

* significant association at $p<0.05$ using T-test for independent samples and one-way ANOVA.

Tab. II. Knowledge on asbestos risk and ARDs.

Item	Yes N (%)	No N (%)	Association with knowledge score
Q9 Does fibers presence in the sputum only indicate a previous asbestos exposure?	19 (67.8)	9 (32.2)	0.80
Q10 Does exertion's dyspnoea followed by rest dyspnoea the represent main symptom of asbestosis?	13 (46.4)	15 (53.6)	0.05
Q11 Should asbestosis be reported to the judicial authority in addition to Italian Workers' Compensation Authority?	13 (46.4)	15 (53.6)	0.05
Q12 Is the latency period of mesothelioma typically longer than 25 years?	11 (39.3)	17 (60.7)	**< 0.01***
Q13 Does the computed tomography the represent medical examination for diagnosis and staging of pleural mesothelioma?	23 (82.1)	5 (17.9)	0.09
Q14 Are asbestos and tobacco smoking synergic risk factors for the development of pleural mesothelioma?	20 (71.4)	8 (28.6)	0.38
Q15 Is asbestos exposure permitted only in case of disposal of areas and/or artefacts containing asbestos?	25 (89.3)	3 (10.7)	**< 0.01***
Q16 Which diseases are associated with asbestos exposure?			
(a) Pulmonary asbestosis	26 (92.8)	2 (7.2)	**0.01***
(b) Pleural plaques and/or thickness	18 (64.3)	10 (35.7)	0.18
(c) Pleural mesothelioma	27 (96.4)	1 (3.6)	0.7
(d) Pericardial mesothelioma	12 (42.9)	16 (57.1)	**< 0.01***
(e) Peritoneal mesothelioma	12 (42.9)	16 (57.1)	**0.03***
(f) Mesothelioma of tunica vaginalis testis	9 (32.1)	19 (67.9)	**0.03***
(g) Lung cancer	20 (71.4)	8 (28.6)	**0.04***
(h) Larynx cancer	8 (28.6)	20 (71.4)	**0.02***
(i) Ovarian cancer	2 (7.2)	26 (92.8)	0.05
(j) Meningioma	0 (0)	28 (100)	nc
(k) Hodgkin lymphoma	5 (17.9)	23 (82.1)	0.29
(l) Non-Hodgkin lymphoma	3 (10.7)	25 (89.3)	0.17
Q17 Which are the radiological signs of asbestosis?			
(a) Pleural plaques	17 (62.9)	10 (37.1)	**< 0.01***
(b) Thin basal reticular aspects	11 (40.7)	16 (59.2)	0.10
(c) Diffuse reticular-nodular pulmonary framework	19 (70.4)	8 (29.6)	0.40
(d) Air bronchogram	2 (7.4)	25 (92.6)	nc
Q18 From which anatomical structures does the malignant mesothelioma originate?			
(a) Pleura	28 (100)	0 (0)	nc
(b) Pericardium	27 (96.4)	1 (3.6)	0.06
(c) Peritoneum	27 (96.4)	1 (3.6)	0.06
(d) Tunica vaginalis	22 (78.6)	6 (21.4)	0.14
(e) Lymph nodes	14 (50.0)	14 (50.0)	**0.01***
(f) Meninges	9 (32.1)	19 (67.9)	**< 0.01***
(g) Myocardium	13 (46.4)	15 (53.6)	0.05

nc = non-computable; wrong options are underlined; * significant association for $p < 0.05$.

limiting factors were also recognized, including the complexity of the list occupational diseases and the lack of sufficient background on diagnostic criteria (Tab. I). Thirty-nine percent of GPs considered their knowledge on asbestos adequate for addressing patients' questions, and only 14% evaluated the quality of regional continuing medical education (CME) on this topic to be appropriate (Tab. I). We found an overall level of perception ranging from 62% to 84% (median: 71%), high and level of perception (score 120-160) was found only for 35%. A significant association was observed between perception and lack of time and inadequate professional updating for reporting ARDs (Tab. I).

The question on the latency period of mesothelioma showed the lowest knowledge score, followed by the question on radiological signs of asbestosis (Tab. II). ARDs other than pleural mesothelioma were under-reported. We observed an overall knowledge ranging from 18% to 42% (median 53%), and majority (42%) gained an adequate score level (50-74% score), while only 17% achieved an optimal (75-100%) level. A significant association between knowledge score and the latency period of mesothelioma, radiological signs of asbestosis, types of ARDs and of anatomical structures affected by mesothelioma comma was observed (Tab. II). Furthermore, evaluation of the association between awareness/knowledge score on asbestos risk and age, gender, year of graduation, and achievement of

a medical specialization did not provide any significant result among the study sample (Chi-square/Fisher's Exact test, $p > 0.05$).

Discussion

Asbestos exposure is still an ongoing risk, causing 1,200-1,500 mesothelioma cases per year in Italy [1]. GPs' role is significant for reporting undetected cases where the surveillance network could be poor, including those who occurring among people have retired or exposed to asbestos during work abroad, and cases in novel occupational settings, in the self or temporary employment.

In this pilot survey, we observed a satisfactory perception of general features about asbestos among recruited GPs in line with a previous study [8], reporting that family physicians were conscious of patients' exposure through knowledge of their workplace's history and experiences of issuing certificates for occupational diseases. However, exposure from living with asbestos exposed workers was not recognized as a mesothelioma determinant, even though fibers inhalation by clothes handling is a significant component in disease aetiology [11, 12].

Lack of knowledge of governmental procedures and complexity of diseases the list were the highest-rated limiting factors for their reporting, according to previous evidences [8], likely due to few opportunities to issue medical certificates [13]. GPs believed that they do not have an adequate background for replying to patients' questions on asbestos, as reported elsewhere [10].

Indeed, we found an incomplete knowledge of specific aspects, because ARDs other than pulmonary asbestosis and pleural mesothelioma were less linked to asbestos exposure. Concerns further emerged for mesothelioma onset, because GPs who selected erroneous symptoms obtained a low knowledge score. Therefore, a proper update and communication with patients can improve knowledge and case management in primary healthcare [14]. In our Region, courses on this topic in the last 10 years were not planned for GPs, suggesting that the need may be under recognised, and knowledge likely referred to self-study or medical academic background, although no statistical association emerged between knowledge/perception and demographic or education characteristics. Hence, training in occupational medicine and proper communication with patients can improve the management of work-related health problems in primary health care to improve long-term science knowledge retention, and CME may represent the most feasible solution to update and refresh acquired knowledge. GPs should also cooperate each other and with occupational medicine specialists [9, 15-7].

Conclusions

This pilot survey has strengths. To our knowledge, studies reporting a questionnaire on this topic are not available, hence, this tool could be used elsewhere. Furthermore, this is the first study carried out amongst GPs practicing in Molise region to investigate in-depth their level of perception and knowledge on asbestos and ARDs, which may represent an issue that does not receive adequate attention together with other work-related diseases in general practice. This was a pilot study aiming to test various aspects of the methods planned for conducting a larger, more rigorous, and confirmatory investigation.

In conclusion, our survey revealed high perception and knowledge of general aspects related to asbestos amongst GPs, while a limited understanding of specific items emerged, supporting the need to update education and strategies to increase their awareness. Indeed, additional importance should be placed on training in occupational medicine and proper communication with patients for better management of work-related health concerns in primary healthcare.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

GR conceptualized and designed the study and participated in the critically editing of manuscript.

AS contributed to the development of the questionnaire, data analysis, and writing.

MLS helped in the questionnaire predisposition and manuscript writing.

MT contributed to the statistical data analysis and interpretation, writing and editing of the manuscript.

All Authors have read and approved the final version of the paper.

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REVIEW

A policy analysis of agenda-setting of Brucellosis in Iran using a multiple-stream framework: health policy and historical implications

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Keywords

Agenda setting • Brucellosis • Iran • Policy analysis

Summary

Background. *Brucellosis, a major zoonotic disease, is highly present in Iran, especially in Lorestan province. The aim of this study was to understand the issues related to Brucellosis utilizing the multiple streams framework.*
Methods. *A two-step method was adopted: 1) assessment of brucellosis-related documents and 2) interviews with stakeholders. As a first step, all documents related to Brucellosis were reviewed at provincial and national levels. Policy documentation on health issues included the consultation of guidelines, rules and regulations, websites, reports, books, guides, and conferences. These documents were collected by referring to specialized centers, institutions, and organizations. In the second step, semi-structured interviews were conducted to determine the burden of disease with actors and stakeholders involved with the brucellosis program in the Lorestan province. More in detail, physicians, healthcare workers, managers, policy- and decision-makers were selected for interviews.*
Results. *The problem stream was characterized by: 1) high prevalence of the disease, 2) traditional livestock production, 3) unsafe animal slaughtering, 4) centers for the sale and distribution of non-authorized dairy products, 5) raw milk and 6) traditional unsafe dairy products consumption, 7) incomplete livestock vaccination, 8) lack of knowledge of Brucellosis, 9) neighboring countries with high prevalence of Brucellosis, 10) lack of livestock quarantine, and 10) nomadic immigration. The policy stream was characterized by 1) primary healthcare networks, 2) guidelines, 3) medicines, insurance, and 4) diagnostic services. Finally, the political stream was characterized by: 1) support of the University of Medical Sciences, 2) sponsorship by the Ministry of Health and Medical Education, 3) Health transformation plan, and 4) Working Group on Health and Food Security in Lorestan.*
Conclusion. *This study examined the brucellosis-related agenda setting: if different issues are taken into consideration, it can be perceived as a health priority.*

Introduction

Health decision- and policy-makers worldwide have to face a variety of increasingly complex and multifactorial health challenges, which can have both direct and indirect effects on people's health [1]. Brucellosis is one of these challenges, being one the major causes of zoonotic disease [2], which imposes a considerable epidemiological, clinical and economic burden in several countries [3]. Brucellosis is a great public health concern, resulting in significant health and economic losses [4], especially in low-income and developing countries [5].
Various factors such as socioeconomic status, hygiene, cattle husbandry practices, and dairy production procedures can affect the transmission of this disease [6]. Brucellosis can be transmitted to humans through milk, cream, butter and non-pasteurized cheese [7]. Bacteria responsible of the disease can also be transmitted through raw or semi-milled meat of infected animals. They can be easily dispersed in the air and farmers, laboratory technicians and slaughterhouse workers can inhale them [8]. From the blood and semen of infected animals, bacteria can enter the bloodstream through the wound and lead to the development of the disease [9].
Brucellosis interferes with the patient's family and social activities [10], dramatically impacting on his perceived health-related quality of life. Weight loss, fever, joint pain, headache, sweating and fatigue are complications of the disease, which may take from weeks to months to manifest and may lead to testicular, endocarditis, bone abscess formation, and neurological complications [11].
Brucellosis is commonly widespread in areas like the Middle East, Latin America, the Mediterranean basin, Asia and Africa [12]. However, the prevalence varies among the different countries due to the various economic, social, occupational and demographic factors. The low quality of the health system in some

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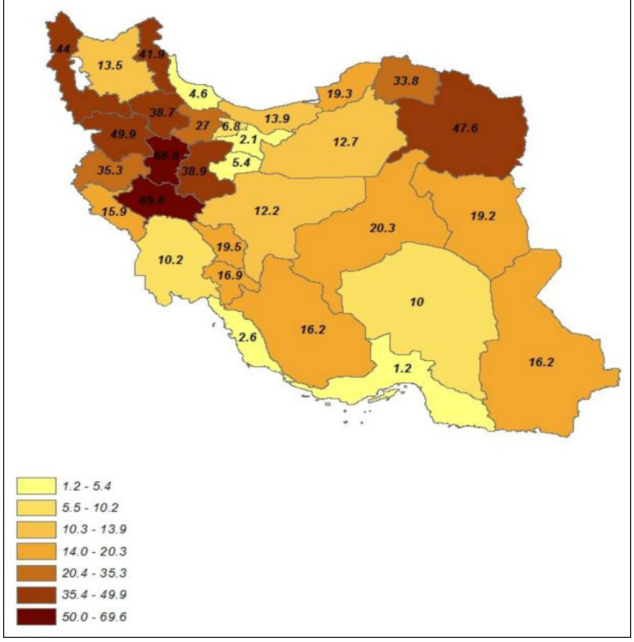
countries has led to an increase in the incidence and prevalence of the disease [12]. It is estimated that around 500,000 new people become infected each year, and this trend can increase with the absence of disease control and management policies [13].

Activities related to Brucellosis in the Iranian health system

Currently, Brucellosis-related healthcare programs in Iran are carried out with a coherent and extensive structure within the health system of the Iranian Ministry of Health and Medical Education (MoHME). The Center for Disease Control (CDC) of the MoHME conducts various activities related to the management of this disease. The National Technical Committee at the level of the MoHME is responsible for macro-policy making for the programs, monitoring the disease status on an annual basis, and determining care and treatment guidelines. At the provincial level, medical universities are responsible for implementing the programs. Public and private laboratories perform diagnostic tests on suspected cases. After an ascertained diagnosis of the disease, people are referred to specialized doctors for treatment. In the case of livestock vaccination, the veterinary organization also does this extensively. The number of newly identified cases is reported to the MoHME on a monthly basis (Fig. 1) [14].

Brucellosis is present in all provinces of Iran and is reported to be particularly prevalent in provinces such as Khorasan, Hamedan, East Azarbaijan, Fars, West Azarbaijan, Kermanshah and Lorestan [15]. Between 2009 and 2015, the trend has increased from 34.6 to 71.4 cases per 100,000 persons. The incidence and the death rate have as well increased from 120.74 to 251.43 cases per 100,000 persons and from 198 to 412 cases per 100,000 persons, respectively [16].

Fig. 1. The incidence of Brucellosis in Iran up to 2017 (rate is per 1,000,000 person).



Methods

Lorestan province with a total area of 28064 square kilometers is located in the western part of Iran, north of the central provinces of Hamedan, east of Isfahan province, southeast to Chahar Mahal and Bakhtiari, south to Khuzestan province, and west to Kermanshah and Ilam provinces. According to the latest available census, the province's population comprises of 1,760,649 people. This province has 11 cities. Lorestan is located on the slopes of the Zagros Mountains, throughout the forest area. Vegetation has led livestock farming to become one of the most popular jobs in the province. Lush meadows, rainy lakes in Lorestan provide a good environment for nomadic life. Since Lorestan has a suitable climate, and a fertile soil, and therefore the mainstay of the people's economy is the livestock and agriculture.

MSF is one of the most important and practical tools used in the healthcare decision-making process [17]. It defines what constitutes a policy and why a given policy is put on the agenda, and includes three streams: problem, policy, and political. The theoretical framework states that when these three streams are interconnected, a window of opportunity is formed. This framework emphasizes the role of policy entrepreneurs, who are actors trying to link these three streams together. When the window of opportunity is formed, policy entrepreneurs should take advantage of this and take further steps to put politics on the agenda, in such a way that is taken into consideration by decision- and policy-makers.

Two steps were taken to collect data (retrieval and assessment of Brucellosis related documents and interviews with relevant actors and stakeholders).

Tab. I. Types of documents utilized in the present research.

Type of document	Number
National and provincial letter section	5
Health and treatment guidelines	3
Reports	11
Scientific texts (books and articles)	19
Rules, regulations, laws	6
Websites	14

Documents retrieval and assessment

First, all documents related to Brucellosis were reviewed at provincial and national levels. Policy documentation on health issues included the consultation of guidelines, rules and regulations, websites, reports, books, guides, and conferences. These documents were collected by referring to specialized centers, institutions, and organizations. Data were extracted after a proper process of validation. Table I shows the type and number of documents.

Scholarly databases, such as ISI/Web of Science, PubMed/MEDLINE, Scopus, Embase, as well as Iranian repositories, including MagIran, Scientific Information Database (SID), and Barakatkns, were searched by two researchers from inception until December 2020. The purpose of this phase was to collect scientific articles related to Brucellosis and its epidemiology in Iran. Further searches were conducted, mining Google, websites of government agencies, and NGOs involved in the program of controlling and managing Brucellosis. Two authors systematically coded textual data identified according to the MSF.

Interviews

In the second step, semi-structured interviews were conducted to determine the burden of disease with actors and stakeholders involved with the brucellosis program in the Lorestan province. More in detail, physicians, healthcare workers, managers, policy- and decision-makers were selected for interviews. A sample of 16 people participated in the interview. Interviews were conducted by two authors face-to-face (one PhD and one MS). The selection of participants was done utilizing a snowball and purpose-based sampling approach. Interviews were conducted in the period from July to December 2020. The duration of the interviews varied between 60 and 75 minutes. Three major questions developed based on the MSF were asked. Interview guide used was developed specifically for this study. The questions asked to participants are reported in the supplementary material 1.

Besides these questions, participants were also requested to express further comments regarding the Brucellosis in Lorestan province. The date and place of the interviews were determined with respect to the participants' views and previous coordination with them. At the beginning of the interview, the researchers provided a thorough explanation of the study and its objectives, ensuring the confidentiality of sensitive data. In addition to taking notes, interviews were recorded with the consent of the participants utilizing a digital voice recorder. In order to increase the validity of the results, specific measures were undertaken and protocols followed, such as involving qualified researchers, selecting relevant participants, and allocating sufficient time to collect data.

Interviews were transcribed *verbatim* and analyzed using the MSF tool. All interview transcripts were imported into MAXQDA Version 10 software. After removing similar and duplicate codes, the content was analyzed according to the three themes of the MSF (problem, policy, and politics). Interviews and related results were reported according to the consolidated criteria for reporting qualitative research (COREQ) [18, 19].

Results

Problem stream

1. High prevalence of the disease

In the recent years, studies conducted in the province of Lorestan, the reports of the Ministry of Health and the disease surveillance and response system provided by the University of Medical Sciences at the level of a complex network of laboratories, hospitals and health centers have shown an increasing trend in the incidence and prevalence rates.

2. The traditional livestock production

Despite the many efforts undertaken, many obstacles affect the traditional livestock production, such as the need of using new equipment and developing industrial plans, which require adequate funding. Other barriers are the lack of support from livestock breeders and their scarce knowledge of common zoonotic diseases. Many livestock keep their livestock near their homes, usually in unhealthy situations.

3. Unsafe slaughtering of animals

Many people slaughter livestock at home and, as such, are not fully compliant to the health principles, since they can establish direct unprotected contacts with the livestock. Meat is also consumed immediately after the slaughtering, without being kept in cold. Furthermore, livestock is sold, without taking into account health and hygiene issues.

4. Centers for the sale and distribution of non-authorized dairy products

One of the jobs in the province is the supply and sale of dairy products. These people buy raw milk directly from stocks. Despite being supervised by health care units, negligence in hygiene is very high in the

provision of dairy products. This increases the risk of Brucellosis.

5. Buying and consuming raw unsafe milk

To collect milk, people go to villages and utilize caravans, often in unsuitable health conditions. Because of cheaper prices, many people use this milk, so the health chain that is being used by milk mills is prone to Brucellosis.

6. People tend to consume traditional and local dairy products

There is an effort to use healthy dairy products from industrial factories. Due to the old beliefs of people and their lack of knowledge concerning the production chain and the observance of the health, many people are keen to consume traditional dairy products. They assume that milk salts are removed in the process of pasteurization and sterilization.

7. Incomplete vaccination of livestock

Problems have arisen due to lack of adequate funding and vaccines. In some cases, vaccination of livestock is not complete.

8. Lack of knowledge of Brucellosis

Despite all the efforts of the relevant institutions, many people still do not have much knowledge about ways to control, diagnose and treat the disease. Many people know the only way to avoid being infected is boiling milk.

9. Neighborhood with provinces with high prevalence of Brucellosis

Lorestan province has neighboring provinces with high prevalence of disease. It should be considered that most livestock is exported to Iraq in western Iran, and the transfer of livestock between these provinces is increasing the chance of entering livestock in the province and infecting people.

10. Lack of quarantine of livestock

Ranchers plan to create places where healthcare organizations have little control over direct sales of their livestock on the margins of the city. Livestock is often sold without sanitary control and quarantine.

11. Nomadic immigration

Livestock farmers live in nomadic huts both in hot and cold seasons, together with their livestock. Moreover, marginalized residents, in addition to establishing direct, unprotected contacts the livestock, buy contaminated dairy products because of their lower prices.

POLICY STREAM

1. Existence of primary health care network

Primary health care network (PHC) is one of the strongest healthcare organization systems in Iran. The network provides a variety of services in villages and cities. The existence of this network has led to the provision of health-related policies and programs by staff, and information and awareness-raising initiatives on various diseases. Due to the presence of appropriate laboratories in this network, there is a high potential for diagnosis of patients. After diagnosis, treatment is done by the physicians of this network, and the process of direct supervision and ease of access to services have increased the adherence to treatment. Also, the health inspectorates have a duty to perform monitoring controls and these centers must receive the necessary health permits.

2. Guidelines

Several programs have been developed to raise awareness, in which target groups are identified and trained with the help of PHC. For hospitals and health centers, guidelines are provided. A comprehensive program for the prevention, control, and treatment of Brucellosis in the form of a systematic comprehensive education model (SHEP model) has been developed.

3. Medicines and insurance

Drug companies in the country have no problems with the provision of drugs for patients. Medications are readily available. On the one hand, insurance provides good coverage for medicines. The price of medicines is good for all patients and, if there are any financial problems, drugs will be provided by the healthcare sector.

4. Diagnostic services

In addition to having diagnostic laboratories in the PHC, private sector laboratories and government hospitals also provide diagnostic services at an affordable cost. Insurance also covers diagnostic services. The diagnostic policies of the disease are designed in such a way that all individuals can use these services and can benefit from the low-cost services both in the village and the city.

POLITICAL STREAM

1. Support of the University of Medical Sciences

The main stewardship is the implementation of health policies in the province, the University of Medical Sciences. Services are provided in all cities under the supervision of the university, which is responsible for planning, decision- and policy-making and coordination within the province. Knowledge, diagnosis and treatment as well as financial and political support are the duties of the university. The various departments of the university, with their local policies and programs, are trying to control the disease. The University has been trying to attract the support of other organizations to properly carry out the implementation of brucellosis-related programs.

2. Sponsor by the Ministry of Health and Medical Education

Brucellosis is one of the most commonly reported diseases. Policies and decisions are made at the national level through the Ministry. The development of effective programs through the establishment of the Zoonotic Disease Organization has led to the special attention paid to the disease and to the control policies.

3. Health transformation plan

The implementation of the health transformation plan (HTP) in Iran in the year 2014 and the political health-oriented approach of the government have created a better health perspective among all people in the community and the issue of health has been prioritized. The use of new financial resources and new approaches to health and the attention of other ministries have led decision- and policy-makers to plan for new interventions for disease control, including Brucellosis.

4. Working Group on Health and Food Security in Lorestan Province

One of the most important coordination levers for implementing health sector programs is the existence of the health and food safety committee in Lorestan province with the administration of the highest political authority, the governor. This group has made the programs run with all stakeholders and actors. If the implementation of the programs encounters a problem, the task force will quickly enter and execute the programs better and more efficiently.

5. International organizations such as the World Health Organization and the Eastern Mediterranean Region Organization

International organizations, such as the World Health Organization (WHO) and the Eastern Mediterranean Region Organization (EMRO), are responsible for determining global and regional policies, according to their mission. They ask the member states to implement their plans to control Brucellosis. International support for national decision- and policy-makers has increased the commitment to implement these programs. National decision- and policy-makers are trying to focus their plans for controlling illnesses in their country to improve health status.

Discussion

Agenda-setting is a process which entails health-related issues of interest to policy- and decision-makers and is the first stage in the development of policy making process [20]. This study aimed to investigate brucellosis-related agenda setting at a provincial level (in Lorestan province in western Iran characterized by a high prevalence of the disease) by using the MSF. The findings of the study showed that there are problems and challenges both inside and outside the health sector that affect the process of prioritizing the disease.

Problem stream

Brucellosis is a serious health problem in Lorestan province. In relation to the problem stream, what is perceptible is the general public's view of the use of dairy products. The public's belief in the use of local dairy products has led to some kind of resistance and a greater likelihood of developing the disease, despite the efforts of health organizations. To change such a view, comprehensive training at provincial level should be implemented. When the belief has changed and this change has resulted in a different, healthier behavior, valuable results can be obtained for disease prevention. Awareness of the community and adequate level of knowledge are vital for changing misconceptions and achieving disease prevention and control [21]. For instance, in a recent meta-analysis by Zhang et al., livestock breeders and slaughterhouse personnel in Asian and African countries had a low awareness of Brucellosis [22]. This problem is especially high in Lorestan province.

Other problems associated with Brucellosis in Lorestan province are financial problems related to the implementation of prevention programs, which does not allow vaccination of animals to be fully implemented. Sustained funding are, indeed, needed for disease prevention programs [23]. Policy- and decision-makers prioritize between different programs when they do not have all the financial resources necessary and allocate funds on more important programs]24]. Given that Brucellosis is not perceived as a major public health problem in Lorestan province, funding has been dedicated to other illnesses. On the other hand, livestock vaccination is one of the most cost-effective policies for the prevention and control of Brucellosis. However, the implementation of vaccination programs is handled by actors outside the health sector, and the lack of allocation of sustainable financial resources as well as the lack of priority for them has increased the disease trend [6].

Policy stream

Knowledge of a given disease is of crucial importance [25], in order to provide patients with all the facilities and appropriate services [26]. Expert opinions and scientific evidence-based, country-specific recommendations are fundamental for the effective management of diseases.

At the level of the patient, it can be difficult to afford to obtain drugs due to the high costs. The insurance coverage of patients leads to the adherence and completion of the treatment process. Insurance as an important actor can play an important role in social support for patients [27]. The Ministry of Health and Medical Education (MoHME) has continuously considered the issue of Brucellosis as a health problem and has developed national laws in this regard. The

disease has been relatively rooted in the ministry's plans. The preparation of guidelines for the cooperation of other organizations also suggests that the ministry is willing to increase inter-agency cooperation. However, many organizations and individuals who can play an important role in the implementation of disease prevention and control programs in the province have little desire to cooperate. The role of NGOs in the province is very poor in cooperating and coordinating with the University of Medical Sciences. Many other organizations do not fulfill their role and duties. The lack of cooperation between organizations represents a major weakness. Intergenerational co-operation in implementing health programs is very important.

Political stream

In Iran, many factors affect the local, national and international political stream and impact on the health-related agenda setting process. One of the most important events that have attracted attention in recent years is the implementation of the HTP. The change in government and the health-based approach have led to a higher focus on health issues. The process of paying attention to less developed regions and decentralization has created more opportunities for different provinces. Paying attention to local diseases has pushed policy- and decision-makers to make local decisions. They are working with the MoHME and political people in the provinces to focus more on issues that cause more problems in the provinces. Representatives of the people in the Iranian parliament are trying to increase the level of accountability of the provincial political authorities to understand and solve the problems of the provinces. This has led to the creation of political responses and the consideration of health issues at a micro-level. New financial resources have managed to solve many problems with the program. The service package created within the HTP has made it more attractive for providers to provide more services to patients as well. Implementing the HTP has created a coalition of many people interested in being involved in the brucellosis-related agenda setting.

Window of opportunity and policy entrepreneurs

According to the MSF, if all the three streams are effectively and properly merged, a window of opportunity can be created and policy entrepreneurs can use this opportunity to run their own programs to solve health-related issues [17, 20].

The findings of this study showed that due to the presence of different problems and obstacles at the level of all the three streams, the window of opportunity has not been created. Policy entrepreneurs have not been able to take actions and steps to change policy programs and adequately tackle Brucellosis. This disease is not perceived as a policy priority by all stakeholders and actors and one of the most important reasons is that only the MoHME and the medical university are paying attention to the complications of this disease, and other organizations do not have a specific program for managing Brucellosis. Based on interviews and documents, decision- and policy-makers in Lorestan province are interested in controlling Brucellosis, but there is no serious commitment to developing prevention and implementation plans. Execution of programs requires the support of all groups, but since this is lacking, the window of opportunity has not been created in these years.

The study showed that there are several indications and reasons why Brucellosis should be considered as a health concern for the population of Lorestan. Lack of proper awareness, lack of sufficient financial resources for other actors to implement their organizational plans, lack of inter-sectoral cooperation and inadequate support have prevented Brucellosis from being included in the agenda of policy- and decision-makers in the province. Paying attention to these obstacles and challenges can be a great help to solve them and put Brucellosis as a priority. Prevention and control programs with the support of all actors can open the window of opportunity.

Despite its novelty and methodological rigor, this study has some limitations. The sample of interviewed stakeholders may not represent all the cultural, economic, and social aspects of the Lorestan province. Furthermore, some participants were reluctant to provide all the information requested.

Conclusions

This study examined the brucellosis-related agenda setting in Lorestan province, which is characterized by a high prevalence rate of this zoonotic disorder. If different issues related to the disease are taken into consideration, this disease can be perceived as a priority and put on the agenda. The findings of this study can be useful for countries with similar conditions: it is expected that health decision- and policy-makers will play an important role in preventing and controlling the disease by planning and implementing appropriate programs.

List of abbreviations

MSF: Multiple streams framework.
COREQ: Consolidated criteria for reporting qualitative research.
HTTP: Health Transformation Plan.
MoHME: Ministry of Health and Medical Education.
WHO: World Health Organization.
EMRO: Eastern Mediterranean Region Organization.

Ethics approval

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Availability of data and materials

Not applicable.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MB, SS, MZ, MKG and MM conceptualized the study and also analysed the data as a team. MB, NLB, MM and MZ wrote up the manuscript. SS, MZ, NLB, and MM reviewed the manuscript. All authors have thoroughly read this manuscript and approved it for submission.

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Supplementary Material

Interview guide

1. Please describe your activities related to the brucellosis.
2. Explain the information on the epidemiology of the disease, its transmission routes in the province.
3. What are the problems and challenges in relation to the brucellosis in Lorestan province?
4. What are the solutions to control and manage the brucellosis in Lorestan province by individuals, groups and organizations?
5. What political factors can affect the control and management of brucellosis in Lorestan province?

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Research paper

Edoardo Maragliano (1849-1940) and the immunogenicity of the tubercle bacillus: the pathway of a great italian physician

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Keywords

Edoardo Maragliano • Immunogenicity • Tuberculosis • History of tuberculosis

Summary

Edoardo Maragliano (1849-1940) was an Italian physician; he played a central role in medicine's "renaissance" in Italy and Europe. After beginning his academic career as a professor of pathology, he became full professor of internal medicine in 1881. While he studied all fields of internal medicine, his research focused mainly on tuberculosis. Thanks to his experiments in the medical clinic, Maragliano announced the possibility of immunization against Mycobacterium tuberculosis. Although criticized for using an inactivated vaccine, Maragliano continued to advocate vaccination with any type of vaccine.
Maragliano keenly contributed to the still ongoing process of understanding the difficult interaction between Mycobacterium tuberculosis and the infected host.

Edoardo Maragliano (1849-1940) was born in Genoa on 1 June 1849 into a family of Ligurian origin. Having studied classics, first at the "Ginnasio" of the Padri Scolopi and then at high school, he matriculated at the Faculty of Medicine of the University of Genoa. After his first years of study, he moved to Naples, where he completed his course in medicine, graduating with full marks in 1870.

In Naples, he was initially a pupil of Prof. Salvatore Tommasi (1813-1888) and Prof. Arnaldo Cantani (1837-1893). Subsequently, on returning to Genoa, he became an assistant to Errico de Rienzi (1839-1921), the director of the Medical Clinic, and in 1877 was appointed to teach General Pathology, which he did until 1881 [1]. Indeed, in that year, he was appointed Ordinary Professor of Clinical Medicine in Genoa, a position he held until 1924. During his tenure, his department became a significant point of reference in medical field.

Maragliano was an indefatigable scholar and a prolific author, publishing 2453 scientific works of notable importance. Among his main publications, his "*Trattato delle malattie dei polmoni*" (Treatise on lung diseases) and his original monographs on nephritis, fever and blood are worth mentioning.

In the present article, we will discuss his contribution to the study of tuberculosis (TB) and the immunity elicited by infection with Mycobacterium tuberculosis and by anti-tuberculosis vaccination.

From 1890 onwards, Maragliano devoted much of his research to studying immunity towards tuberculosis infection. As an astute pioneer in this field, in 1900 he founded an innovative institute for the study of tuberculosis and infectious diseases: the Maragliano Institute in Genoa (Italy). At the end of the 19th century, the existence of immunity to tuberculosis was not yet recognized; it was claimed that TB was an infection" sui generis", different from others, and the notion that a state of immunity could be elicited in humans was rejected. Maragliano was the first to cast doubt on this idea and demonstrated that it was indeed possible to immunize people against TB, just like any other infectious disease. In order to fully understand Edoardo Maragliano's work, we need to go back to the period immediately following the discovery of the TB bacillus by Robert Koch (1843-1910) [2].

In 1882, although immunology was only in its infancy, it was already known that any substance introduced into a biological system displayed antigenicity (immunogenicity), that is to say, the antigen induced the production of antibodies, which then mounted an immune response. Erroneously, however, it was believed that antigenicity was a property intrinsic to any substance, such as its molecular weight or its absorption spectrum, for example. Based on these assumptions, many researchers believed that they could obtain a protective immune response by inoculating bacterial matter into an animal, without taking into account its quantity, and the conditions and mode of inoculation. These researchers, however, saw their hopes dashed, so much so that and as a consequence of their, owing to the failure in demonstrating the immunogenicity of the TB bacillus, they concluded that it would never be possible to create a vaccine against TB [3].

This was the state of research between 1884 and the

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early 1890s. By then, Maragliano had been running the Medical Clinic in Genoa for a decade where he promoted the study and understanding the immunogenicity of Mycobacterium tuberculosis". Nevertheless, his stance was not that of the pure bacteriologist, but rather that of the physician who remained focused on the patient [4].

Maragliano needed to demonstrate the antigenicity of the TB bacillus experimentally in an animal model. To prove the immunogenicity of the bacillus, Maragliano adopted the following stratagems:

1. Firstly, it was necessary to calibrate the intensity of the bacterial load very carefully; i.e., the right amount had to be inoculated: neither too much nor too little. In order to trigger a defensive movement, Maragliano claimed that the "offended cells" had to react. If, however, the "*offense*" were too strong, the ability to react would be weakened and eventually arrested;
2. Secondly, the gradual appearance of antibodies and the disappearance of the bacilli had to be monitored, in order to determine when the immune response had reached its peak (maximum development). According to Maragliano, this should generally occur around the 90th day after inoculation;
3. Thirdly, only after respecting this timing could the animal be tested to determine whether it was capable of *"defending itself"*; i.e., of reacting to a new bacterial load that was equal to the smallest load that would be able to kill a control animal. In Maragliano's view, this last precaution was not only indespensable for the experiment to be successful; it also explained why the tests conducted without these stratagems had failed [5].

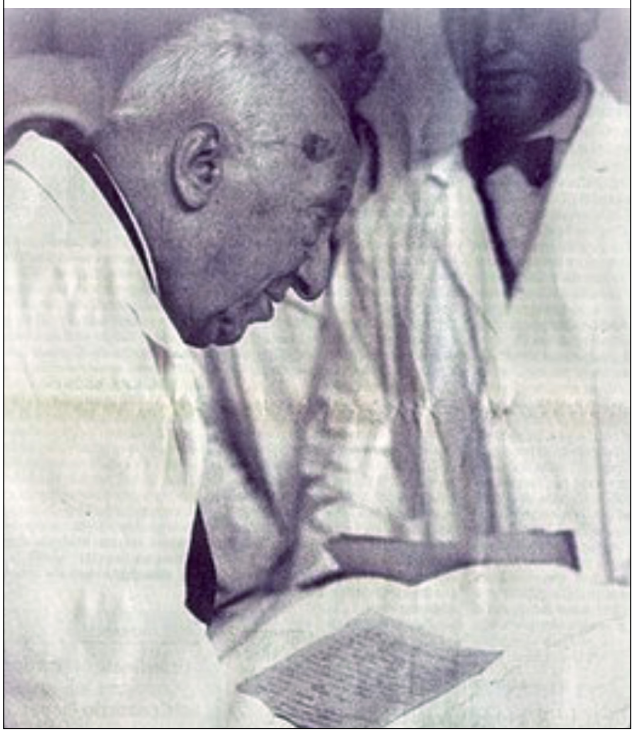
The stratagems implemented by Maragliano led to the development of anti-tuberculosis vaccination: not only that of the Professor himself, the *"Vaccino Maragliano"*, but also of all those that were to follow [6].

Indeed, Maragliano's greatest merit probably lies in the fact that he was the first to introduce what he himself called *"stratagems"*; this was confirmed in his farewell lesson on 28 June 1924 (7) after 43 years of teaching, in which he clearly stated:

"Here, on this solemn occasion, it behooves me to make a declaration. The therapeutic applications of our studies and the specific therapy that has sprung from those studies are of secondary importance. Indeed, what constitutes the chief boast of our School is the discovery of a series of stratagems which demonstrated the existence of an immunogenicity of the bacillus that was functionally dependent on the biological system and the conditions used".

These "stratagems" worked out by Maragliano concerning *Mycobacterium tuberculosis* must, still today, be borne in mind in the case of any other antigen. Indeed, in every immunology textbook, we always find the concept that the formation of antibodies does not depend only on the inoculation of the antigen into a suitable animal, but also on other conditions, such as, for example, the quantity and quality of the antigen injected, the route of inoculation, the immune status of the subject, and the frequency of the various follow-up tests.

Fig. 1. Prof. Edoardo Maragliano (1849-1940) (Wikipedia Commons).



Indeed, the principal merit of the school directed by Prof. Edoardo Maragliano, as he himself pointed out in his farewell lesson, was *"… having discovered a series of facts that demonstrated the existence of a tubercular immunity, which had hitherto been denied, and having laid the foundations of the new conceptions of the pathology of tubercular diseases, conceptions which are now all based on immunity"* (6).

As the great scientist Saturnin Arloing (1846-1911) publicly stated in 1906 in Genoa, in a speech on Maragliano's studies: *"Until 1895, we despaired of being able to obtain tubercular immunity. Through his discoveries, Maragliano raised the spirits of researchers from the depths of despondency into which they had fallen. At first, the announcement was greeted with reservation, but then confirmation came from all sides: what he had said was true. This was the first word of "serene justice" that our school received from the scientific community, and it emanated from a scientist of international eminence"*[8].

Maragliano actively contributed to the still ongoing process of understanding the difficult interaction between *Mycobacterium tuberculosis* and the host [9,10].

Even today we must always observe and emphasize that infection prevention and control measures are particularly important in public health facilities because there is a risk of transmission of the tuberculosis bacterium "Mycobacterium tuberculosis"; the World Health Organization (WHO) developed recommendations according to the methods defined in the WHO handbook for guideline development [11].

Moreover, we should always consider and reflect on one

of the most important aspects in this long pathway: a real and successful vaccine.
We still have to remember today that only a really efficacious vaccine will enable us to eradicate TB.
According to the World Health Organization, tuberculosis (TB) is the leading cause of death from infectious disease worldwide (WHO, 2017). While there is no effective vaccine against adult pulmonary TB, more than a dozen vaccine candidates are in the clinical trial pipeline [12]. But how long will we still have to wait?

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MM and EM designed the study. MM and EM conceived the study; MM and EM drafted the manuscript; MM, NR and FB revised the manuscript. MM, FB performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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Research paper

Socioeconomic inequalities in tobacco smoking in women aged 15-54 in Iran: a multilevel model

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Keywords

Inequality • Tobacco smoking • Socioeconomic status • Women • Iran

Summary

Significant evidence suggests an inverse relationship between socioeconomic status and tobacco smoking, where inequality is visible among different social and economic strata. The aim of this study was to investigate the prevalence and economic and social inequalities in tobacco smoking in women aged 15-54 in Iran. This study is a cross-sectional study. Sampling in this study was a randomized clustered multistage sampling with equal clusters. A total of 35,305 women aged 15-55 enrolled in the study. Data analysis was in two stages. In the first stage, the social and economic inequalities were investigated using the concentration index and concentration curve method, and in the second method, and multilevel method was used to identify the determinants. The prevalence of tobacco smoking in women was 12.24%. The concentration index for smoking was CI = -0.07 [95% CI (-0.09, -0.05)], which represents smoking in people with low socioeconomic status. The results of the multilevel analysis indicated that the marital status of people over the age of 35 and the economic class was related to smoking in women. Inequality in tobacco smoking in women is to the interest of the well-off group, and this inequality varies in different provinces. Marital status, place of residence, age and socioeconomic status of women are factors influencing the prevalence of tobacco smoking in women, and these issues should be noticed to reduce inequalities.

Introduction

Today smoking is one of the challenges of global health, is one of the most significant causes of premature death and disability worldwide, and is one of the risk factors for non-communicable diseases such as cardiovascular disease, cancer, chronic respiratory diseases, and digestive tract [1, 2]. Tobacco smoking causes more than six million deaths every year worldwide [3]. The death rate from tobacco smoking is expected to exceed eight million by 2030, with 80% of these deaths occurring in low-income and middle-income countries [4].

The prevalence of tobacco smoking in different parts of the world varies from 14.2 to 39% [5]. The prevalence of tobacco smoking in the West and Southeast Asia is 23%, East Africa is 18%, South America is 15%, West Africa is 14%; with the lowest and the largest being Southeast Asia, with 12% and the Central European region, with 29% [6]. Statistics show that around 250 million women in the world use tobacco, of which 22% are in the developed countries and 9% in developing countries [7]. The prevalence of smoking in women in Kenya is 3.1%, China is 4.2%, Japan is 7.9%, Ukraine is 10.2%, Bangladesh is 13.3%, Venezuela is 14.4%, Turkey is 18.2%, Germany is 20.3%, Ireland is 21%, Denmark is 22.2%, Croatia is 27.1%, and Australia is 23.8% [8]. Studies have shown that women who use tobacco are at higher risk of various types of cancers, chronic obstructive pulmonary diseases, and the birth of neonates with a genetic defect [9].

Studies have shown that people with a lower socioeconomic status and lower levels of education are more likely to smoke [10-12], so that the prevalence of smoking in high socioeconomic groups is declining and this decline has led to inequality in the prevalence of tobacco smoking in various social economic classes [13]. There has been significant evidence of a reciprocal relationship between the economic situation and tobacco smoking, also international studies have shown that social and economic inequalities in tobacco smoking is stronger for women compared to men [14].

The causes of smoking and inequality are a complex and multifactorial phenomenon. Understanding how these inequalities arise and knowing these factors can provide valuable information for developing effective strategies [15]. Reducing social inequalities in tobacco smoking is a significant strategy to reduce inequality in life expectancy in the future [16, 17], as tackling regional and socio-economic disparities in smoking is one of the major public health goals worldwide. The WHO recommends monitoring and evaluating socioeconomic inequalities in health behaviors, including tobacco use, as one of the social determinants of health [18].

Therefore, considering the importance of examining social inequalities in smoking and considering that there are no studies on tobacco inequality in women, this study aims to investigate the prevalence and socioeconomic inequalities in smoking among women aged 15-54, conducted based on Iran's Multiple Indicator Demographic and Health Survey (IRMIDHS).

Methods

Data collection and sampling

This is a cross-sectional study conducted to determine socio-economic inequalities in tobacco smoking among women aged 15-55 based on IrMIDHS . The study population was all households that participated in the IrMIDHS study in 2010. Given that the size of the population varies in different provinces [19], the sample share for each province was initially determined. Hence, the sample ratio was different in each province. Sampling was performed according to population size in each province. Samples were weighted to reflect the rural and urban population in each region. Each region was selected randomly from clusters based on the sample size allocated to rural and urban households in each region. Each cluster included 10 households. For each province, at least 40 clusters were selected. As a result, a possible sample of about 31,000 families (3,096 clusters including 2,187 urban clusters and 909 rural clusters) was selected for the IrMIDHS sample. The sampling method was a multi-stage random cluster sampling [20]. Rural and urban areas were considered as two different classes. Random sampling of the clusters was conducted at the regional level to allow proper distribution of clusters in the country. A total of 35,305 women aged 15-55 were enrolled in the study.

The dependent variable

The dependent variable for this study was tobacco smoking in women aged 15-54, which was investigated by posing the question “Which of the tobacco products are you currently consuming? (Cigarette, cigar, pip, chickpeas, hookah)". In the present study, second-hand smoking was not considered for women and direct smoking by women at the frame time of the study was considered as an outcome variable.

Data analysis

The data analysis consisted of two steps, performed with the Stata-14 software. The first stage was the study of social and economic inequalities using concentration index and concentration curve methods and the second stage was the study of the relationship between social and economic inequalities in smoking, with demographic variables of the subjects using Multilevel method.

Concentration index for socioeconomic inequality and how to calculate the economic and social status

In this study, the concentration index and concentration curves were used to measure inequality. The concentration index values range from +1 to -1. The negative values indicate that the health variable is concentrated between individuals with inappropriate social and economic status and the concentration curve is above the equality line. But positive values indicate that the health variable is concentrated among the rich, and when the distribution of health is the same among all individuals, the concentration index will be zero. The socioeconomic situation has a wide dimension such that there is no precise method for its measurement. Therefore, other proxies are used as alternatives [21, 22]. In this study, by using principal component analysis (PCA), first, the variables having the greatest effect on the variance of the total variables were identified and then a new variable (SES) was constructed based on these variables [23, 24]. In the present study, by using the principal component analysis method, the asset index was created. Asset index was based on the area of the building, the number of bedrooms, the materials used in the residential unit, household items such as refrigerators, televisions, landlines, mobile phones, washing machines, dishwashers, microwaves, vacuum cleaners, computers or laptops, Internet access, having cars, wristwatches, having private property, farmland, garden and greenhouse and agricultural machinery. Weights were considered for each asset to maximize the variance of the new variable. Using the mean of this variable, 5 quintiles were created which divided the population into 5 groups of very poor, poor, moderate, rich and very rich. In this study, tobacco smoking was assumed to be related to the socioeconomic status of individuals.

Multilevel analysis to identify determinants

At first, the relationship between tobacco smoking and independent variables were investigated using logistic regression. After determining the existence of inequality with the help of the concentration index and the concentration curve earlier described, the level of inequality at different levels was investigated using Multilevel method. Multilevel analysis was done at three levels. The first level included individual variables (age groups, occupation, marital status, place of residence (city/village), and education), the second level included the county of residence, and the third level was the province.

$$\log it\,(\text{smoking}_{ij}) = \beta_0 + \beta_1 age_{ij} + \beta_2 education_{ij} + \beta_3 marriage_{ij} + \beta_4 occupation_{ij} + \beta_5 quintile_{ij} + \beta_6 region_{ij} + \varepsilon_{ij}$$

Level 2 Model

$$\beta_0 = \gamma_{00} + \gamma_{01}\text{county} + \varepsilon_{ij}$$

$$\log it\,(\text{smoking}_{ij}) = \beta_0 + \beta_1 age_{ij} + \beta_2 education_{ij} + \beta_3 marriage_{ij} + \beta_4 occupation_{ij} + \beta_5 quintile_{ij} + \beta_6 region_{ij} + u_{0j} + u_{1j} qu\,\text{intile}_{ij} + \varepsilon_{ij}$$

Level 3 Model

$$\beta_0 = \gamma_{00} + \gamma_{01}\text{province} + \gamma_{02}\text{county} + \varepsilon_{ij}$$

$$\log it\,(\text{smoking}_{ij}) = \beta_0 + \beta_1 age_{ij} + \beta_2 education_{ij} + \beta_3 marriage_{ij} + \beta_4 occupation_{ij} + \beta_5 quintile_{ij} + \beta_6 region_{ij} + u_{0j} + \varepsilon_{ij}$$

$\log it\,(\text{smoking}_{ij})$ = Smoking in person i at level j

Remaining individual level ε_{ij} =

In the multilevel model, the mean estimation of each group and the effect of these variables on the higher levels that vary in each group were examined on the individual response variable. In a simple model, regardless of the average levels, the variance between the groups was ignored, but in Multilevel, the level of relationship between the variance of the dependent

variable and the factors of the level and between the individual factors was determined. The advantage of using the Multilevel analysis is the ability to evaluate the effects of independent two-level variables on the outcome of one level and the value of variance that they can explain. The first model is limited to individual variables and the second model includes both variables, i.e. individual variables and second-level variables [25].

In the present study, Level 1 Model included independent variables such as age, marital status, education, occupation, social class (quantile), place of residence (city/village), Level 2 Model included province and Level 3 model included the province and county of residence.

Results

In this study, a total of 35,305 women aged 15-55 participated in this study, with a mean age of 31.48 ± 10.75. More than half of the study participants were married and housewives. The highest number of people was 15,792 (44.73%) of the first quintile, and 4,158 (12.22%) who smoked tobacco were specified in different sub-groups (Tab. I).

The results of logistic regression showed that a statistically significant relationship exist between tobacco smoking with outcome and location variables, age groups over 35, marital status and economic variables ($p < 0.05$), while no relationship exist between smoking and occupation and education ($P > 0.05$) (Tab. II).

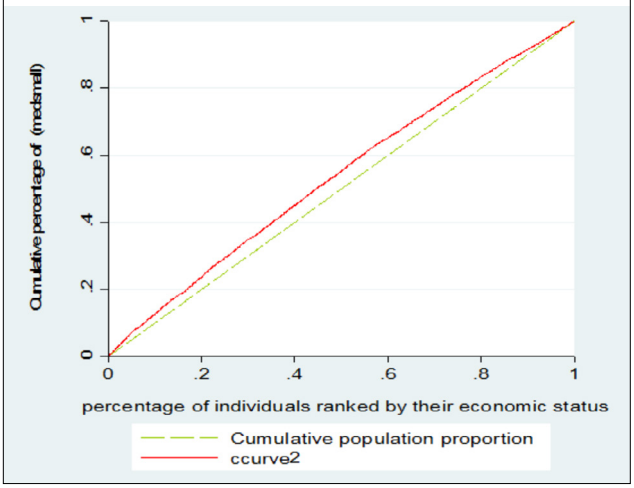
Tab. I. Frequency of demographic variables and the prevalence of smoking in study of IrMIDHS, Iran.

Variable		Frequency (percent)	The prevalence of smoking
Location	City	24,602 (69.7)	3,119 (13.2)
	Village	10,703 (30.3)	1,039 (10)
Age groups	< 20	4,968 (14.6)	617 (12.4)
	20-34	17,158 (50.5)	2,203 (12.8)
	≥ 35	11,848 (34.9)	1,338 (11.2)
Occupation	Employed	10,046 (35.6)	1,246 (12.9)
	Unemployed	18,109 (64.4)	2,110 (12.1)
Education	Illiterate	3,741 (11)	361 (6.9)
	Elementary	8,367 (24.6)	937 (11.2)
	High school	4,919 (14.4)	661 (13.4)
	Diploma	11,453 (33.9)	1,507 (13.1)
	Academic	5,494 (16.2)	692 (12.6)
Marital status	Single	23,493 (69.2)	2,927 (12.4)
	Married	10,481 (30.8)	1,231 (11.7)
Quantile economic	Poor	15,792 (44.7)	2,075 (13.7)
	The poorest	6,539 (18.5)	755 (11.9)
	Average	5,017 (14.4)	539 (11)
	Rich	4,231 (11.9)	423 (10.3)
	The richest	3,726 (10.5)	366 (10.3)

Tab. II. The relationship between the smoking and independent variables according to logistic regression model.

Variable		OR (crude)	OR (adjust)	P-value
Location	City	1	1	
	Village	0.73 (0.68-0.79)	0.77 (0.7-0.86)	0.04
Age groups	< 20	1	1	
	20-34	1.03 (0.94-1.14)	0.98 (0.87-1.1)	0.6
	≥ 35	0.89 (0.81-0.99)	0.8 (0.69-0.91)	0.04
Occupation	Employed	1	1	
	Unemployed	0.93 (0.86-1)	0.96 (0.89-1.04)	0.7
Education	Illiterate	1	1	
	Elementary	1.18 (1.03-1.34)	1.12 (1.04-1.46)	0.046
	High school	1.45 (1.26-1.6)	1.23 (1.04-1.46)	0.048
	Diploma	1.419 (1.25-1.54)	1.17 (1-1.38)	0.5
	Academic	1.34 (1.17-1.54)	1.07 (0.9-1.29)	0.65
Marital status	Single	1	1	
	Married	0.93 (0.87-1)	0.84 (0.77-0.92)	0.038
Quantile economic	Poor	1	1	
	The poorest	0.85 (0.77-0.93)	0.85 (0.76-0.94)	0.001
	Average	0.78 (0.7-0.86)	0.78 (0.69-0.88)	0.001
	Rich	0.72 (0.65-0.81)	0.75 (0.65-0.86)	0.001
	The richest	0.71 (0.63-0.8)	0.8 (0.68-0.94)	0.001

Fig. 1. Concentration Index.



The concentration index for smoking was CI = -0.07 [95% CI (-0.09, -0.05)], which indicate the existence of inequality in smoking, and smoking in the lower socioeconomic group was higher. This inequality is also specified in the concentration curve, and the curve is above the equal line representing the tobacco smoking in people with low socioeconomic status (Fig. 1).

Table III shows the prevalence of smoking in women in different provinces, and the relationship between the prevalence of tobacco smoking and the socioeconomic quantiles and inequality in the prevalence of tobacco smoking in each province. The highest prevalence of smoking in women was related to the provinces of Boushehr (28.98%), Sistan and Balouchestan (24.42%), Kohkiluyeh and Boyerahmad (21.44%), Hormozgan (20.46%) and the lowest prevalence of Tobacco smoking in women was, respectively in the provinces of Ilam (1.39%), West Azarbaijan (2.52%), Ardabil (3.49%) and West Azarbaijan (3.71%). In the majority of the provinces of the country, except the provinces of Ardebil, Ilam, Chaharmahal Bakhtiari, North Khorasan, Semnan, Fars, Qom, Golestan, Lorestan, Markazi, Hamedan and Yazd, there was a statistically significant relationship between the social classes and the prevalence of tobacco use. The lower social classes are more likely to use tobacco ($P < 0.05$). In the study of the concentration index, the results of the study showed that the prevalence of smoking was higher in lower social economic classes in all provinces except Boushehr, Khorasan Razavi, Hormozgan, Golestan, Yazd and Sistan and Baluchestan provinces (Tab. IV, Fig. 2).

After determining the inequality, using the Multilevel method, the contribution of each of the determinants associated with tobacco smoking was analyzed in regard with the inequality creation between the two poor and rich groups.

The results of Model 1 that were performed on individual level showed that location, marital status, age over 35

Tab. III. Multilevel analysis, factors associated with socio-economic inequality in smoking (35,305 individuals of 337 county of 30 provinces).

Variable		Model 1 with individual			Model 2 with individual and county			Model 3 with individual and province and county		
		Coef	CI 95%	P-value	Coef	CI 95%	P-value	Coef	CI 95%	P-value
Location	City	1			1			1		
	Village	-0.25	(-0.35,-0.16)	0.0001	-0.24	0.0001	(-0.31, -0.09)	-0.2	(-0.31, -0.09)	**0.0001**
Age groups	< 20	1			1			1		
	20-34	0.11	(-0.03, 0.26)	0.12	0.03	0.7	(-0.12, 0.18)	0.03	(-0.12, 0.18)	**0.7**
	≥ 35	0.21	(0.04,0.38)	0.01	0.13	0.29	(-0.08, 0.27)	0.09	(-0.08, 0.27)	**0.29**
Occupation	Employed	0.16	(0.003, 0.32)	0.04	0.04	0.62	(-0.12, 0.21)	0.04	(-0.12, 0.21)	**0.62**
	Unemployed	0.07	(-0.1, 0.25)	0.4	-0.03	0.73	(-0.22, 0.15)	-0.03	(-0.22, 0.15)	**0.73**
Education	Illiterate	1			1			1		
	Elementary	-0.16	(-0.25, -0.07)	0.0001	-0.15	0.0001	(-0.27, -0.08)	-0.18	(-0.27, -0.08)	**0.0001**
	High school	1			1			1		
	Diploma	-0.06	(-0.13, 0.09)	0.77	-0.04	0.52	(-0.17, 0.06)	-0.05	(-0.17, 0.06)	**0.52**
	Academic	-0.22	(-0.35, -0.08)	0.001	-0.27	0.0001	(-0.44, -0.15)	-0.29	(-0.44, -0.15)	**0.0001**
Marital status	Single	1			1			1		
	Married	-0.03	(-0.11, 0.04)	0.37	-0.04	0.18	(-0.13, -0.02)	-0.05	(-0.13, -0.02)	**0.18**
Quantile economic	Poor	1			1			1		
	The poorest	-0.16	(-0.26, -0.05)	0.002	-0.11	0.02	(-0.22, -0.01)	-0.11	(-0.22, -0.01)	**0.02**
	Average	-0.24	(-0.36, -0.12)	0.0001	-0.19	0.007	(-0.3, -0.04)	-0.17	(-0.3, -0.04)	**0.007**
	Rich	-0.28	(-0.42, -0.14)	0.0001	-0.3	0.006	(-0.35, -0.06)	-0.20	(-0.35, -0.06)	**0.006**
	The richest	-0.22	(-0.37, -0.06)	0.007	-0.55	0.001	(-0.47, -0.11)	-0.29	(-0.47, -0.11)	**0.001**
Variance province										**0.56 (0.3,1.04)**
Covariance county, quintile							0.029 (-0.007, 0.06)			
Variance quintile							0.02 (0.01, 0.05)			
Variance county							0.23 (0.11, 0.48)			**0.56 (0.41, 0.75)**

Tab. IV. Prevalence of tobacco use in different provinces of the country based on Quantiles Socioeconomic and calculation of concentration index in provinces.

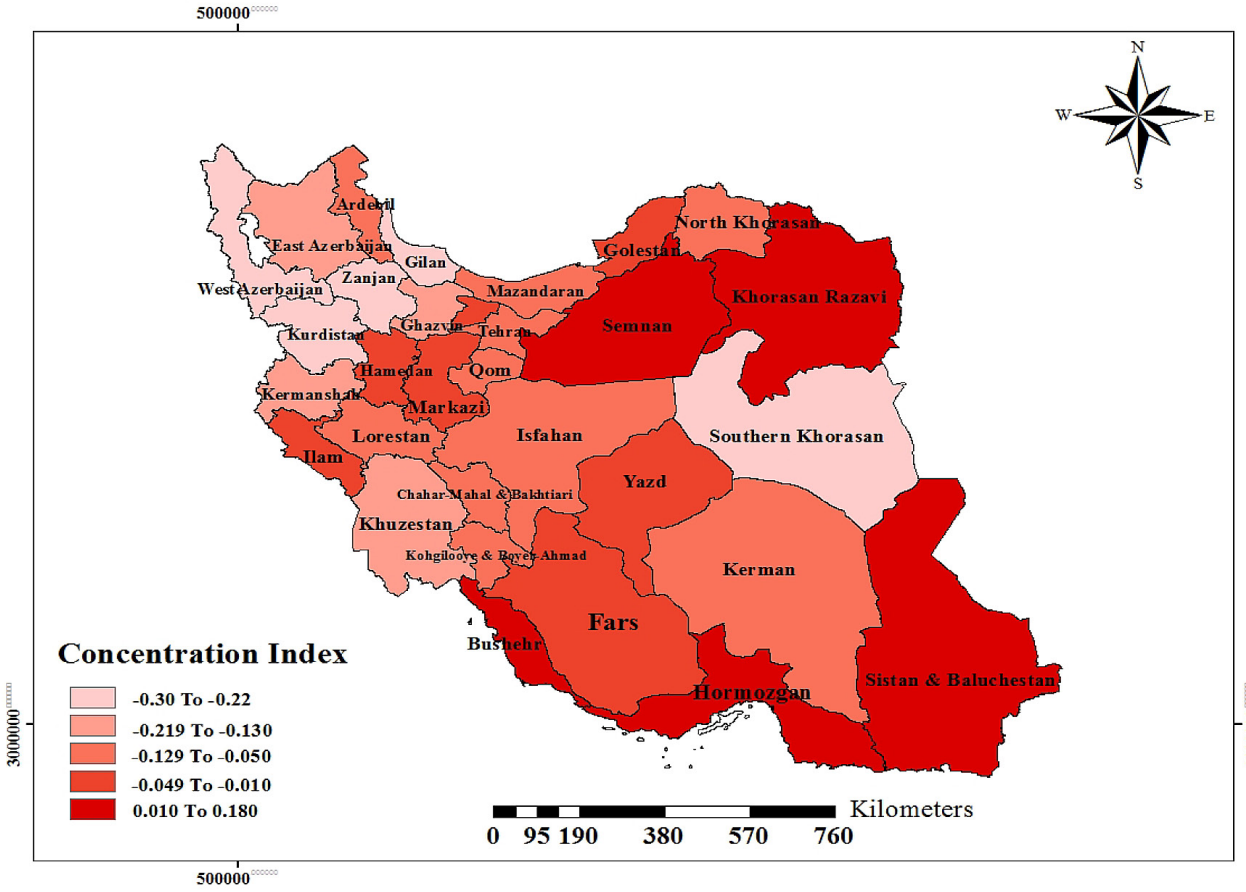
	Province	Prevalence of smoking	The prevalence of smoking on quintiles					OR (CI 95%)	Concentration Index (CI 95%)
			First	Second	Third	Fourth	Fifth		
1	East Azerbaijan	64 (3.7)	2 (3.13)	7 (10.94)	9 (14.06)	13 (20.31)	33 (51.56)	0.79 (0.64-0.97)	-0.16 (-0.31, -0.2)
2	West Azerbaijan	33 (2.5)	0 (0)	0 (0)	11 (33.33)	6 (18.18)	16 (48.48)	0.65 (0.48-0.88)	-0.29 (-0.51, -0.08)
3	Ardebil	20 (3.4)	0 (0)	4 (20)	6 (30)	3 (15)	71 (35)	0.87 (0.62-1.21)	-0.07 (-0.32, 0.17)
4	Isfahan	288 (11.8)	2 (0.69)	12 (4.17)	21 (7.29)	72 (25)	181 (62.85)	0.81 (0.71-0.93)	-0.11 (-0.17, -0.04)
5	Ilam	7 (1.4)	1 (14.29)	2 (28.57)	0 (0)	0 (0)	4 (57.14)	0.98 (0.57-1.69)	-0.03 (-0.45, 0.39)
6	Busher	129 (29)	8 (6.2)	16 (12.4)	16 (12.4)	20 (15.15)	69 (53.49)	1.21 (1.02-1.42)	0.08 (-0.002, 0.16)
7	Tehran	1020 (16.7)	7 (0.69)	30 (2.94)	78 (7.65)	154 (15.1)	751 (73.63)	0.78 (0.72-0.85)	-0.07 (-0.11, -0.04)
8	Chahar-Mahal & Bakhtiari	83 (17)	9 (10.84)	12 (14.46)	5 (6.02)	16 (19.28)	41 (49.4)	0.87 (0.74-1.03)	-0.1 (-0.21, 0.01)
9	Southern Khorasan	22 (5.2)	0 (0)	2 (6.09)	6 (27.27)	1 (4.55)	13 (59.09)	1.08 (1.04-0.95)	-0.22 (-0.47, 0.02)
10	Khorasan Razavi	436 (17.9)	38 (8.72)	55 (12.61)	93 (21.33)	91 (20.87)	159 (36.47)	1.08 (1.04- 0.04)	0.06 (0.01, 0.11)
11	North Khorasan	38 (9)	7 (18.42)	8 (21.05)	8 (21.05)	10 (26.32)	5 (13.16)	0.95 (0.75- 1.19)	-0.05 (-0.22, 0.12)
12	Khuzestan	119 (5.9)	10 (8.4)	13 (10.92)	15 (12.61)	19 (15.97)	62 (52.1)	0.79 (0.69-0.91)	-0.18 (-0.28, -0.07)
13	Zanjan	39 (8.9)	0 (0)	5 (12.82)	8 (20.51)	3 (7.69)	23 (58.97)	0.68 (0.51-0.89)	-0.3 (-0.49, -0.1)
14	Semnan	26 (6)	0 (0)	2 (7.69)	3 (11.54)	6 (23.08)	15 (57.69)	0.99 (0.67-1.44)	0.18 (-0.04, 0.4)
15	Sistan & Baluchestan	231 (24.4)	115 (49.78)	47 (20.35)	21 (9.09)	25 (10.82)	23 (9.96)	1.11 (0.05-1.15)	0.07 (0.008, 0.13)
16	Fars	295 (14.3)	24 (8.14)	41 (13.9)	43 (14.58)	50 (16.95)	137 (46.44)	0.99 (0.9-1.08)	-0.01 (-0.07, 0.05)
17	Gazvin	37 (7)	1 (2.7)	3 (8.11)	4 (10.81)	11 (29.73)	18 (48.65)	0.74 (0.55-1.01)	-0.14 (-0.23, 0.03)
18	Qom	70 (14.8)	0 (0)	7 (10)	11 (15.71)	10 (14.29)	42 (6)	0.94 (0.73-1.2)	-0.08 (-0.2, 0.04)
19	Kordestan	27 (4)	0 (0)	5 (8.52)	6 (22.22)	4 (14.81)	12 (44.44)	0.75 (0.56-1.01)	-0.22 (-0.45, 0.002)
20	Kerman	154 (13.2)	30 (19.48)	21 (13.64)	16 (10.39)	18 (11.69)	69 (44.81)	0.9 (0.81-1)	-0.1 (-0.19, -0.01)
21	Kermanshah	53 (5.8)	7 (13.21)	5 (9.43)	5 (9.43)	17 (32.08)	19 (35.85)	0.84 (0.68-1.03)	-0.13 (-0.29, 0.01)
22	Kohgilooye & Boyer-Ahmad	116 (21.4)	25 (14.97)	18 (15.52)	14 (12.07)	28 (24.14)	31 (26.72)	0.9 (0.79- 1.02)	-0.06 (-0.15, 0.02)
23	Golestan	59 (7.6)	8 (13.56)	14 (23.73)	13 (22.03)	6 (10.17)	18 (30.51)	1.03 (0.84-1.25)	0.01 (-0.12,0.16)
24	Gilan	120 (10.8)	8 (6.67)	14 (11.67)	11 (9.17)	25 (20.83)	62 (51.67)	0.68 (0.58-0.79)	-0.27 (-0.38, -0.17)
25	Lorestan	69 (8.7)	11 (15.94)	4 (5.8)	20 (28.99)	13 (18.84)	21 (30.43)	0.88 (0.74-1.04)	-0.11 (-0.24, 0.01)
26	Mazandaran	226 (13.3)	10 (4.42)	20 (8.85)	33 (14.6)	53 (23.81)	110 (48.67)	0.84 (0.75-0.94)	-0.11 (-0.18, -0.04)
27	Markazi	84 (13.5)	1 (1.19)	6 (7.14)	17 (20.24)	20 (23.81)	40 (47.62)	0.93 (0.76-1.15)	-0.02 (-0.14, 0.08)
28	Hormozgan	134 (20.5)	29 (21.64)	25 (18.66)	25 (18.66)	29 (21.64)	26 (19.4)	1.18 (1.04-1.33)	0.12 (0.03, 0.21)
29	Hamedan	112 (14.5)	10 (8.93)	21 (18.75)	15 (13.39)	23 (20.54)	43 (38.39)	0.97 (0.83-1.12)	-0.02 (-0.12, 0.07)
30	Yazd	47 (9.9)	3 (6.38)	4 (8.51)	6 (12.77)	9 (19.15)	25 (53.9)	1.14 (0.9-1.45)	0.006 (-0.15, 0.16)
31	Total country	4158 (12.24)	366 (8.8)	423 (10.1)	539 (12.9)	755 (18.16)	2075 (49.9)	0.9 (0.88- 0.93)	-0.07 (-0.09, -0.05)

years and the economic status of people were related with smoking ($P < 0.05$).

The results of Model 2, which was performed in the province, showed that the place of residence ($\beta = -0.21$, $P = 0.000$), the marital status of individuals ($\beta = -0.1$, $P = 0.015$), age over 35 ($\beta = -0.2$, $P = 0.0001$) and the economic class ($\beta = -0.29$, $P = 0.0001$) were related to tobacco smoking. From the results of the analysis, smoking in women living in the village was lower than that of women living in the city, so that women living in the village ($1-e^{-0.21}$) had 19% less chance of smoking). Also the chances of smoking in wives were more than single women, and single women had a lower incidence ($1-e^{-0.1}$) of tobacco use. The results showed that women aged 35 and over in comparison with women under the age of 20, had less smoking chance ($1-e^{-0.2}$) (19.0%). In the study of socio-economic classes in the province, people in higher economic classes had a lower chance of smoking than those in lower economic categories, so that people in the fifth quintile were 26% ($1-e^{-0.29}$) less likely to smoke than those in the first quintile.

The results of the survey at the county level (Model3) showed that at the level of the city, between the place of residence ($\beta = -0.18$, $P = 0.000$), the marital status of individuals ($\beta = -0.13$, $P = 0.003$), age over 35 years ($\beta = -0.23$, $P = 0.001$) and the economic class ($\beta = -0.3$, $P = 0.000$), a significant relationship existed with tobacco use. The results of the county-level analysis

Fig. 2. Dispersion of concentration index in different provinces of Iran.



also confirmed that smoking in women who live in the village was lower than that of women living in the city, so that women living in the village smoked tobacco 17% ($1-e^{-0.18}$) less than them, and the chance of smoking in wives was more than single women, and single women had a lower chance of smoking as 13 percent ($1-e^{-0.13}$). In the study of age groups in the county, the results of the study showed that women over the age of 35 had a chance of smoking 21% ($1-e^{-0.23}$) less than women under the age of 20. In the study of socioeconomic classes in the county level, the results of the analysis showed that those in higher economic classes were less likely to use tobacco than those in lower economic classes, so that people in the fifth quintile were less likely to smoke than those in the first quantile, as 26% ($1-e^{-0.3}$) (Tab. III).

Discussion

The prevalence of tobacco smoking as a major public health problem has been widespread in Iran and in the world [8]. Today, in most high-income countries, there is a negative trend in tobacco use, so smoking is more common in people with a lower socioeconomic status [15]. There is a negative social and economic slope in all age and gender groups, and this slope is poor in the age group under 40 and strong in the age group above 40 [26].

The results of this study showed that the prevalence of smoking in women was 12.24%. A significant relationship existed between tobacco smoking and place of residence, age groups over 35, marital status and economic variables. The concentration Index for tobacco was CI = -0.19 [95% CI (-0.20, -0.18)], which indicated the existence of inequality in tobacco smoking, and the rate of tobacco smoking was lower in the lower socioeconomic group. Multilevel analysis showed that marital status, age, and economic status of people were related to tobacco use. Model1 showed that the marital status of individuals (β = 0.206, P = 0.0001), age (β = -0.009, P = 0.0001) and economic class (β = -0.107, P = 0.0001) were related to tobacco smoking.

The present study showed that the prevalence of smoking in women aged 15-54 was 12.24%. The study by Bosdriesz et al. showed that the prevalence of smoking in women was 3.3% in Kongo, Senegal 2.1%, Brazil 18.9%, Mexico 14.4%, Kazakhstan 6.6%, Pakistan 6.7%, India 18.3% and South Africa 14.4% [8] . The results of Yang et al. in China showed that the prevalence of smoking in women was 6.7% [27]. This difference in the prevalence of tobacco smoking can be due to differences in culture, education level and socioeconomic status of people in different countries.

Significant social and economic inequalities exist in the health sector [28]. Socio-economic inequality in smoking is well known in previous studies [29]. Various studies have reported similar results that tobacco smoking is strongly linked to the household's economic situation [22, 30].

In the present study, the prevalence of smoking in Iranian women was unevenly distributed in the socio-economic classes of society. Also in this study, the concentration index for tobacco was CI = -0.19 [95% CI (-0.20, -0.18)], which indicates a higher prevalence of tobacco smoking in lower social classes. In studying the multilevel results, the results also showed that at the individual level, the province level, and the county level, people who at higher social classes were less likely to smoke, but in studying the multilevel results which were done separately in urban and rural areas of Iran, the results showed that a significant relationship existed between the socioeconomic status of women and the chance of smoking in urban areas, and people with higher social classes had lower chances of smoking. In rural areas there was no significant relationship between smoking and social classes.

Thakur et al., in India [28], the prevalence of tobacco smoking was higher in more deprived economic classes, which was consistent with the results of our study [29].

The study by Bosdriesz et al. showed that in Latin America and the Eastern Mediterranean countries, the prevalence of tobacco smoking among women in higher socio-economic classes was higher, which did not match the results of our study in Iran [8].

In lower socioeconomic classes, tobacco smoking costs replaces other essential health costs, which in the long run lead to serious complications, the incidence of illness and death due to the use of tobacco, and consequently enlarges the gap between economic and social inequalities [31].

The results of Badr's study in multilevel analysis showed that educational level does not cause socioeconomic inequality in smoking, while in the urban areas, the results of the multilevel analysis revealed that the chances of smoking in people with a high school education was higher than the illiterates.

In the study of Wang et al. [32], Sarkar et al. [33] and Hoebel et al. [34], there was a significant relationship between education level and smoking inequality, which was consistent with the results of our study.

From the present study, social economic inequality in tobacco smoking had a significant relationship with marital status of women, and the prevalence of smoking in wives was more than single women. These results were consistent with the results of the study by Si et al. [35] in Australia and Emamian et al. [15], in iran.

The results of this study showed that smoking inequality has a significant relationship with the age of women and the prevalence of tobacco smoking in all socioeconomic groups is higher among women aged over 35 than those under 35, which is consistent with the results of Corsi et al. in India [36], the study of Hamrah et al. [37], while the study of Yang et al. in Taiwan found an inverse relationship between age and tendency to smoking, which was not consistent with the results of this study [38].

Studies have shown that to effectively address inequalities in health new interventions are required which can reduce inequity by identifying and organizing inequities in social health factors and promoting appropriate interventions through public health programs [39, 40].

It is expected that in the future decades the mortality from tobacco smoking will increase, especially in developing countries, thus the need is more felt for taking effective measures such as advertising bans, increasing tobacco prices and providing effective solutions for people to quit smoking [40, 41].

Conclusions

The results of our study represented that inequality exists in the prevalence of smoking among women. In addition, the prevalence of smoking among women living in lower socioeconomic status is higher. Therefore, considering to the socio-economic factors and other factors related to smoking such as marital status, place of residence and age among women can help the government to run programs to reduce the prevalence of smoking in these women.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

EG carried out the design of the study and carried out analyzing the data and prepared the manuscript. GM and EG critically reviewed the manuscript, applied comments and finalized the manuscript. AKh and EG participated in the design of the study. All authors have read and approved the content of the manuscript.

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RESEARCH PAPER

Bacterial lysates (OM-85 BV): a cost-effective proposal in order to contrast antibiotic resistance

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Keywords

Antibiotic resistance • General practice • Bacterial lysates • Adults

Summary

Background. *Chronic Obstructive Pulmonary Disease (COPD) is one of the most frequent pathologies in which antibiotics are used because 50% of the exacerbations are attributable to a bacterial infection. The aims of our study were: i) to perform a meta-analysis on the efficacy of the bacterial lysate OM-85 BV in preventing acute exacerbations in patients with COPD; ii) to evaluate whether this preventive treatment can lead to significant savings for the National Health Service (NHS).*
Methods. *A systematic research was conducted in the electronic database MEDLINE (PubMed) in June 2017-July 2020, collecting evidences without time restrictions. Only randomized controlled trials (RCTs) were included. The keywords used were "OM 85 BV AND chronic bronchitis" and "OM 85 BV AND COPD". A cost-effectiveness analysis (CEA) was performed considering the costs for a treatment with OM-8BV, the costs for the treatment of an acute exacerbation and the number of prevented exacerbations.*
Results. *59 publications were found, but the meta-analysis was conducted on 13 studies that met the inclusion criteria. OM-85 BV is responsible of a statistically significant reduction in the mean number of COPD exacerbations ($p < 0.01$; WMD = -0.86; CI 95%: -1.38, -0.34) and in the days of antibiotic therapy ($p < 0.01$; WMD = -9.49; CI 95%: -11.93, -7.05). The cost-effectiveness ratio with a negative value is in favor to treatment.*
Conclusions. *OM-85 BV is effective in reducing exacerbations, and could lead to significant savings for the NHS. Moreover, reducing the number of exacerbations it could avoid an over-use of antibiotics and the consequent antibiotic resistance.*

Introduction

The development and use of antibiotics, since the second half of the twentieth century, has revolutionized the approach to the treatment and prevention of infectious diseases and of infections considered incurable in the past. However, although resources and energy have been invested in order to increase the knowledge about the mechanisms of resistance and in the search for increasingly effective molecules, the antibiotic resistance is currently faster than the development of new molecules [1]. Antibiotic resistance is spread anywhere in the world, compromising the treatment of infectious diseases and undermining many other advances in health and medicine [2-5].
One of the most frequent conditions of antibiotic use is the Chronic Obstructive Pulmonary Disease (COPD). It is in fact known that the development of an infection in the bronchial tree is one of the most frequent causes of COPD exacerbations. Furthermore, more than half of the exacerbations are attributable to a bacterial infection [6].
The evidence shows that the use of antibiotics and corticosteroids strongly reduce the hospitalization rate during exacerbations [7] and today the tendency is to prefer broad-spectrum antibiotics, given the increasing antibiotic resistance shown by *Streptococcus pneumoniae* and *Haemophilus influenzae* [6]. However, multi-drug resistant bacteria (MDR) are increasingly common, especially in cases of exacerbation of the disease requiring intubation and mechanical ventilation. In fact t is well known that an overuse and misuse of antibiotics is responsible for most of the recent increases in antibiotic resistance [8].
The preventive use of bacterial lysates (such as OM-85 BV) in reducing exacerbations in patients with COPD is well documented in several randomized controlled trials [9]. OM-85 BV is the product of alkaline proteolysis of the following bacteria: *Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus viridans* and *Moraxella catarrhalis* [10]. The effects of OM-85 BV in patients with COPD and the cost effectiveness of this preventive treatment has been already investigated by other authors [9, 11]. So, the aims of the present study were to update what has been already published in literature and, therefore, i) to perform a meta-analysis on the efficacy of OM-85 BV in preventing acute exacerbations in patients with COPD and ii), to evaluate whether this preventive treatment can lead to significant savings for the National Health Service (NHS) thanks to an absolute reduction in the number of disease exacerbations.

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Methods

Search strategy

A systematic research of peer-reviewed literature was conducted in the electronic database MEDLINE (PubMed) in the period June 2017-July 2020, collecting all the evidences without time restrictions.
The keywords used were "OM 85 BV AND chronic bronchitis" and "OM 85 BV AND COPD".

Inclusion criteria

Only Randomized Controlled Trials (RCTs) conducted on an adult population affected by COPD were considered suitable for the meta-analysis. Articles were included only if they contained clear and statistically assessable data on: i) average or absolute number of acute exacerbations; ii) total days of antibiotic therapy; iii) days of hospitalization. Other data useful to demonstrate or not the efficacy of OM-85 BV have been registered.
Studies that provided ambiguous or insufficient data were excluded.
Only studies written in English and French have been analyzed.

Study selection and data extraction

Studies were selected in a 2-stage process. First, titles and abstracts from electronic searches were scrutinised and then full manuscripts were analysed to select the eligible manuscripts according to the inclusion criteria. A further manual research analyzing the references of the articles was then carried out to avoid losing publications of a certain importance.

Statistics

Statistical analysis was performed using Review Manager Version 5.2 (The Cochrane Collaboration, Software Update, Oxford, London).
Continuous variables have been described as averages and standard deviations (SD). The analysis of continuous variables was performed using the weighted mean difference (WMD), which indicates the difference between groups based on sample size. The significance level was set at $P < 0.05$.
To evaluate heterogeneity, the Higgins heterogeneity test or I^2 test was used. The value of I^2 describes the percentage of variability due to heterogeneity rather than a simple sampling error. In fact, I^2 does not depend on the small number of the sample. "Low" heterogeneity is considered when the I^2 value is less than 30%, moderate if between 30 and 50%, high if higher than 50%. When heterogeneity is described by an I^2 above 30% it was decided to report the models with both "fixed" and "random" effects in order to emphasize the role of heterogeneity between studies. The difference between the two models consists in excluding or including the heterogeneity in the calculation of the overall estimate: the one with fixed effects excludes any heterogeneity, while the random effects model includes it; therefore, the overall estimate thus obtained will have wider confidence intervals.
In the case of low heterogeneity, both models give very similar results and for this reason it was decided to present the results only with random effects that are more conservative [12].
Specifically, variables analyzed through meta-analysis were: average and mean number of acute exacerbations, days of antibiotic therapy and of hospitalization, Severity score (the COPD severity score is based on responses to survey items that comprise five domains of COPD severity; the possible COPD severity score range is 0 to 35, with higher scores reflecting more severe disease) [13].

Cost-effective analysis (CEA)

The cost-effective analysis was performed following the same methodology used by Bergemann et al. [9]. The estimation of cost for the management of severe or non-severe exacerbation was based on the results of an observational study evaluating the costs of chronic obstructive pulmonary disease in Italy (ICE Study - Italian Costs for Exacerbations in COPD) [14].
Dividing the average annual direct health cost of a patient with exacerbations (€ 2,423) by the average number of exacerbations [15, 16] the average cost of an exacerbation was calculated as equal to € 1,730. The average cost of a non-severe exacerbation was estimated by applying the same calculation methodology, but excluding the amount associated with hospital admission; it was thus obtained an amount of € 400.
For the cost-effectiveness analysis (CEA) the following formulas have been applied:

$$CM = CBV - (CTAE * PAE)$$

$$CER = [CBV - (CTAE * PAE)]/PAE$$

Where CM indicates the marginal costs, CER indicates the cost-effectiveness ratio (ie costs for each single prevented exacerbation), CBV indicates the costs for a treatment with OM-85 BV, CTAE indicates the costs for the treatment of an acute exacerbation and PAE indicates the number of prevented exacerbations.

Results

Bibliographic research yielded 59 publications. After the analysis of the titles and abstracts, 36 studies were excluded: 9 because they were duplicates, 6 because they were review, 16 because they focused on outcomes not in line with the present study, 9 because in other languages (2 in Russian, 3 in Polish, 1 in Romanian, and 3 in German). Of the 19 remaining articles, the full text was analyzed: 1 article was excluded because review, 1 excluded because editorial, 9 excluded because they focused on a population or outcome not in line with the study. After the analysis of the bibliographies it was decided to add, for completeness, 4 congress abstracts containing original data and 1 full text. The overall analysis was therefore conducted on 13 studies (Fig. 1). [17-29].

The main characteristics of the studies included in the review with authors, year of publication, description of the treatment protocol, observation period, cases and controls and outcomes is shown in Table I.

The studies have been conducted between 1981 and 2015 and involved a total of 1,366 patients undergoing treatment (range 33-192) and 1,282 undergoing placebo (range 20-192). The treated were aged 48.1-82 years, controls 48.4-82 years.

In 10 of the studies taken into consideration, the observation period was 6 months, in one 10 weeks, in one 22 weeks and in the last study 1 year.

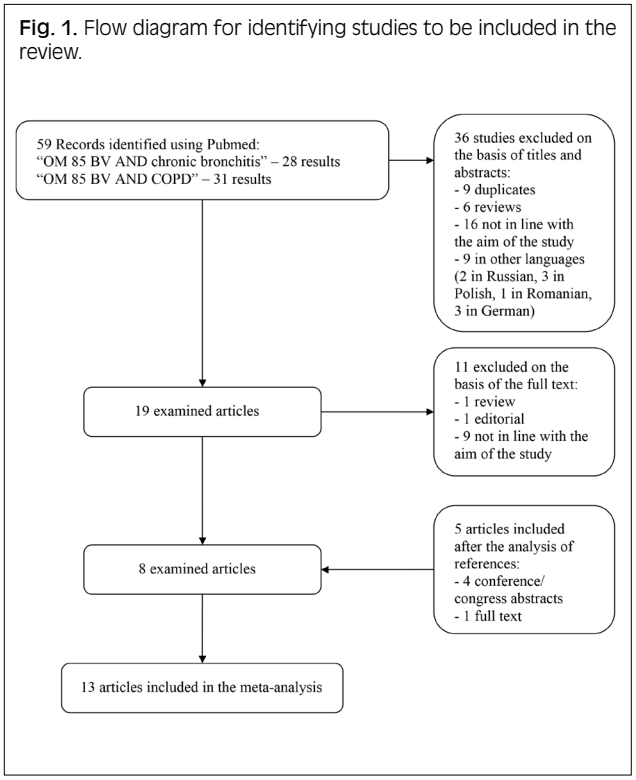


Fig. 1. Flow diagram for identifying studies to be included in the review.

Average number of exacerbations (Fig. 2)

The meta-analysis conducted on the 6 studies that reported these data demonstrates, using the random effects model, that OM-85 BV treatment is responsible for a statistically significant reduction in the average number of COPD exacerbations in the observation period ($p < 0.01$; WMD = -0.86; 95% CI: -1.38, -0.34).

Absolute number of exacerbations (Fig. 3)

The meta-analysis conducted on the 6 studies reporting these data shows, using the random effects model, that OM-85 BV treatment is a protective factor against the absolute number of COPD exacerbations in the observation period ($p < 0.01$; RR = 0.79; CI 95%: 0.70, 0.90).

Days of antibiotic therapy (Fig. 4)

The meta-analysis conducted on the 4 studies reporting these data shows, using the random effects model, that OM-85 BV treatment is responsible for a statistically significant reduction in antibiotic therapy days in the observation period ($p < 0.01$; WMD = -9.49; CI 95%: -11.93, -7.05).

Hospitalization days (Fig. 5)

The meta-analysis conducted on the 3 studies reporting these data shows, using the random effects model, that OM-85 BV treatment is responsible for a non-statistically significant reduction in hospitalization days in the observation period ($p = 0.12$; WMD = -7.28; CI 95%: -16.39, 1.83).

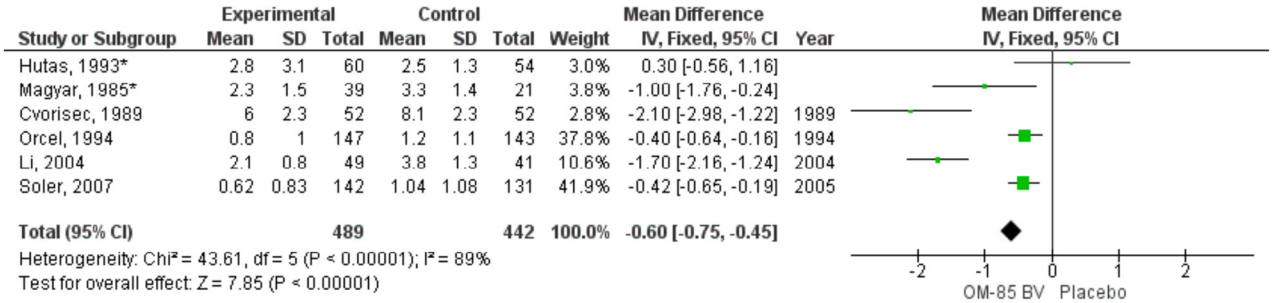
Severity Score (Fig. 6)

The meta-analysis conducted on the 2 studies that reported these data shows, using the random effects model, that the treatment with OM-85 BV is responsible for a non-statistically significant reduction of the Severity Score ($p = 0.09$; WMD = -0.72; CI 95%: -1.55, 0.11).

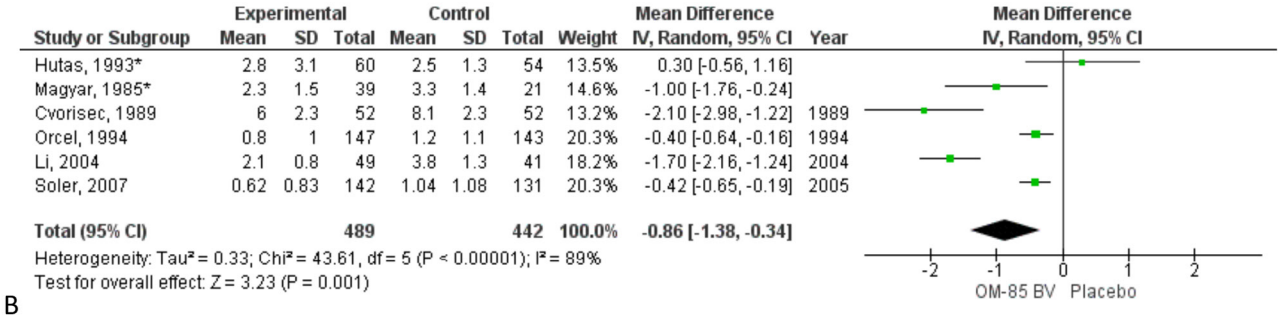
Tab. I. Main characteristics of the studies included in the systematic review (T = treatment, P = placebo; n.r. = not reported; *= conference abstract; SD = standard deviation; RCT = randomized controlled trial; A = 1 capsule per day for 30 days, 1 month without treatment, and then 1 capsule/day for 10 days/month for 3 consecutive months; B = 1 capsule for 10 days/month for 3 consecutive months).

Author, year of publication	Study design	Treatment protocol	Observation period	Treated patients (T)	Placebo patients (P)	Selected sample	Age (T)	Age (P)	Mean number of acute exacerbations (T)	Mean number of acute exacerbations (P)	Absolute number of acute exacerbations (T)	Absolute number of acute exacerbations (P)	Total days of antibiotic treatment (T)	Total days of antibiotic treatment (P)	Days of hospitalization (T)	Days of hospitalization (P)	Severity score (T)	Severity Score (P)
Tang, 2015	RCT	B	22 weeks	183	171	Age 40-75 years	63.2 (SD 8.9)	63.0 (SD 9.4)	n.r.	n.r.	84	88	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Soler, 2007	RCT	A	6 months	142	131	Age 40-75 years	57.3 (SD 1.6)	57.9 (SD 1.7)	0.62 (SD 0.83)	1.04 (SD 1.08)	96	121	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Orcel, 1994	RCT	B	6 months	147	143	> 65 years	82 (SD 7)	82 (SD 8)	0.8 (SD 1.0)	1.2 (SD 1.1)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Li, 2004	RCT	B	1 year	49	41	Age 55-82 years	67 (SD 4)	65 (SD 5)	2.1 (SD 0.8)	3.8 (SD 1.3)	n.r.	n.r.	16.7 (SD 7.0)	28.6 (SD 6.5)	21.3 (SD 6.1)	39.6 (SD 8.7)	1.6 (SD 0.6)	2.7 (SD 0.8)
Debbas, 1990	RCT	B	6 months	198	198	Mean age 82 years	81.8 (SD 8.0)	81.89 (SD 8.2)	n.r.	n.r.	113	156	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Cvorisec, 1989	RCT	A	6 months	52	52	Age 20-69 years	48.1 (SD 3.5)	48.4 (SD 3.1)	6 (SD 2.3)	8.1 (SD 2.3)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Collet, 1997	RCT	B	6 months	191	190	Adult patients	65.3 (SD 7.7)	66.9 (SD 7.7)	0.57	0.57	85	83	n.r.	n.r.	6.5 (SD 7.9)	10.2 (SD 14.4)	n.r.	n.r.
Magyar, 1985*	RCT	A	6 months	39	21	Adults	51.7 (SD 12.4)	52.8 (SD 8.8)	2.3 (SD 1.5)	3.3 (SD 1.4)	n.r.	n.r.	32.3 (SD 29.1)	52.4 (SD 28.0)	n.r.	n.r.	n.r.	n.r.
Orlandi, 1985*	RCT	A	6 months	45	40	Adults	61.4 (SD 8.8)	59.6 (SD 14.5)	n.r.	n.r.	n.r.	n.r.	4.8 (SD 5.6)	11.3 (SD 9.4)	n.r.	n.r.	n.r.	n.r.
Hutas, 1993*	RCT	A	6 months	60	54	Adults	52.8 (SD 11.9)	51.1 (SD 13.0)	2.8 (SD 3.1)	2.5 (SD 1.3)	n.r.	n.r.	9.6 (SD 1.3)	18.6 (SD 2.4)	n.r.	n.r.	n.r.	n.r.
Messerli, 1981	RCT	B	6 months	35	20	Adults	54.6	55.5	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.11	1.25
Tang, 2011*	RCT	B	10 weeks	192	192	Adults	n.r.	n.r.	n.r.	n.r.	45	64	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Xinogalos, 1993	RCT	A	6 months	33	29	Adults	56.03 (SD 12.67)	59.75 (SD 12.89)	n.r.	n.r.	13	16	n.r.	n.r.	2.67 (SD 1.84)	2.83 (SD 1.96)	1.33 (SD 1.27)	1.58 (SD 1.26)

Fig. 2. Meta-analysis of the average number of exacerbations.



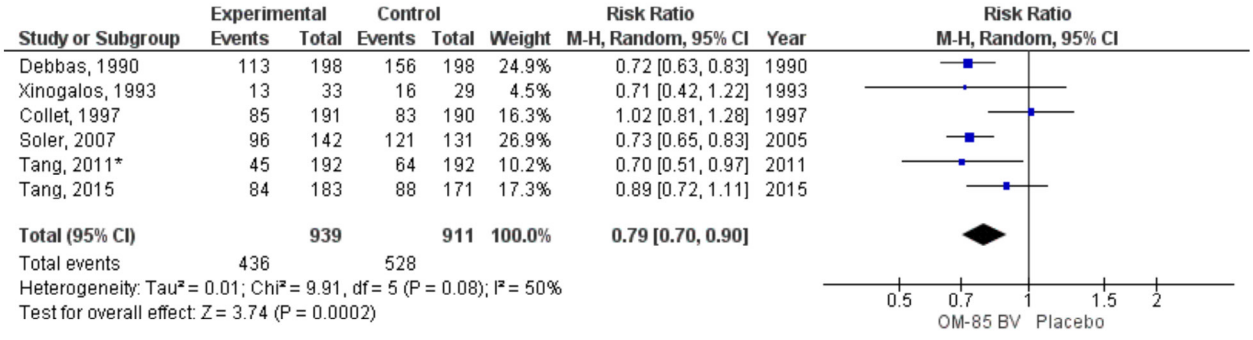
A



B

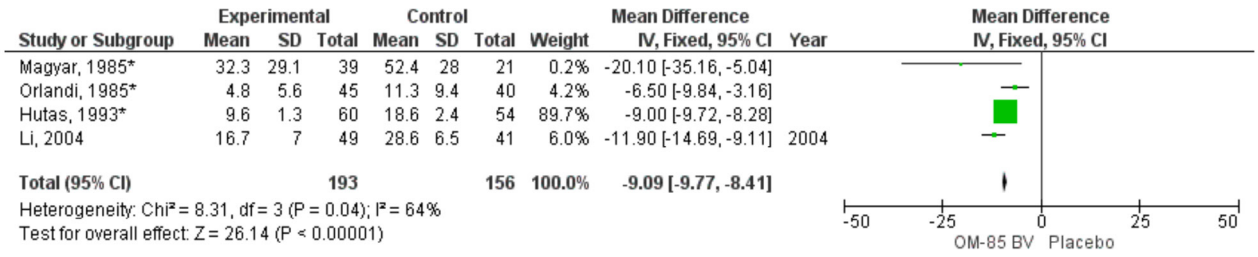
Fig. 3. Meta-analysis of the absolute number of exacerbations.

A

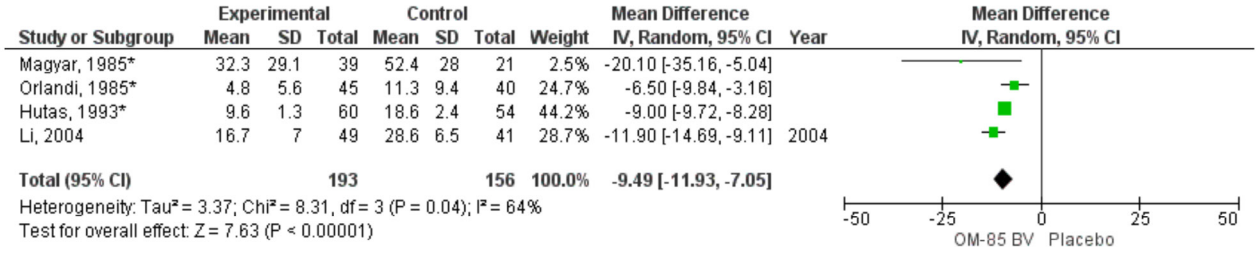


B

Fig. 4. Meta-analysis of the days of antibiotic therapy.

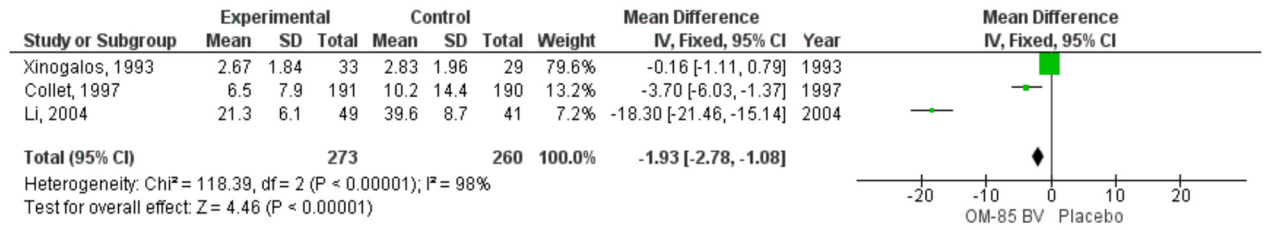


A

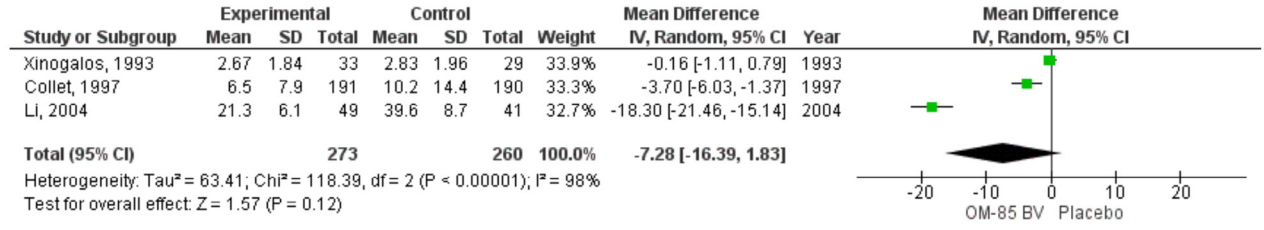


B

Fig. 5. Meta-analysis of the hospitalization days.



A

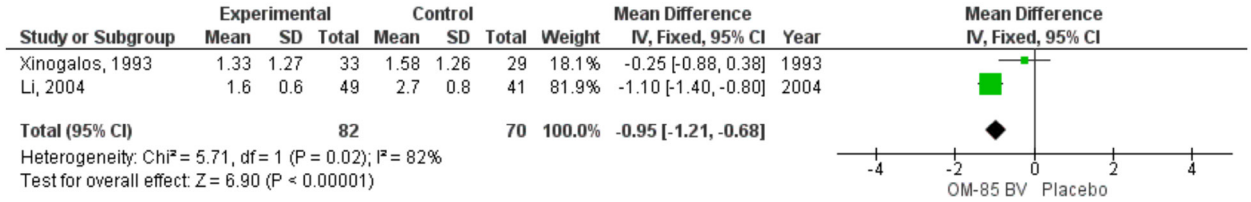


B

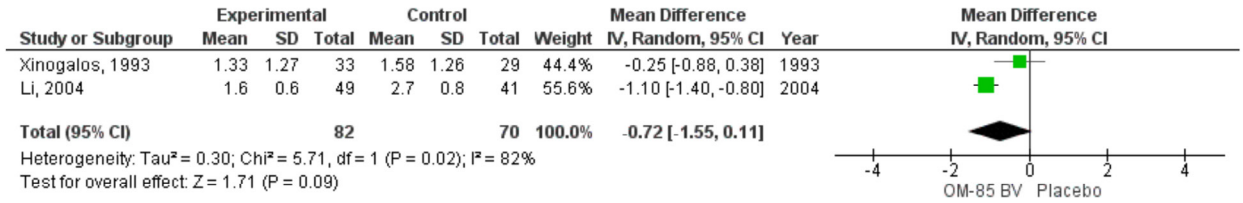
Cost-effective analysis

The OM-85 BV lysate recruitment protocols, as described in the studies included in our study, are two: i) one tablet a day of lysate for 30 days, followed by a period of 1 month suspension and then a 3 month period in which one tablet is taken a day only for the first 10 days of the month; ii) one tablet a day for the first 10 days of the month for three months. Considering that the price of OM-85 BV adults 30 tablets is equal to € 25 per pack[30], a treatment can cost from € 25 to € 50. The summary of the cost-effectiveness analysis is shown in the following figures (Figs. 7, 8).

Fig. 6. Meta-analysis of the Severity Score.



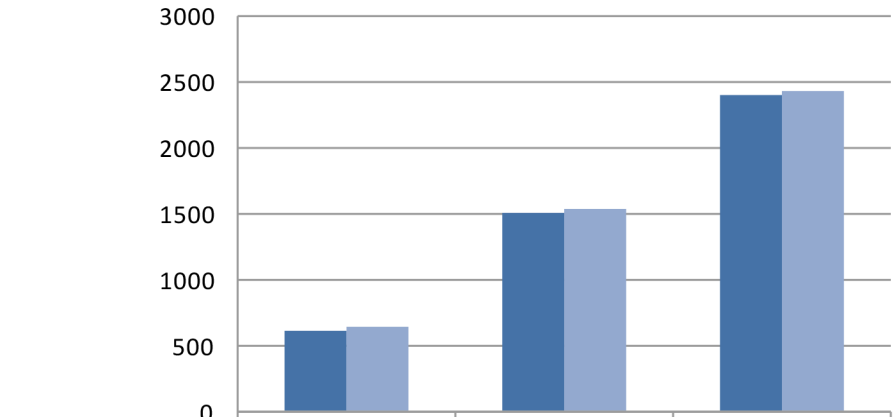
A



B

Fig. 7. Cost-effectiveness analysis: (**A**) savings, in Euros, on an exacerbation with Hospitalization, (**B**) CER.

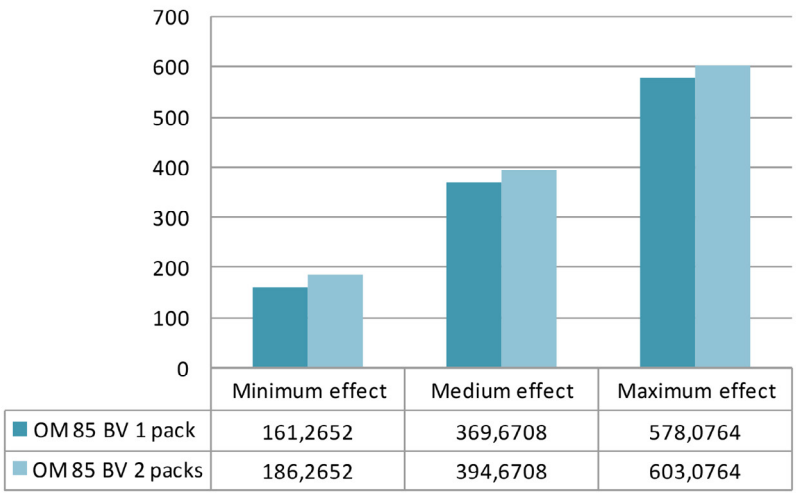
A



B

	Minimum effect	Medium effect	Maximum effect
OM-85 BV 1 pack	-1804.31	-1759.85	-1748.9
OM-85 BV 2 packs	-1877.84	-1788.92	-1767.01

Fig. 8. Cost-effectiveness analysis: (**A**) savings, in Euros, on an exacerbation without hospitalization, (**B**) CER



A

	Minimum effect	Medium effect	Maximum effect
OM-85 BV 1 pack	-474.309	-429.85	-418.896
OM-85 BV 2 packs	-547.839	-458.92	-437.012

B

Discussion

Acute exacerbations have a significant negative impact on several aspects of COPD, including the rapid decline in lung function, poor prognosis, impaired quality of life, and increased socioeconomic costs. Various studies have extensively shown that the prevention of acute recurrent exacerbations is able to slow down the progression of COPD [31]. Bacterial infections are the most common cause of exacerbation of the disease, contributing to 40% of all exacerbations [32]. This is the reason why the use of bacterial vaccines, such as those containing pneumococcal polysaccharides, is a highly recommended strategy for managing COPD [15].

The administered orally OM-85 BV (bacterial lysate obtained from eight pathogenic bacteria), is effective in preventing respiratory tract infections in adults and children.

In our study we conducted a meta-analysis of randomized clinical trials comparing the efficacy of OM-85 BV *vs* placebo. The most important parameters were the number of exacerbations in the months following the treatment and the days of antibiotic therapy. From the meta-analysis of the analyzed studies, OM-85 BV treatment is responsible of a statistically significant reduction in the mean number of COPD exacerbations in the observation period ($p < 0.01$; WMD = -0.86; CI 95%: -1.38, -0.34) and also a statistically significant reduction in days of antibiotic therapy ($p < 0.01$; WMD = -9.49; CI 95%: -11.93, -7.05). The cost-effectiveness analysis gathered the three elements: the cost of treatment with the lysate, the number of prevented exacerbations and the average cost of each exacerbation (for completeness divided into "with admission" and "without admission"). Considering an average of 0.86 prevented exacerbations, treatment with OM-85 BV is responsible (applying the formula for calculating marginal costs) of a saving of € 1,513 in the case of exacerbation requiring hospitalization, and € 369 in the case of exacerbation that does not require hospitalization. The meta-analysis and cost-effectiveness analysis therefore confirm not only the efficacy of OM-85 BV in reducing the exacerbations, but highlight further positive effects of the lysate: in fact it allows a considerable saving for the National Health System (considering the almost 3 million patients affected in Italy) [33] and can improve the quality of life by reducing the number of infectious episodes. Reducing the number of exacerbations also slows the further progression of the disease towards respiratory failure, and avoids over-use of antibiotics and the consequent antibiotic resistance. The cost-effectiveness ratio with a strongly negative value is remarkably favorable to treatment.

The mechanisms that explain the effectiveness of OM-85

BV are not totally understood: it is supposed that it acts on the cells of the immune system and on the mediators of inflammation [34-36].
The theoretical basis for oral immunization is that the administered bacterial fractions can be recognized by the gut-associated lymphoid tissue (GALT), then they could activate the bronchial-associated lymphoid tissue (BALT) through cooperation and cellular traffic between these two systems [37]. It should be remembered that the intestine is the largest organ producing antibodies and, in humans, more than 80% of activated B cells reside in the intestinal mucosa. Once the respiratory tract is reached, the B cells, transformed into plasma cells, release specific IgA which represent the most important form of defense against respiratory tract infections [38]. In addition, the upregulation of the expression of the adhesion molecules of the phagocytes, the increase in the number and activity of T helper with an increase in the production of interferon gamma and CD4 +, and the increase in antibodies in the respiratory tract represent further mechanism activated after lysate administration [11, 36].
Mauel et al. [35] demonstrated that lysates are able to increase the production of superoxide and nitrite anion by alveolar macrophages, enhancing microbicidal and cytolytic activity. In the same way they enhance the production of proinflammatory cytokines (tumor necrosis factor (TNF-)α, IL-8, IL-6, monocyte chemotactic protein (MCP) -1).
Finally, lysates are able to stimulate a Th1 response and increase the CD4 + / CD8 + cells ratio in the airways [39].
Our study has several limitations: as already highlighted by Pan et al. in their previous meta-analysis [11], the enrolled patients were very different from each other (by age, ethnicity and stage of the disease), and this can contribute to increasing the risk of selection bias; the index of heterogeneity was high; for the hospitalization days and the Severity Score only few studies reported analyzable data.
Moreover, one important limitation is the exiguous number of new studies on this topic that could add only a limited contribution to what has been already published in previous meta analyses [9, 11].
It is also important to say that vaccinations (such as the influenza vaccine) could prevent some exacerbations in patients with COPD [40-42]: in fact, influenza is a frequent cause of exacerbations of chronic obstructive pulmonary disease (COPD) [43].
It is therefore possible to create an overlap between the protection provided by the influenza vaccine and that provided by the OM-85 BV which may alter the estimate of its real effectiveness.

Conclusions

Exacerbations in patients with COPD are associated with a more rapid deterioration of lung function, reduction of quality of life, and a prolongation of days of hospitalization and antibiotic therapy.

The meta-analysis conducted on randomized clinical trials in which the effect of lysate was compared with placebo partially updated what has been previously published in literature and confirmed the protective capacity of OM-85 BV against bacterial exacerbations in patients with COPD. The cost-effectiveness analysis subsequently carried out highlighted the considerable savings for the National Health Service deriving from the use of the lysate and, secondly, the reduction in the use of antibiotics, which are normally used in bacterial infections, can represent an additional strategy to contain the phenomenon of antibiotic resistance.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

GT had the idea of the study, collected data and wrote the article. GM and NN helped to conceptualize the ideas and to write the article

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Review

Epstein-Barr Virus (EBV) acute acalculous cholecystitis in an immunocompromised adult patient: a case report and a literature review through the history of a neglected clinical presentation

CORRIGE

Review

Epstein-Barr Virus (EBV) acute acalculous cholecystitis in an immunocompromised adult patient: a case report of a neglected clinical presentation and a literature review over the last 30 years


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