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LETTER TO THE EDITOR

Living with COVID-19: could SARS-CoV-2 infection present a ping-pong effect?

ALESSANDRO LAGHI¹, DONATO DI NUNNO¹, ALESSANDRO AMBROSIO²,
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Keywords

COVID-19 • SARS-CoV-2 • RT-PCR • False-negative • Swab

Dear Editor,

on March 11 2020, the World Health Organization (WHO) declared pandemic the disease caused by a novel coronavirus named SARS-CoV-2 (Severe Acute Respiratory Syndrome-CoronaVirus-2) that still now causes symptoms like fever, cough, sore throat, breathlessness, vomiting among others. The disease is mild in most people; in some patients (usually the elderly and those with comorbidities), it may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction [1]. Many people are asymptomatic, but able to transmit the infection to others [2]. Mortality estimated rate is about 5.6% [3]. Coronaviruses are enveloped, positive single-stranded large RNA viruses that infect humans, but also a wide range of animals. SARS-CoV-2 apparently succeeded in making its transition from animals to humans on the Huanan seafood market in Wuhan, China [4].

For the previous reasons, it is extremely important to individuate SARS-CoV-2 reservoirs: real-time fluorescence quantitative reverse transcriptase polymerase chain reaction (reverse transcriptase-polymerase chain reaction, RT-PCR) is the gold standard method in order to detect the infection [5]. A study suggests that the favorite biological sample should be sputum and nasopharyngeal swabs that minimize as much as possible the risk of false negative results (respective sensibility of 48.68 and 38.13%) [5]. Other authors propose oropharyngeal swab as a procedure less sensible than nasopharyngeal [6].

In Italy, we normally run both nasopharyngeal and oropharyngeal swabs in every patient who suffers from symptoms suspicious for COVID-19 [7]. In our country, serological tests are not diffusely available and nobody demonstrated that the presence antibodies against SARS-CoV-2 can protect from a reinfection [8, 9]. So patients, who are hospitalized or quarantined because of SARS-CoV-2 infection, in order to interrupt the confinement, have to obtain two consecutive negative results for virus research in oropharyngeal and nasopharyngeal swabs, using RT-PCR [7].

Here we report the peculiar history of a patient, now still hospitalized in Celio Hub Covid-Hospital, in Rome, Italy.

The requirement of informed consent was waived since patient information was anonymized to ensure privacy.

A 30-year-old woman, no smoker, with no comorbidities, no allergies and no previous hospitalization, started feeling fever (37.5°C), cough, and shortness of breath, anosmia and ageusia on 23rd March 2020. She was not taking any drugs, except for birth control pill. She is a medical doctor and she worked in February and March 2020 in some nursing home care near Milan, in the north of Italy. On 27th March she underwent oropharyngeal and nasopharyngeal swabs: the test result was positive, so she started the quarantine period at home alone. Then, her boyfriend, that lived with her, had smart-worked since 10th March 2020 and had not developed symptoms, immediately left their house and started living without any contact in his own apartment, but he has never undergone a PCR test.

Without using any therapy, the young woman recovered in one week without any social interaction and she underwent new swabs on 14th and 15th April with negative results. All the three swabs were carried out in Milan by the same nurse. On 16th April she met again her boyfriend. Since she had to work in Rome, the couple travelled to the Italian capital and there she felt symptoms again: in particular, temperature (37.7°C) and fatigue. No cough, sore throat, or vomiting were reported.

On 17th April she and her boyfriend underwent oropharyngeal and nasopharyngeal swabs: all of them were positive and they were precautionarily hospitalized.

On admission, physical examination of the young woman revealed normal vital signs with oxygen saturation of 99% breathing ambient air. Lung auscultation revealed no rhonchi. Blood routine tests, liver function, renal function, electrolytes were normal. Serological tests for SARS-CoV-2 were not run [9]. Now she is still in the hospital and she is taking only enoxaparin 4,000 IU/die.

Since RT-PCR test serves as the gold standard method to confirm the infection of SARS-CoV-2 and leads the decision of patients' discharging or quarantine interruption, false-negative results could hinder the prevention and control of the epidemic.

Some studies found a potentially high false negative rate of RT-PCR testing for SARS-CoV-2 in hospitalized patients with COVID-19 [5, 7]. In our case, the result of the two consecutive negative swabs should be trusted even because the personnel and the laboratory were the same of the first positive result. Nevertheless, the RT-PCR results showed a fluctuating trend [10], but nobody demonstrated that recurrence of RT-PCR positivity for the novel coronavirus is not associated with new risk of being a virus spreader again, even if asymptomatic. Additionally, nobody demonstrated that all the recovered patients cannot get the symptomatic (or poorly symptomatic) infection again, even with a shorter incubation time. In our situation, we cannot rule out that our patient has been infected by her boyfriend who previously got the virus from her, in a ping-pong effect. The recurrence rate in recovered – suggested by two consecutive negative swabs and absence of clinical symptoms [7] – patients after the hospital discharging or the end of quarantine is unknown and should be investigated. Further studies are needed in order to understand deeper the clinical and the epidemiological features of the virus. Several countries in the world, after a necessary period of lock down, are starting again their working activities and the infective risk will increase again in the next weeks. Since we are not able to rule out the risk of reinfection in patients clinically recovered and the possibility that they can spread the virus again, we should treat every citizen as infected and contagious, even if clinically recovered, until proven otherwise. In conclusion, we must be prepared to a future in which social distancing, face masks and virtuous sanitization procedures will be mandatory.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

AL: Data Curation, Investigation, Writing - Original Draft Preparation. DDN: Data Curation, Writing - Original Draft Preparation. AA: Investigation, Visualization. FRB: Data Curation, Writing - Original Draft Preparation. NP: Data Curation, Visualization. AM: Visualization, Writing - Review & Editing. CC: Supervision, Writing - Review & Editing. GM: Conceptualization, Supervision. BM: Conceptualization, Project Administration, Supervision.

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LETTER TO THE EDITOR

The possible impact of SARS-CoV-2 on neglected tropical diseases in Europe: the out of spotlights emerging of schistosomiasis

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Keywords

SARS-CoV-2 • Neglected diseases • Tropical diseases • Europe • Schistosomiasis

Dear Editor,

The novel SARS-CoV-2 coronavirus and the resulting infection, CORONA VIRUS Disease 19 (COVID-19), is posing an enormous threat to healthcare, economy and society [1]. Globally, over the last year, the efforts of most Nations and non-governative health care organizations have been directed towards the containment of the infection, the reorganization of health care systems, the research for treatments and vaccines against this disease. COVID-19 has been under spotlights regarding every aspect of our life during the whole 2020, monopolizing the attention of the media as well as the provider of health care policies. Needless to say that when there is something under spotlights, there must be some other things out of these lights. In particular, little is known about how COVID-19 is impacting the millions of people worldwide with neglected diseases.

Over the last decades, Europe is facing a slow increasing incidence of neglected tropical diseases that were previously considered as uncommon [2]. In particular, schistosomiasis is one of the neglected diseases that has increasingly been reported in healthcare facilities in Europe. Schistosomiasis, also known as snail fever or bilharzia, is a parasitic infection that has evolved together with the humankind and its presence were already documented in Egyptian medical papyri, Assyrian medical texts and some Hebrew Bible passages [3]. Schistosomiasis is a disease spread by contact with fresh water, in endemic areas, contaminated with parasitic flatworms called schistosomes. Literature has linked bladder cancer, mostly squamous cell type, with long-term *Schistosoma haematobium* infections.

Until few years ago, urogenital schistosomiasis was not endemic in Europe. However, in the last decade, the first cases of autochthonous outbreak have been reported in Corse (France) and a few hundred cases have been diagnosed since then [4]. Similarly, patients suffering from schistosomiasis, mostly migrants or travelers returning from endemic areas, have been diagnosed in numerous hospitals in other European countries, such as Italy, Spain, Germany and Slovakia [5-8]. In Europe, schistosomiasis is an underreported disease

that can certainly be defined as neglected. There is little knowledge of the disease, its symptoms, effects and therapies not only by patients and public opinion, but also by doctors themselves. In fact, a recently published survey highlighted an insufficient preparation of European urologists on natural history, diagnosis and management of this pathology, especially for those who had not previously worked in a endemic area [9].

To confirm this, an Italian multicentric study conducted on more than a hundred of patients, highlighted that an high proportion of migrant patients were tested late after arrival (median delay about 31 months) [5].

SARS-CoV-2 represents a threat to schistosomiasis control.

The pandemic has taken away that little spotlight from this neglected pathology, further worsening the little efforts to screen and treat it. SARS-CoV-2 reduced the time spent by Infectious Diseases specialists training on tropical medicine and imported diseases [10].

Furthermore, patients with schistosomiasis, mainly migrants, afraid of looking for care in times of pandemic, may decrease the chance of effective treatment and care. In this light, the possible role of infectious disease specialists might be to raise awareness among health care professionals in order to implement adequate management strategies.

Ultimately, a coordinated effort by the European urological, infectious diseases and preventive scientific societies may be required in order not to forget this already neglected disease.

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The authors declare no conflict of interest.

Authors' contributions

GM and NR conceived the study, GM, MM, NR drafted and revised the manuscript, performed a search of the literature. All authors critically revised the manuscript and all authors have read and approved the latest version of the manuscript.

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LETTER TO THE EDITOR

Healthcare activity as a major risk of dying of COVID-19: medical doctors pay the price

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Keywords

Healthcare activity • COVID-19 • Medical doctor mortality

Dear Editors,

We recently read the interesting article by Wang et al. on the spatio-temporal characteristics of the COVID-19 epidemic in the United States; they reported that COVID-19 cases diagnosed in the United States displayed statistically significant differences related to geographic and socio-demographic factors, including rural/urban context, the percentage of ethnic minorities, the percentage of the population aged 65 years or more etc [1]. However, they failed to report another important factor: the role of working activity.

In Italy, COVID-19 mortality among medical doctors has been significantly higher than nurses or pharmacists. Indeed, at 1 March 2021 332 deaths have occurred among 403,454 medical doctors [2, 3], 81 among 426,707 nurses [4], and 23 among 127,513 pharmacists [5]. Two-tailed Chi-square test reveals statistically significant differences in COVID-19-related mortality, with a p value < 0.00001, between physicians and nurses (Chi-square test value with Yates correction: 165.8748) (relative risk > 1 = 4.33) and between medical doctors and pharmacists (Chi-square test value with Yates correction: 58.9093) (relative risk > 1 = 4.56). In addition, in the 25-70-year age-range, on comparing COVID-19 mortality among medical doctors (240/358161) [3] and in the general population (12500/35665609) [6], the Chi square test and relative risk yielded values of 102.3566 and 1.91 respectively, confirming the higher COVID-19 mortality risk among medical doctors than in the general population in this age range. Moreover, a study on serum conversion to COVID-19 in Italy showed conversion in 2.5% of the general population and in 5.6% of healthcare personnel [7] indicating increased circulation of the virus in healthcare workers than the general population in the first pandemic period.

In conclusion, the Chi square test, and relative risk have demonstrated that medical doctors have a higher risk of dying from COVID-19 than nurses, pharmacists and, in the 25-70-year age range, also versus the general population. Interestingly, the same results have been obtained in the USA and

other countries. This is a major problem and one that could be tackled through extensive vaccination of the general population and healthcare personnel. In this regard, a particular effort should be made to convince skeptics that COVID-19 vaccination is of crucial importance not only to the individual but also to the community.

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Authors' contributions

AC: idea, write, statistical analysis, correction; SA: Journal selection, correction; EA: correction.

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SHORT ARTICLE

COVID-19: Black Swan or clumsy use?

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Keywords

COVID-19 • SARS-CoV-2 • Laboratory test

Summary

“Black Swan” is an unexpected and catastrophic event characterized by three conditions: the anomalous and exceptional value, the extreme impact, and predictability a posteriori. On many sides – by politicians, commentators, scientists – there have been attempts to give the COVID-19 pandemic event the meaning of Black Swan. In reality, one should wonder if the Black Swan was not, instead (or even), the way the epidemic was handled. In Italy, an unreasonable use of a two-step protocol - IgM/IgG anti-COVID followed by RT-PCR in the serologically positive

only has caused considerable uncertainty, particularly relevant in measures for maintenance or readmission to work of health personnel. This protocol could be affected by serious uncertainties arising from the analytical limitations of the tests used. To quantify this defect, we evaluated the analytical specifications of serological tests under different prevalence conditions. In conclusion, although laboratory diagnostics represent a useful tool, it can only be used for epidemiological purposes and not to provide healthy pass.

Introduction

Borrowing from Juvenal, Nassim Nicholas Taleb developed his “Black Swan” theory as an unexpected and abnormal event of great importance, capable of generating significant environmental changes whose meaning, although implicit, is grasped only a posteriori [1].

Politicians and commentators, scientists even, regarded the COVID-19 pandemic as a Black Swan event; actually, we should wonder whether the black swan could be not the pandemic rather than its epidemiological management.

Laboratory test results drove most decisions to manage the pandemics spread; however, their use is often clumsy and inappropriate and deserves to be discussed.

Laboratory tests are useful in distinguishing positive from negative, i.e., sick from healthy. This characteristic is relevant during an epidemic event because it allows the adaptation of both therapeutic and health policy choices to contain the disease’s spread.

The characteristics that allow bettering separate the healthy population from the affected one must be verified for the latter use. Negative predictive values (NPV) and false omission rate (FOR) are the parameters that need consideration. NPV is a test capability to be negative in non-affected people [$NPV = (1 - prevalence) \text{ specificity} / (1 - prevalence) \text{ specificity} + prevalence (1 - sensitivity)]$. FOR is the complementary quantification of false-negatives (FN).

In the early pandemic stages, the lack of knowledge of various diagnostic tests’ analytical performances was a weak point for infection containment measures’ effectiveness.

Later, most serological qualitative tests seemed inadequate in detecting anti-COVID19 antibodies. The window-phase bounding and IgM timing to IgG seroconversion proved to be the most criticalities [2-4]. In Italy, serological tests’ unreasonable use has caused considerable uncertainty, which has proved relevant for the maintenance or readmission to health personnel’s work. These measures include a two-step protocol – IgM/IgG anti-COVID followed by RT-PCR in the serologically positive only – to identify health workers who could continue to be operational or, conversely, to be quarantined [5].

This protocol could be affected by severe uncertainties arising from the analytical limitations of the tests used.

Methods

We evaluated serological tests’ analytical specifications under different prevalence conditions to quantify this defect.

By way of example the serological tests considered are: 1) COVID-19 IgG/IgM (Screen Italia, Perugia, Italy); 2) Liaison SARS-CoV-2 S1/S2 IgG (Diasorin, Saluggia, Italy); 3) Maglumi 2019-nCoV IgG; and 4) Maglumi 2019-nCoV IgM+IgG (Snibe Diagnostic, Shenzhen, China).

Concerning the direct research of the COVID-19 virus with RT-PCR method, we referred to the performances reported for different technologies and [6] on nasopharyngeal swabs (NP) and bronchoalveolar washes (BAL), for which sensitivity of 63% and 93% respectively were reported [7].

The exact prevalence of COVID-19 infection is affected by various factors such as regional variability [8] and an unspecified number of non-swab-tested healthy carriers [9, 10]. We calculated each serological test for FN rate related to their NPV and FOR in different prevalence values. Since FN rate rises as prevalence increases, the resulting number might consider an estimate of health care providers admitted to caring services, despite their infectivity.

Results

As shown in Table I, depending on the NPV and FOR showed by the used test, FNs subjects range between 11 and 134, in a population of 1,000 inhabitants with infection prevalence equal to 0.3 (300 positives). Unfortunately, in the second phase of viral research on serologically positive subjects, further FNs will be added. For example, in the same population prevalence, an RT-PCR method with a sensitivity of 0.7 will demonstrate VNP and FOR values that will result in 16 FN out of a total of 166 VP [11].

The result of two-step screening is that 152 positive subjects out of 300 could be classified incorrectly as negative. This result comes from 134 IgM/IgG FNs with 18 FNs resulting from RT-PCR under the given conditions. Fewer FNs are achieved using other methodologies and/or different prevalence values; however, the best result of 43 FN remains equally worrying because of the obvious fallout on the possible expansion of contagion.

Discussion

Two step protocol could be affected by serious uncertainties arising from the analytical specifications of the tests under different prevalence conditions.

Our analysis shows that performing RT-PCR research exclusively on positive IgM/IgG subject prevents the discovery of numerous infected operators due to the combined methodological error of used tests in the two steps.

The risk of two-stage screening is that a critical number of positive subjects may be wrongly classified as negative. This risk become more relevant the higher the amount of prevalence of those affected.

Therefore, the consequent unknown presence of false negatives can be a danger and source of outbreaks.

Conclusions

Unreasonable use of serological tests may have caused considerable uncertainty, particularly relevant in maintenance or readmission to work of health personnel, using a two-step protocol - IgM/IgG anti-COVID followed by RT-PCR in the serologically positive only.

The non-segregation of these subjects and their free working activity in the healthcare environment represents an insidious source of new disease outbreaks, making containment null.

This appraisal could be evoked to explain the high incidence of infections (and deaths) among operators and patients in some Italian regions with the highest prevalence, such as Lombardia and Emilia Romagna.

These pieces of evidence could have suggested the combined use (instead of sequential) of both serology and RT-PCR [12]. Such choice would have enhanced the ability to intercept affected subjects and perhaps have

Tab. I. NPV, FOR and FN rate in different prevalence of infection. NPV is calculated on the basis of sensitivity and specificity values.

	Screen test COVID-19 IgG/IgM			Screen test COVID-19 IgG/IgM			Liaison SARS-CoV-2 S1/S2 IgG (> 15 days)			Maglumi 2019 - nCoV IgG (CLIA)			Maglumi 2019 - nCoV (CLIA) IgM + IgG		
	Se 95.0 Sp 98.0 (BAL)			Se 65.0 Sp 97.0 (NF)			Se 97.4 Sp 98.5			Se 91.21 Sp 97.33			Se 95.80 Sp 96.00		
Pre	NPV	FOR	FN	NPV	FOR	FN	NPV	FOR	FN	NPV	FOR	FN	NPV	FOR	FN
0.10	0.994	0.006	6	0.961	0.039	39	0.997	0.003	3	0.990	0.010	10	0.995	0.005	5
0.20	0.987	0.013	13	0.917	0.083	83	0.993	0.007	7	0.978	0.022	22	0.989	0.011	11
0.30	0.979	0.021	21	0.866	0.134	134	0.989	0.011	11	0.963	0.037	37	0.982	0.018	18
0.40	0.967	0.033	33	0.806	0.194	194	0.983	0.017	17	0.943	0.057	57	0.972	0.028	28
0.50	0.951	0.049	49	0.735	0.265	265	0.974	0.026	26	0.917	0.083	83	0.958	0.042	42
0.60	0.929	0.071	71	0.649	0.351	351	0.962	0.038	38	0.881	0.119	119	0.938	0.062	62
0.70	0.894	0.106	106	0.543	0.457	457	0.942	0.058	58	0.826	0.174	174	0.907	0.093	93
0.80	0.831	0.169	169	0.409	0.591	591	0.904	0.096	96	0.735	0.265	265	0.851	0.149	149
0.90	0.685	0.315	315	0.235	0.765	765	0.808	0.192	192	0.552	0.448	448	0.717	0.283	283

Pre: prevalence; Se: sensitivity; Sp: specificity; NPV: negative predictive value; FOR: false omission rate; FN: false negative per thousand. Screen test Se and Sp are relative – RT-PCR reference gold standard. Real Se and Sp are obtained by considering RT-PCR Broncho Alveolar Lavage (BAL) and RT-PCR nasopharyngeal (NF) as gold standard.

averted the Black Swan spread of Covid-19, increasing safety levels.

In conclusion, Laboratory tests can help to distinguish positive from negative, i.e., sick from healthy; but it depends on their characteristics. Although both serological tests and RT-PCR are useful tools, they can only be used for epidemiological purposes and not to provide healthy pass. At present, the correct behavior would be to consider all subjects present in hospitals as potentially infected, in order to enhance security.

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The authors declare no conflict of interest.

Authors' contributions

All authors contributed equally to this work.

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SHORT ARTICLE

COVID-19 emergency in Sicily and intersection with the 2019-2020 influenza epidemic

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Keywords

SARS-CoV-2 • Influenza • Molecular surveillance • Italy • Sicily

During the 2019-2020 winter season, the Northern Hemisphere was called to face the experience of a simultaneous epidemic of coronavirus disease 2019 (COVID-19) and seasonal influenza [1]. Recent studies have documented in SARS-CoV-2 positive patients, early in the COVID-19 pandemic, a co-infection with other respiratory pathogens, including influenza [2-4]. The potential occurrence of co-infection underscored the need for simultaneous detection and evaluation in order to improve the differential diagnosis in patients with acute respiratory syndromes [5].

In Italy, the SARS-CoV-2 epidemic started around mid-February 2020 in Lombardy (Northern Italy) and, since then, new cases of infection have been reported in a number of other northern Italian regions, such as Veneto, Emilia-Romagna, Piedmont, Liguria, and Marche. More in depth, following the detection of two imported cases involving Chinese travelers on January 31st, 2020 [6, 7], the first autochthonous patient affected by COVID-19 (“patient zero”) was identified on February 19, 2020 in a 38-year-old Caucasian male from Codogno town. On February 21, 2020 the first cluster of 16 Italian cases was reported in Lombardy, followed by a number of new notified cases exponentially growing, until when, on February 22nd, 2020, public health authorities established a “red zone” encompassing 11 municipalities to contain the epidemic. Thereafter, in a short time, the epidemic spread to the neighboring regions located in the northern and central part of the country [8, 9], with a substantially lower impact on the rest of the country.

In Sicily, the largest and southernmost region of Italy, as well as the fourth most populated one, the first confirmed case of SARS-CoV-2 infection was a 65-year-old woman from Bergamo (Lombardy), who was already on holiday in Palermo city a couple of days before the detection of “patient zero” in Codogno. This subject showed symptoms possibly referring to COVID-19 on February 23rd, 2020 and tested positive at SARS-CoV-2 molecular investigation on February 24th, 2020, followed the day after by two of the other twenty-nine fellow companions.

Nevertheless, the first Sicilian autochthonous SARS-CoV-2 cases occurred early in March, most of them in close association with individuals who had travelled to or returned back from Lombardy in the previous week. Early in the course of the outbreak, severe containment measures were adopted by the Italian government throughout the entire country, which resulted in lockdown restrictions since March 9, 2020. These measures determined different local patterns of viral spread and Sicily took a clear advantage of this provision, experiencing low incidence of COVID-19 in the first semester of pandemic [10].

Of interest, chronologically-speaking, the early phase of SARS-CoV-2 epidemic partially overlapped the latter part of the seasonal influenza outbreak, which is annually explored during the winter through a nationwide sentinel surveillance network (InfluNet) [11], to which the Sicilian Reference Laboratory belongs.

However, to date, no official laboratory data have been made available in order to get a shot of the real beginning of the spread of SARS-CoV-2 in Sicily. Therefore, to gain further understanding on the local transmission of SARS-CoV-2, respiratory specimens routinely collected in the framework of the 2019-2020 seasonal influenza virus surveillance were retrospectively re-evaluated by molecular testing for SARS-CoV-2. To this end, 2,330 samples collected from patients presenting with Influenza-like illness, between October 2019 and February 2020, were analyzed by reverse transcriptase real-time PCR, targeting different segments of the N gene of the SARS-CoV-2 genome [12]. Briefly, collected data showed that none of these samples tested positive for SARS-CoV-2, documenting no co-infection with influenza virus and confirming at the same time that in Sicily there has not been any circulation of the pandemic virus prior to the first documented cases.

As stated above, from an epidemiological point of view, in Italy SARS-CoV-2 spread in an asynchronous way, showing different local patterns either in terms of incidence rates or affected geographic areas. Our data confirmed that SARS-CoV-2 appeared in Sicily at a

later stage of the outbreak documented in Italy and, according to severe containment measures adopted by the Italian government, slowly spread with low incidence. Nevertheless, despite the epidemiology of COVID-19 and of seasonal influenza is different, symptoms related to the two mentioned diseases overlap, and their confluence has been expected to result in higher morbidity and mortality rates, with additional stress to the entire public health system [13, 14]. Therefore, a widespread use of influenza vaccination has been promoted during the current season 2020-2021 in combination of containment measures (i.e. correct use of personnel protection equipment, hand washing, social distancing, etc.). At the midterm of the current surveillance season, we were able to demonstrate also in Sicily the dramatic global decline in influenza virus circulation, as clearly documented through the national virological surveillance networks in Italy [15] and elsewhere [16-18]. Lastly, the body of the previous evidences highlights the importance of molecular diagnostic testing for SARS-CoV-2 both to distinguish between influenza and COVID-19 in patients with acute respiratory illness, and to provide continuous surveillance and timely tracing to define and rapidly implement effective containment measures.

Ethics approval

This study was conducted in accordance with the World Medical Association Declaration of Helsinki and the approval was obtained from the local ethics committee.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Methodology: FT, WM, CMM, FRV.

Formal analysis: GMEC, DDN.

Investigation: all authors.

Writing, review and editing: all authors.

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REVIEW

Clinical features of COVID-19 and SARS epidemics. A literature review

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Keywords

COVID-19 • SARS-CoV-2 • SARS-CoV • SARS • Clinical features

Summary

SARS-CoV-2, responsible for the current pandemic, is a novel strain of the Coronaviridae family, which has infected humans as a result of the leap to a new species. It causes an atypical pneumonia similar to that caused by SARS-CoV in 2003. SARS-CoV-2 has currently infected more than 9,200,000 people and caused almost 480,000 deaths worldwide. Although SARS-CoV-2 and SARS-CoV have similar phylogenetic and pathogenetic characteristics, they show important differences in clinical manifestations.

We have reviewed the recent literature comparing the characteristics of the two epidemics and highlight their peculiar aspects. An analysis of all signs and symptoms of 3,365 SARS patients

and 23,280 COVID-19 patients as well as of the comorbidities has been carried out. A total of 17 and 75 studies regarding patients with SARS and COVID-19, respectively, were included in the analysis. The analysis revealed an overlap of some symptoms between the two infections. Unlike SARS patients, COVID-19 patients have developed respiratory, neurological and gastrointestinal symptoms, and, in a limited number of subjects, symptoms involving organs such as skin and subcutaneous tissue, kidneys, cardiovascular system, liver and eyes.

This analysis was conducted in order to direct towards an early identification of the infection, a suitable diagnostic procedure and the adoption of appropriate containment measures.

Introduction

The Coronavirus Disease 2019 (COVID-19) outbreak represents a serious public health problem that is straining health systems around the world.

As of June 25th, 2020, as many as 9,296,202 cases of COVID-19 have been confirmed and 479,133 patients have died globally, according to the World Health Organization (WHO) [1].

In addition to confirmed cases, there are also suspected cases of COVID-19 which should be promptly tested where possible in order to immediately implement isolation measures and trace contacts. In a context of uncertainty, since the infection is caused by a new and still little understood virus for which no vaccines or specific medications are currently available, the recognition of clinical signs and symptoms as well as clinical features in affected subjects is of vital importance. Severe Acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is the latest known virus that has spread worldwide. Viruses, particularly RNA viruses, have high mutation rates and are characterized by a particularly high virulence and transmissibility and can cause more or less severe infections. To date, SARS-CoV-2 appears to be highly virulent and easily transmissible, it can affect many organs of the body and manifest in many ways [2]. Applying the lessons learned from past epidemics can help us to better address the new challenges. The previ-

ous Coronavirus (CoV) epidemic that hit the world population was Severe Acute Respiratory Syndrome (SARS) in 2003 which manifested as an atypical pneumonia with reported symptoms including fever, dry cough, dyspnea, diarrhea and sore throat [3]. The modes of transmission and the clinical features of the two infections initially seemed to be superimposable. Both infections are transmitted through respiratory droplets or secretions and by close person-to-person contact [4]. In some cases, COVID-19 patients do not show the typical signs of respiratory infections but have unusual symptoms or only very mild symptoms [5].

Furthermore, the presence of underlying health conditions increases the risk of developing severe illness [6]. Therefore, early recognition of suspected cases through the evaluation of clinical and symptomatic characteristics should represent the first tool that can direct towards the most appropriate diagnostic and therapeutic strategies and that can help interrupt the chains of transmission of the virus.

This review is a comparative analysis of the characteristics of the SARS and COVID-19 epidemics and summarizes in detail the clinical signs and symptoms as well as the comorbidities of subjects with SARS and COVID-19, analyzed in studies published worldwide to date.

Virological characteristics

This century has been characterized by the presence of several zoonotic coronavirus epidemics spread from southern China, which have infected humans as a result of genetic recombination that have allowed to make the leap to a new species [7]. Phylogenetic analysis revealed that SARS-CoV-2, like Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), belongs to the genus *Betacoronavirus* of the *Coronaviridae* family, exhibiting about 79% sequence identity with SARS-CoV and sharing the same receptor-binding domain (RBD) structure [8]. The complete genome sequence contains 29,751 bp for SARS-CoV [9] and 29,811 bp for SARS-CoV-2 [10]. The mutation rate in the SARS-CoV genome is similar to that of other coronaviruses and moderate compared to other RNA viruses [11], unlike that of SARS-CoV-2 which appears to have a higher evolutionary rate estimated (mean 2.15×10^{-6} subs/site/day corresponding to 7.8×10^{-4} subs/site/year) (Tab. I) [12].

Epidemiological characteristics

The first cases of atypical pneumonia of unknown etiology of SARS were reported on November 16th, 2002 in Guangdong Province, China and then spread mainly among household contacts and healthcare workers [13]. It was only after 300 people became infected and 5 died, on February 11th, 2003, that the Chinese Ministry of Health informed the WHO of an outbreak of acute respiratory syndrome [14]. At the end of February 2003, the infection was transmitted to Hong Kong by an infected doctor and in a few months the infection spread to other countries of the world mainly through intercontinental flights. The epidemic spread rapidly to Hong Kong, Taiwan, Singapore and Hanoi, mostly related to the movement of people during the Chinese New Year holiday season [15].

The number of reported cases increased exponentially, prompting the WHO to issue a global alert about the disease on March 13, 2003 (Tab. I) [14].

The outbreak was contained in July 2003 with a total of 8,098 cases and 774 deaths in 32 countries, with an estimated overall case fatality rate (CFR) estimate of 9.6%. In mainland China, the country where the epidemic started and where the greatest number of cases was reported, there were 5,327 infected people and 349 deaths [16].

A number of hospitals in various regions of China were designated to treat SARS patients only. The outbreak came under control and the number of new cases gradually declined. On June 24th, 2003, Beijing was removed from the WHO's list of areas with recent local transmission of SARS [15].

The country most affected after China was Hong Kong with 1,755 cases and a mortality rate of 17%. The most affected country outside Asia was Canada with 251 cases and 43 deaths. The European region was slightly affected, with 33 total cases and one death in France. In Italy, only 4 cases

Tab. I. Summary of virological and epidemiological characteristics of SARS-CoV and SARS-CoV-2 infections.

Characteristics	SARS-CoV	SARS-CoV-2
First occurrence	Nov. 16, 2002 in Foshan, Guangdong	Dec. 07, 2019 in Wuhan, Hubei
Global alert declaration (WHO)	March 13, 2003	Jan 30, 2020
Pandemic declaration (WHO)	-	March 11 th , 2020
Genome	RNA	RNA
Length, bp	29,751	29,811
Mutation rate RNA	$0.80-2.38 \times 10^{-3}$ subs/site/year	7.8×10^{-4} subs/site/year
	Moderate	High
Mode of transmission	Respiratory droplet	Respiratory droplet
	Contact	Contact
	-	Fecal-oral (?)
	-	Airborne (?)
Incubation period (median)	4.0 days (95% CI: 3.6-4.4)	5.1 days (95% CI: 4.5-5.8)
R0	2-4	1.4-7.23
Asymptomatic rate	2.3-13%	5-8%
Case fatality rate	9.6%	5.1%

SARS-CoV: severe acute respiratory syndrome; SARS-CoV-2: coronavirus disease-2019; bp: base pairs; R0: basic reproduction number; CI: confidence interval.

have been observed [17]. The epidemic was declared ended on July 5th, 2003 [14].

Another global epidemic is currently underway which started on December 7th, 2019, the day when the first positive COVID-19 case was detected.

The first cases of pneumonia of unknown origin were found in China, connected to those who frequent the wholesale market of seafood and wet animals located in Wuhan, in the province of Hubei, assuming also in this case a zoonotic source [18]. A new coronavirus, named SARS-CoV-2, was isolated from the epithelium of these patients. It then spread, through person-to-person transmission in family homes and hospitals, outside Hubei Province in China to many countries across the world. The family of the causative agent of this outbreak as well as the country where this epidemic started are the same as those of SARS [19].

The announcement of this epidemic was provided by the Wuhan government to the WHO on January 3rd, 2020, after the involvement of 27 persons and no deaths [20]. Following a rapid spread in China and around the world, on January 30, 2020, the International Health Regulations Emergency Committee of the WHO declared the outbreak a Public Health Emergency of International Concern (PHEIC) [21].

About 40 days after the declaration of the global emergency, with over 118,000 cases in 114 countries and territories worldwide and 4,291 deaths, on 11 March 2020, WHO announced the state of pandemic (Tab. I). The last time the WHO used the label was on June 11, 2009 for the H1N1 flu, known as “swine flu”, which spread across the world, whereas the 2002-2004 SARS outbreak was never declared a pandemic.

Since the end of December 2019 and as of June 25th, 2020, the infection has been detected in all countries causing more

than 9,200,000 confirmed cases and almost 480,000 deaths, with an overall CFR estimate of 5.1% (Tab. I).

At present, in China there are 85,119 confirmed cases and 4,647 deaths. The virus initially spread exponentially in China and in the Western Pacific Region, exceeding 100,000 cases. In the last few months, the situation seems to have stabilized in China and in other Asian countries after weeks of rigid control measures. In the last month, new cases have emerged, causing fear of a second epidemic wave.

The European Region has exceeded 2,600,000 infections, reaching nearly 200,000 deaths, and is currently the most affected Region with a higher lethality rate (7.5%). America has over 4,600,000 infections and 230,000 deaths, followed by the Eastern Mediterranean Region with almost 970,000 confirmed cases and 22,000 deaths.

The countries worst affected in terms of number of infected people are the United States of America (USA) and the Brazil with 2,329,463 and 1,145,906 cases, respectively, followed by the Russian Federation, the United Kingdom, Peru e Chile with 613,994, 306,866, 260,810 and 254,416 cases, respectively [1]. The country with the highest number of COVID-19 deaths is the USA where 120,955 have lost their lives, with an average lethality of 5.2%. Belgium and United Kingdom are currently the worst affected countries in terms of the case fatality rate (15.9 and 14.0%, respectively) [1].

Transmission

Both viruses are transmitted from human to human via droplets generated by coughing and sneezing, through exposure to fomites and through direct contact of mucous membranes (eyes, nose and mouth).

Whether the infection can be transmitted by the oral or conjunctival routes has not yet been demonstrated. However, SARS-CoV2 has been detected in tears [22], similar to SARS-CoV [23]. Although there is a low prevalence of SARS-CoV-2 in the tear fluid of patients, it cannot be excluded that the infection could be transmitted via the eyes [24].

The role of fecal-oral transmission for SARS-CoV is still unknown. Although some coronaviruses are known to be spread by the fecal-oral route [25], there is currently no evidence that this mode of transmission plays a key role in SARS [3]. There is still limited knowledge regarding fecal-oral transmission of SARS-CoV2, although Chen Y et al. have demonstrated the presence of SARS-CoV-2 RNA in the feces of COVID-19 patients suggesting that, in addition to respiratory and body contact, fecal-oral transmission is a potential route for SARS CoV-2 infection [26]. In a meta-analysis, SARS-CoV-2 RNA was detected in 48.1% of the stool samples derived from a cohort of patients with COVID-19 and persisted even after respiratory samples were negative (Tab. I) [27].

In spite of the fact that the data on intrauterine vertical transmission are scarce, there is little, if any, clinical or serologic evidence suggestive of SARS-CoV and SARS-CoV-2 transmission from pregnant mothers to newborn

infants [28, 29]. Contact with infected droplets on a surface can be a source of infection, too [3, 30]. Van Doremalen et al. found that SARS-CoV-2 can remain viable and infectious in aerosols for 3 hours and on surfaces up to days. The stability of this virus is similar to that of SARS-CoV [30]. This study has also shown that the virus is most stable on plastic and stainless steel with viable virus detected up to 72 hours in the absence of any intervention. Viruses lose their infectivity after exposure to common disinfectants such as Clorox, 75% ethanol and fixatives such as formaldehyde and paraformaldehyde [31, 32]. Careful attention should also be paid to asymptomatic cases whose role in viral transmission is still controversial. During the SARS epidemic, some studies reported the absence of asymptomatic cases, while, where reported, the incidence of asymptomatic cases corresponded to 13% of all SARS-positive cases [33]. The rate of asymptomatic or mild infections of COVID-19 ranges between 5 and 78% (Tab. I) [34, 35]. Asymptomatic SARS infection was associated with lower SARS antibody titers and the transmission from asymptomatic patients appeared to play no or only a minor role [33].

SARS-CoV viral load in upper respiratory tract secretions was low in the first 5 days of illness, then increased progressively and peaked early in the second week, which helped reduce more effectively the infection transmission in the first days of illness [36].

In a study, Zou L et al. showed that the viral RNA levels in people with COVID-19 appear to be higher soon after symptom onset compared with later in the illness [37], which suggests that transmission is more likely to occur at an earlier stage of infection even when symptoms are relatively mild. The high rate of asymptomatic infections is often the result of a long incubation period. The median incubation period for COVID-19 is estimated to be 5.1 days, (95% CI: 4.5 to 5.8) [38], slightly longer than for SARS-CoV (4.0 days, 95% CI: 3.6-4.4) (Tab. I) [39]. The incubation period for SARS in children and adolescents was 2-10 days, with a mean of 6.4 days (95% CI: 5.2-7.7) [39]. The average incubation period for COVID-19 in children is 6.5 days (95% CI: 4.6-8.4), with a range from 2 to 10 days [40]. The interval during which an individual with COVID-19 is infectious is still uncertain.

The transmissibility of SARS was determined by a basic reproduction number (R_0) of approximately 3, with values oscillating between 2 and 4, consistent with a disease spread by direct contact or larger virus-laden droplets that travel only a few meters rather than by lighter airborne particles [3, 41]. Some studies have estimated the mean R_0 for COVID-19 to range from 1.4 to 7.23 (Tab. I) [2]. R_0 is used when there is a dynamic infectious disease and the population is not vaccinated, and it is usually estimated on the basis of the growth rate of the number of cases. The estimated values of R_0 were lower in the early phase of the epidemic. They subsequently increased during the other phases of the epidemic and then returned to the initial levels [42].

Therefore, COVID-19 can be considered as a highly transmissible disease compared with SARS. Epidemiological factors, such as the ability to recognize

the infection at an early stage, the measures of social distancing adopted, the access to public health resources can cause considerable variations of this parameter.

Pathogenesis and clinical features

SARS-CoV and SARS-CoV2 cause severe acute respiratory syndrome and appear to have the same pathogenesis. Both viruses use the angiotensin-converting enzyme 2 (ACE2) as cell receptor to gain entry into the human cells. The infection is triggered by the binding of the virus spike protein to ACE2 and causes both upper and lower respiratory tract infections [43, 44].

Based on past studies on SARS-CoV, both viruses bind to epithelial cells in the nasal cavity and start replicating. The viruses then propagate and migrate down the respiratory tract along the conducting airways, also becoming clinically manifest [45]. A study reports that SARS CoV-2 has higher affinity for binding than SARS CoV and this contributes to its more efficient infection of humans [46]. About 20% of the infected patients develop severe disease. The virus reaches the gas exchange units of the lung causing a progressive respiratory failure due to alveolar damage, resulting in apoptosis and even cell death [44, 47]. ACE2 receptors are present in the lung alveolar cells, but are also expressed in numerous other organs, in the enterocytes of the small intestine, as well as in the heart, kidney, bile duct, liver, esophagus and testicle, and in arterial and venous endothelial cells and arterial smooth muscle cells. This tissue distribution of ACE2 correlates with the sites of infection and with the pathology [43].

Signs and symptoms

SARS is characterized as a viral pneumonia with rapid respiratory deterioration [48]. COVID-19 has many clinical features similar to those of SARS but COVID-19 infection presents with a wide spectrum of severity and often with non-specific symptoms. About 80% of patients experience no signs or mild symptoms of disease, 14% have severe clinical manifestations and only 5% critical conditions. Older age and presence of comorbidities appear to be important factors associated with clinical severity of disease [4].

We analyzed the clinical characteristics reported in patients with SARS-CoV and SARS-CoV-2. A total of 17 and 75 studies regarding patients with SARS and COVID-19, respectively, were included in the analysis. Overall, 3,365 patients with SARS-CoV and 38,318 patients with SARS-CoV-2 were analyzed.

The results are detailed in Table II. In the first part of the Table, signs and symptoms of 3,365 SARS patients and 23,280 COVID-19 patients were considered. This analysis revealed an overlap of some symptoms between the two infections. SARS-CoV2 infection presents a greater variety of symptoms and involves several organ systems. SARS-CoV affects a few organs and a limited

number of symptoms are present in a high percentage of the infected subjects. In particular, the most common clinical manifestations were systemic [fever (87.90%), chills (53.52%), and malaise (49.18%)]. In addition, respiratory symptoms [cough (58.31%)], neurological symptoms [headache (44.40%)], and musculoskeletal and connective symptoms [myalgia (40.62%)] were detected. SARS-CoV2, on the other hand, preferentially infects the cells of the respiratory tract, but it also has high affinity for other organs. Therefore, symptomatic patients present a greater variety of symptoms affecting many organs but in a smaller number of subjects. Typical symptoms are respiratory among which cough is the most frequent (62.50%). Other frequent symptoms are: fever (58.9%), myalgia/arthritis (35.62%), headache (32.48%), shortness of breath/dyspnea (27.46%), and diarrhea (18.52%). Unlike SARS patients, COVID-19 patients have developed numerous other respiratory, neurological and gastrointestinal symptoms, and, in a limited number of subjects, symptoms involving organs such as skin and subcutaneous tissue, kidneys, cardiovascular system, liver and eyes.

Comorbidities

Seventeen studies have been included in the analysis of comorbidities and risk factors for a total of 3,365 patients with SARS-CoV.

In the 3,365 SARS patients analyzed, the most common comorbidities, present in a very low percentage of subjects, were diabetes (0.21%), cardiovascular disease (0.12%), COPD and chronic liver disease, both present in 0.09% of subjects. A total of 72 studies and 26,650 patients with COVID-19 have also been analyzed. The results showed the most prevalent comorbidities were hypertension (21.00%) and diabetes (15.37%), followed by cardiovascular disease (11.28%). The data also showed numerous COVID-19 infected subjects with hyperlipidemia (10.20%) or obesity (9.77%). Furthermore, diseases of the respiratory system such as COPD and asthma were present in 2.57 and 2.26% of patients, respectively. Chronic kidney disease was also found in 2.02% of patients.

Smoking habits have been reported in 2.75% of patients. There are numerous differences in the prevalence of comorbidities among the studies analyzed. In one recent study conducted, the authors presented the comorbidities of 5,700 patients hospitalized for COVID-19 in the New York City area. The most common comorbidities were hypertension (3,026; 56.6%), obesity (1,737; 41.7%) and diabetes (1,808; 33.8 %) [49]. The data are significantly different from those obtained in other studies from various areas of the world.

Guan WL et al. analyzed the clinical characteristics of more than 1,000 patients from mainland China. The most common comorbidities were hypertension in 15% of patients and diabetes in only 7.4% of patients. No other comorbidities were observed in over 2.5% of the COVID-19 patients analyzed [50].

Tab. II. Clinical features of patients with SARS-CoV and SARS-CoV-2 infections.

Characteristics	N. of studies	SARS-CoV % (95% CI)	N. of studies	SARS-CoV-2 % (95% CI)
Patients, n.	17	3,365	71	23,280
Gender				
Male, n. (%)	17	1,360 (40.4)	67	6,530 (55.8)
Female, n. (%)	17	2,005 (59.6)	67	5,179 (44.2)
Age group				
Children (<18 ys), n. (%)	4	92 (2.7)	15	807 (3.5)
Adults/Older, n. (%)	14	3,273 (97.3)	55	22,374 (96.5)
Systemic/General symptoms				
Fever	17	87.90 (86.80-89.01)	71	58.9 (58.23-59.49)
Fatigue/Malaise	17	49.18 (47.49-50.87)	71	8.91 (8.54-9.27)
Chills	17	53.52 (51.84-55.21)	71	0.96 (0.84-1.09)
Influenza-like	17	30.61 (29.05-32.17)	71	-
Night sweats	17	11.80 (10.71-12.89)	71	-
Respiratory, thoracic and mediastinal symptoms				
Cough	17	58.31 (56.64-59.97)	71	62.50 (61.87-63.12)
Shortness of breath/Dyspnea	17	26.48 (24.99-27.97)	71	27.46 (26.89-28.03)
Sputum production	17	26.54 (25.05-28.03)	71	7.32 (6.99-7.65)
Rhinorrhea/Runny nose	17	2.97 (2.40-3.55)	71	4.90 (4.62-5.18)
Sore throat	17	21.63 (20.24-23.03)	71	3.69 (3.45-3.94)
Acute respiratory distress	17	-	71	0.77 (0.41-0.88)
Nasal congestion/Stuffiness	17	-	71	0.55 (0.46-0.65)
Chest pain	17	1.84 (1.39-2.30)	71	0.34 (0.26-0.41)
Pharyngeal erythema	17	-	71	0.34 (0.26-0.41)
Chest distress	17	-	71	0.31 (0.24-0.38)
Haemoptysis	17	0.68 (0.41-0.96)	71	0.30 (0.23-0.37)
Tachypnea	17	1.58 (1.15-2.00)	71	0.22 (0.16-0.28)
Voice hoarse	17	-	71	0.06 (0.03-0.10)
Coryza	17	15.75 (14.52-16.98)	71	0.03 (0.01-0.05)
Oropharyngeal pain	17	-	71	0.004 (0.00-0.01)
Rhonchi	17	1.10 (0.75-1.45)	71	-
Percussion dullness	17	0.21 (0.05-0.36)	71	-
Pleurisy	17	0.09 (0.00-0.19)	71	-
Wheezing	17	0.03 (0.00-0.09)	71	-
Cardiovascular symptoms				
Cardiac injury	17	-	71	0.12 (0.07-0.16)
Palpitation	17	2.91 (2.34-3.48)	71	0.12 (0.08-0.17)
Tachycardia	17	1.96 (1.49-2.34)	71	0.03 (0.01-0.06)
Shock	17	-	71	0.02 (0.00-0.04)
Gastrointestinal symptoms				
Diarrhea	17	19.82 (18.47-21.17)	71	18.52 (18.12-19.12)
Abdominal pain	17	5.65 (4.87-6.43)	71	6.51 (6.19-6.82)
Vomiting	17	9.30 (8.32-10.28)	71	5.00 (4.72-5.28)
Nausea	17	13.16 (12.02-14.31)	71	4.63 (4.36-4.90)
Anorexia	17	24.07 (22.63-25.52)	71	1.40 (1.25-1.56)
Dehydration	17	-	71	0.03 (0.01-0.05)
Neurological symptoms				
Headache	17	44.40 (42.72-46.08)	71	32.48 (31.88-33.08)
Ageusia	17	-	71	1.89 (1.72-2.07)
Dizziness	17	20.48 (19.11-21.84)	71	0.37 (0.30-0.45)

Anosmia	17	-	71	0.34 (0.26-0.41)
Impaired consciousness	17	-	71	0.27 (0.20-0.33)
Agitation	17	-	71	0.17 (0.12-0.23)
Corticospinal tract signs	17	-	71	0.17 (0.11-0.22)
Dysexecutive syndrome	17	-	71	0.06 (0.03-0.09)
Perfusion abnormalities	17	-	71	0.05 (0.02-0.08)
Acute cerebrovascular disease	17	-	71	0.04 (0.01-0.06)
Guillain-Barré syndrome (GBS)	17	-	71	0.03 (0.01-0.05)
Leptomeningeal enhancement	17	-	71	0.03 (0.01-0.06)
Nerve pain	17	-	71	0.02 (0.00-0.04)
Seizure	17	0.03 (0.00-0.09)	71	0.01 (0.00-0.03)
Ataxia	17	-	71	0.004 (0.00-0.013)
Miller Fisher Syndrome	17	-	71	0.004 (0.00-0.013)
Polyneuritis cranialis	17	-	71	0.004 (0.00-0.013)
Anxiety	17	0.03 (0.00-0.09)	71	-
Kidney symptoms				
Dialysis	17	-	71	0.15 (0.10-0.21)
Kidney injury	17	-	71	0.11 (0.07-0.15)
Musculoskeletal and connective symptoms				
Myalgia/arthritis	17	40.62 (38.96-42.28)	71	35.62 (35.00-36.23)
Hypodynamia	17	-	71	0.25 (0.19-0.32)
Back discomfort	17	-	71	0.01 (0.00-0.03)
Rigor	17	19.17 (17.84-20.50)	71	-
Neck pain	17	0.09 (0.00-0.19)	71	-
Skin and subcutaneous tissue symptoms				
Itch	17	-	71	0.91 (0.79-1.04)
Maculopapular rash	17	-	71	0.76 (0.64-0.87)
Urticaria	17	-	71	0.33 (0.25-0.40)
Pseudo-chilblains	17	-	71	0.30 (0.23-0.38)
Chickenpox-like vesicles	17	-	71	0.15 (0.10-0.20)
Pain	17	-	71	0.14 (0.09-0.19)
Livedo/necrosis	17	-	71	0.09 (0.05-0.13)
Erythematous rash	17	-	71	0.07 (0.04-0.25)
Burning	17	-	71	0.09 (0.06-0.13)
Rash	17	00.3 (0.00-0.09)	71	0.02 (0.00-0.04)
Cyanosis	17	-	71	0.004 (0.00-0.013)
Eye symptoms				
Conjunctival congestion	17	-	71	0.05 (0.02-0.08)
Vision impairment	17	-	71	0.01 (0.00-0.03)
Hepatic symptoms				
Liver injury	17	-	71	0.37 (0.29-0.45)

Comorbidities and risk factor

Characteristics	N. of studies	SARS-CoV % (95% CI)	N. of studies	SARS-CoV-2 % (95% CI)
Patients, n.	17	3,365	72	26,650
Gender				
Male, n. (%)	17	1,360 (40.4)	68	15,163 (58.3)

Female, n. (%)	17	2,005 (59.6)	68	10,860 (41.7)
Cardiovascular diseases	17	0.12 (0.00-0.24)	72	11.28 (10.90-11.66)
Hypertension	17	0.03 (0.00-0.09)	72	21.00 (20.51-21.49)
Cardiac arrhythmia	17	-	72	1.14 (1.01-1.27)
Coronary artery disease	17	-	72	6.43 (6.13-6.72)
Congestive heart failure	17	-	72	2.29 (2.11-2.47)
Cerebrovascular disease	17	0.03 (0.00-0.09)	72	0.89 (0.78-1.01)
Respiratory system diseases	17	-	72	0.58 (0.49-0.67)
Asthma	17	-	72	2.26 (2.08-2.44)
COPD	17	0.09 (0.00-0.19)	72	2.57 (2.38-2.76)
Chronic lung disease	17	-	72	0.81 (0.71-0.92)
Nervous system disease	17	-	72	0.36 (0.29-0.43)
Chronic kidney disease	17	0.06 (0.00-0.14)	72	2.02 (1.85-2.19)
End-stage kidney disease	17	-	72	0.70 (0.60-0.80)
Chronic liver disease	17	0.09 (0.00-0.19)	72	0.67 (0.57-0.67)
Cirrhosis	17	-	72	0.15 (0.10-0.20)
Hepatitis B	17	-	72	0.14 (0.10-0.19)
Hepatitis C	17	-	72	0.01 (0.00-0.02)
Tuberculosis	17	-	72	0.04 (0.02-0.07)
Digestive system disease	17	-	72	0.54 (0.46-0.63)
Hyperlipidaemia	17	-	72	10.20 (9.84-10.56)
Hypercholesterolemia	17	-	72	0.71 (0.61-0.81)
Obesity	17	-	72	9.77 (9.41-10.13)
Diabetes	17	0.21 (0.05-0.36)	72	15.37 (14.93-15.80)
Endocrine system disease	17	-	72	0.51 (0.42-0.60)
Rheumatologic disease	17	-	72	0.02 (0.00-0.04)
Immunosuppression	17	-	72	1.09 (0.96-1.21)
HIV infection	17	-	72	0.18 (0.13-0.23)
Transplant	17	-	72	0.22 (0.16-0.27)
Blood disorder	17	-	72	0.04 (0.01-0.06)
Myelodysplastic syndrome	17	0.06 (0.00-0.14)	72	-
Malignancy	17	0.03 (0.00-0.09)	72	2.22 (2.04-2.39)
Allergic rhinitis	17	-	72	0.39 (0.32-0.47)
Hyoxemia	17	-	72	0.02 (0.00-0.03)
Pregnancy	17	-	72	0.03 (0.01-0.05)
Smoking	17	-	72	2.75 (2.55-2.95)

Prognosis

Characteristics	N. of studies	SARS-CoV-1 % (95% CI)	N. of studies	SARS-CoV-2 % (95% CI)
Patients, n.	17	3,365	75	38,318
Gender				
Male, n. (%)	17	1,360 (40.4)	71	15,532 (58.1)
Female, n. (%)	17	2,005 (59.6)	71	11,215 (41.9)
Prognosis				
Hospital admission	17	55.66 (53.98-57.34)*	73	91.60 (91.17-91.83)*
Discharge	17	91.41 (90.46-92.36)*	65	52.53 (51.92-53.15)*

Death

17

5.26 (4.51-6.01)*

72

7.80 (7.48-8.12)*

* At the time of writing reports; for clinical features: 4 studies do not report gender differences, 1 study do not report age group; for comorbidities: 4 studies do not report gender differences; for prognosis: 2 studies do not report hospital admission, 10 studies do not report discharge, 3 studies do not report death.

Prognosis

Of the 3,365 patients hospitalized for SARS-CoV and the 38,318 patients hospitalized for SARS-CoV-2 that were included in our analysis, 55.66% and 91.60%, respectively, were admitted to hospital.

At the time the reports were written, 91.41% of patients hospitalized for SARS-CoV and only 52.53% of patients with SARS-CoV-2 were discharged.

Based on data from 17 studies on SARS and 72 studies on COVID-19, the percentage of deaths stood at 5.26% and 7.80% for SARS-CoV and SARS-CoV-2, respectively.

Diagnostic tests

The 2003 pandemic of SARS profiled the ability of modern diagnostic microbiology and molecular biology to identify, isolate and characterize, within weeks, a previously unknown virus. On 10 April 2003, quantitative TaqMan-format assay for SARS-associated coronavirus was published for the first time [51]. Diverse protocols were proposed within the different molecular testing approaches over time. Most conventional polymerase chain reaction (PCR) assays were designed with the Orf1b or nucleoprotein gene for nucleic acid amplification, and SYBR Green based PCR protocol was reported as a benefit to screen samples with sequence variations in the virus [52]. Also, monoclonal antibodies or monospecific polyclonal antibody directed to the nucleocapsid (N) protein were found to be a sensitive and specific test for antigen detection; however, most of these rapid tests have never been exhaustively investigated in prospective cohort studies owed to the short-lived epidemic [48].

Given the current epidemiology and the high risk of transmission, the rapid and accurate identification of the infection is crucial for effective COVID-19 containment. At writing time, real-time PCR molecular assays for detecting SARS-CoV-2 in respiratory specimens are the current reference standard for infection diagnosis. The technique is generally very sensitive and specific and may be used for routine diagnostics of COVID-19 [53]. However, Yong and colleagues showed the ineffectiveness of real-time PCR as the only diagnostic test due to its inability to detect previous infections highlighting the importance of using serological tests as well [54]. Where epidemiological information warns people might have been node of disease transmission, but they had recovered from sickness, SARS-CoV-2 IgG serology allows establishing past infection. In addition, if carried out within the correct timeframe after symptoms onset, serology assays can detect both active

and past infections [55]. Remarkably, the importance of serological tests for epidemiological investigation of COVID-19 cases rapidly emerged in a much more pressing way than in SARS full epidemic happened.

At the end of April 2003, tests to detect antibodies produced in response to the SARS coronavirus infection are under development but not still commercially available. ELISA (Enzyme Linked ImmunoSorbant Assay) test for the detection of IgM and IgG antibodies in serum produced positive results reliably after 21 from the onset of the disease and IFA (Immunofluorescence Assay) test for the detection of IgM produced positive results after about 10 days of illness [56].

Later studies revealed that specific serum antibodies against whole SARS-CoV by indirect immunofluorescence or neutralization tests starts to appear at about day 7 and, while IgM were not detectable after 2 to 3 months, IgG maintained for over one year [57].

The titer of neutralizing antibodies peaked from 20 to 30 days after infection and was sustained for a long time in those who survived, while the neutralizing antibody level of those who died peaked at day 14 and then gradually diminished [58].

In these months, a flood of novel rapid serologic immunoassays designs as long as point-of care technologies are proposed, and a lot of them are commercially available. Despite the considerable role they play, some evidences suggest that many kits currently available are not adequately accurate [59] and several challenges remain, to which we must pay attention. Recognizing the disease, during the acute phase of infection, needs high sensitivity and specificity; cross-reactivity with other viral agents should be weighed; antibody kinetics over time must also be investigated, to determine thresholds of immunity [60]. Both these testings, molecular and serological, are expected to support welfare decision-makers about measures to contain the outbreak.

Containment measures

During an unpredictable and unprecedented pandemic such as that caused by COVID-19, anxiety and stress – often boosted by the media as well as by the political decisions themselves – alter how people perceive new diseases and their consequent actions. Moreover, whenever decision-making involves risks, individuals can become irrational in several dysfunctional ways [61]. Consequently, the ideal approach to improve decision-making and crisis management should be reducing anxiety and stress through rapid diagnosis [62]

and specific antiviral treatments. However, in the real world, most countries are usually unprepared to face such a pandemic. In particular, during COVID-19, an initial lack of positive control, primers and/or probes as long as a lack of personnel/time and of specific therapies together with a large number of paucisymptomatic and asymptomatic people yielded most policies to shift towards lockdown measures rather than modern laboratory-based testing and consequent quarantine [62, 63]. European countries, for instance, implemented a series of containment measures, ranging from lockdown to an intermediate safe distancing (Italy, France, Spain, Denmark, Norway, Switzerland, Austria, Belgium, UK and Germany), with only one country that has chosen not to adopt lockdown (Sweden) [64]. Most States in the world added in an unprecedented way lockdown measures to the other traditional containment measures adopted during the last epidemics, such as SARS [65]. However, this widespread governance resolution generated new research challenges. Currently, scientific and political institutions do not require any type of comparative study on the risks and benefits before implementing lockdown measures. This happens despite the consequences of these old measures to the overall mental and physical health of the population's remain mostly unexplored [66].

Conclusions

COVID-19 and SARS are infections with similar phylogenetic and pathogenetic characteristics that primarily affect the respiratory and gastrointestinal systems. The knowledge acquired so far has allowed us to highlight some distinctive features of COVID-19 in comparison to SARS. SARS has a high prevalence of severe illness but with a low infectivity in the first days of illness, before the development of severe illness. Conversely, COVID-19 can be considered as a disease with a lower lethality rate but with high risk of transmission compared to SARS even in the presence of mild symptoms or in the absence of any visible signs of infection.

A rather high percentage of SARS patients had typical symptoms such as fever, cough, chills, headache, fatigue and myalgia. Among the most common symptoms in COVID-19 patients are cough, fever, myalgia, and headache, but there is no highly prevalent symptom such as fever that was detected in almost 90% of the SARS patients analyzed. Gastrointestinal and cardiovascular symptoms seem to be more common in SARS. Based on reports of more than 23,000 COVID-19 cases, numerous other less common and atypical manifestations including neurological symptoms (ageusia, anosmia), dermatologic manifestations and ocular symptoms, have also been identified. In light of this, the detection of fever, cough and shortness of breath as an identification method should be reviewed. In addition, COVID-19 patients exhibit a wide range of comorbidities. Therefore, it is very important to know what signs and symptoms to

look out for and recognize and which diagnostic tests to use for prompt treatment and prevention of further infections.

If clinical manifestations are mild and there is no need to seek medical care, it is very important that symptoms are monitored and national public health measures are followed in order to control the spread of the first epidemic wave in the countries where it is still in place or prevent a further wave of COVID-19.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

AZ reviewed the articles related to virological, epidemiological, and transmission aspects; VR investigated the containment strategies; AA examined the diagnostic laboratory tests; MG carried out the analysis of data on clinical features and comorbidities. All authors contributed to the preparation of the manuscript related to their sections and approved the final version to be submitted.

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RESEARCH ARTICLE

The COVID-19 pandemic as a factor of hospital staff compliance with the rules of hand hygiene: assessment of the usefulness of the “Clean Care is a Safer Care” program as a tool to enhance compliance with hand hygiene principles in hospitals

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Keywords

Hand hygiene • Educational program • Efficiency • Disinfection • COVID-19

Summary

Introduction. Hand cleansing and disinfection is the most efficient method for reducing the rates of hospital-acquired infections which are a serious medical and economic problem. Striving to ensure the maximum safety of the therapeutic process, we decided to promote hand hygiene by implementing the educational program titled “Clean Care is a Safer Care”. The occurrence of the COVID-19 pandemic affected the compliance with procedures related to the sanitary regime, including the frequency and accuracy of hand decontamination by medical personnel.

Objective. The objective of the study was to assess the usefulness of the educational program titled “Clean Care is a Safer Care” as a tool for increasing compliance with hand hygiene principles.

Methods. We monitored the compliance with the hygiene procedure before implementation of the program as well as during the

hand hygiene campaign by means of direct observation as well as the disinfectant consumption rates.

Results. In the initial self-assessment survey, the hospital had scored 270/500 points (54%). Preliminary audit revealed the hygiene compliance rate at the level of 49%. After broad-scaled educational efforts, the semi-annual audit revealed an increase in hand hygiene compliance rate up to 81% (hospital average) while the final audit carried out after one year of campaigning revealed a compliance rate of 77%. The final score for the hospital increased to 435/500 points.

Conclusions. COVID-19 pandemic dramatically increased accuracy of proper hand hygiene procedures and consumption of disinfectant agents. The educational program has succeeded to reach its goal; however, long-term educational efforts are required to maintain and improve the quality of provided services.

Introduction

Every year, millions of patients acquire infections during hospital treatment. The scale of the problem is best illustrated by data indicating that hospital-acquired infections development in nearly 10% of all hospitalized patients while reaching nearly 50% in case of high-risk groups such as ICU patients, patients subjected to prolonged artificial ventilation, or immunosuppressed patients.

These serious complications increase the length of hospital stay by about 5-10 days, leading to potential disabilities as well as double the morbidity rates in affected patients [1].

Hospital-acquired infections are also a serious economic problem due to the increased treatment costs. As estimated by Urban et al., treatment of mild infections may increase the individual treatment costs by at least 400 USD while the average costs of the treatment of severe nosocomial infections exceed 30,000 USD per patient. In many cases, nosocomial

infections are transmitted by the medical staff due to their failure to comply with aseptic and antiseptic procedures [2].

Strict compliance with hand hygiene principles is of special importance in reducing the nosocomial infection rates. Hand cleansing and disinfection practices are the most economical and most efficient methods to prevent transmission of microorganisms and reduce hospital-acquired infection rates [3]. Despite the simplicity of this measure, non-compliance with its principles is a global problem in the health care sector [1].

The pioneer of hand hygiene as a measure to prevent hospital-acquired infections was Ignaz Philipp Semmelweis (1818-1865) who discovered the correlation between dirty hands of obstetricians and the incidence of postpartum infections and was the first to implement appropriate hand disinfection procedures.

Today, nearly 200 years later, proper compliance with hand hygiene principles is still a problem for medical professionals [4]. The importance of this simple

procedure appears to be underestimated by medical professionals as the World Health Organization estimates that the compliance rates range from 5% to 89% [5].

In 2009, WHO published the guidelines for proper hand hygiene in the medical sector. All around the globe, training is organized for medical professionals as part of the First Global Patient Safety Challenge “Clean Care is a Safer Care” [6]. Poland joined the initiative in 2013. Many hospitals in our country decided to implement the WHO guidelines as a measure to reduce the hospital-acquired infection rates.

The guidelines were also adopted by the Medcover Hospital in Warsaw as a means to ensure the maximum safety of the therapeutic services provided to our patients. Program implementation was coordinated by the Hospital-Acquired Infections Team which worked to increase the awareness of hospital workers in relation to the importance of hand hygiene as well as to strengthen good behavior models to promote proper hand hygiene.

The outbreak of the COVID-19 epidemic provided completely new observations of behavior among medical staff. Measurements of the use of liquid soap and hand disinfectant, carried out at that time showed dramatic increase in use.

Objective

The objective of the study was to assess the usefulness of the educational program titled “Clean Care is a Safer Care” as a tool to enhance the compliance with hand hygiene principles before and during COVID-19 pandemic.

Material and methods

Medcover Hospital is a large, broad-profile hospital which provides its patients with high quality, comprehensive health care. The educational program was implemented there in 2014. Education included special training workshops, repeated worksite training for all staff members, and visual accents to remind the personnel of the hand hygiene principles. The promotional material was prepared in collaboration with Ecolab company. Posters highlighting the importance of hand hygiene and information on the efficiency of this measure were placed in strategic locations and points of care across the institution. Care was taken to ensure the constant availability of alcohol-based disinfectant at points of care at every department. In addition, disinfectant dispensers are placed in special holders at all patient beds. An observation study of hand hygiene behaviors was commenced.

The awareness of the role of institutional involvement in the desired change in personnel behaviors led the hospital management and staff administration team to define hand hygiene a priority task for the entire hospital personnel. The study group consisted of all the hospital’s nurses, auxiliary staff, physicians, and other

employees of all hospital departments and the outpatient consultation center.

The study was based on the tools to implement multi-aspect strategy for hand hygiene as developed by the WHO. The strategy consists of 5 key components [7]:

1. systemic change;
2. training and education of health care professionals;
3. assessment and feedback;
4. visual instructions at worksite;
5. promotion of institutional safety.

A maximum of 100 points may be scored in each of these areas (for a maximum overall score of 500).

The package of implementation tools includes the Hand Hygiene Self-Assessment Questionnaire as a validation tool to assess the implementation of the 5 components of the WHO strategy at health care institutions.

Based on the total number of points obtained after completion of the questionnaire, the institution is assigned with one of the four possible levels of hand hygiene promotion and practice, including insufficient, basic, intermediate, and advanced. Institutions classified into the advanced level provide answers to 20 questions in the leaders’ section to obtain a maximum of 20 points. Twelve points are enough to achieve the status of a leader [7].

This study was carried out by means of a diagnostic survey based on the Polish version of the “2010 WHO Self-Assessment Questionnaire” for hand hygiene published in April 2013. The tool facilitates the analysis of current capabilities and knowledge of hand hygiene issues as well as identification of future goals and measures. The compliance with the hand hygiene principles was monitored in a direct as well as an indirect fashion.

Direct monitoring of hand hygiene consisted in direct observation carried out by a specially trained staff and based on the “Five Moments for Hand Hygiene” WHO guidelines. The guidelines present five indications for hand hygiene procedures: before touching a patient, before clean/aseptic procedures, after body fluid exposure/risk, after touching a patient, and after touching patient surroundings [8].

Another WHO implementation tool, *i.e.* the disinfectant consumption rate, was also used to determine the hand hygiene level at the Medcover Hospital. The rate corresponds to the quantity of hand disinfectant consumed per 1,000 person-days at individual departments or in the entire hospital [9]. Based on the form for recording nursing tasks requiring hand hygiene measures, hand hygiene compliance rate was calculated on the basis of average consumption of soap and disinfectant. All these factors were monitored in “non-pandemic” and “pandemic” season.

Results

In the initial self-assessment survey taken in 2014, the Hospital scored a total of 270/500 points (54%), corresponding to the intermediate compliance level. The

poorest scores were obtained in institutional safety and training/education components.

The hand hygiene compliance rate calculated on the basis of the consumption of soap and disinfectants by the hospital staff was 49%. While the overall compliance with hand hygiene measures was 50%, it varied in individual personnel groups, ranging from 63% in nursing staff to as little as 9% in the auxiliary personnel. Soap consumption was 630 L per year, corresponding to 31 mL per person/day; the annual consumption of 460 L of disinfectant corresponded to 22 mL per person/day. The average compliance with the “Five moments for hand hygiene” was 60%.

Hand hygiene was measured in general and in individual departments. As shown by the initial audit, the lowest compliance score was observed at the admission room. Subsequent audits suggested a constant improvement in these parameters until final audit. During observation period the ICU became the institution’s leader in this regard.

After initial assessment and identification of institution-specific principles for implementation of the “Clean Care is a Safer Care” educational program, training workshops and worksite training were commenced, and educational materials such as posters and reminders were distributed around the hospital. UV lamps were used to assess the correctness of hand cleansing during the training sessions.

After these broad-scaled educational efforts, the semi-annual audit revealed an increase in hand hygiene compliance rate up to 81% (hospital average, observation day 180) while the final audit carried out after one year of campaigning revealed a compliance rate of 77%.

The largest problem was identified in relation to hand hygiene following the contact to patient surroundings, with relevant principles being complied with only in 22% of cases. This aspect was also associated with the highest increase in the compliance rate, with the percentage of desirable behaviors rising to 60%.

Following the exposure to body fluids, the procedures were complied with in 60% at day 0 to reach 95% at the end of the observation period. The highest mean compliance rates were observed before the commencement of aseptic procedures (77% before the program vs. 88% on observation day 365) as well as following the contact with the patient (51% before the program vs 79% on observation day 365).

According to the final assessment survey (took on observation day 365), the final score for the entire institution in the year 2016 was 435/500 points, with hand hygiene compliance rate reaching the final value of 77%. The increase in the compliance to hand hygiene principles varied in different health care professionals. It increased in physicians and nurses, but the most significance increase was observed in the auxiliary staff (from 9 to 63%). This might be due to the awareness in this workers’ group being initially low and increasing significantly as the result of the educational efforts.

High results were achieved in all individual aspects of hand hygiene, with the change in the preferred alcohol-

based hand disinfectant being generally accepted. Organizational culture-related measures for promoting safer health care require further attention and continued improvement. The analysis carried out at the Medcover hospital during the COVID-19 pandemic compared the use of disinfection fluids in 2019 and the first two months of the epidemic in 2020 an dramatic increase in the use of detergents and disinfectants has been observed. The results of the analysis are collected in the Table I.

Discussion

Hospital hand hygiene is one of the cardinal principles for reducing the transmission of pathogens during therapeutic procedures. Appropriate assessment of the compliance with hygienic guidelines and procedures is an important tool for modeling appropriate behaviors of the medical staff. Methods for the monitoring of the compliance with hand hygiene principles at health care institutions include direct observation, measurement of hand hygiene agents consumption, measurements and studies [10] or electronic devices installed at worksites [11]. However, no standardized assessment method has been developed and none of the existing methods can be considered ideal due to their high costs, subjective nature, or staff behaviors being changed while under observation. It was mainly for this reason that out of 36 campaigns held in 36 European countries in years 2000-2012, only 50% could be assessed for efficiency with the WHO guidelines being implemented in only 55% of this latter group [12].

Nowadays, direct monitoring by specially trained personnel is considered to be a gold standard [13-15]. The method provides detailed information on the hand hygiene behaviors in different groups of the medical staff at the crucial moments that determine the risk of patient-personnel-patient transmission of pathogens. As part of the “Clean Care is a Safer Care” program, the WHO developed a special observation form which facilitates monitoring of hand cleansing and disinfection behaviors on the basis of “Five Moments for Hand Hygiene”, *i.e.* before touching a patient, before clean/aseptic procedures, after body fluid exposure/risk, after touching a patient, and after touching patient surroundings. The Hospital-Acquired Infections Team at the Medcover Hospital used this observation tool in the development of a program to monitor and improve hand hygiene in the personnel involved in patient care [9]. Another WHO implementation tool developed as part of the “Clean Care is a Safer Care” program, *i.e.* the disinfectant consumption rate, was also used to determine the hand hygiene level at the Medcover Hospital. The rate corresponds to the quantity of hand disinfectant consumed per 1,000 person-day at individual departments or in the entire hospital [9]. According to the WHO guidelines, the minimum consumption of hand disinfectants should be at the level of 20 liters per 1,000 person/day [9]. The

Tab. I. Hands sanitizer's use analysis during the SARS-CoV-2 coronavirus epidemic and 2019 year.

	Consumption per 1 patient in 2019 year	Number of hospitalizations, epidemic (March-April 2020)	Consumption of disinfectant on the ward during the epidemic in liters	Consumption per patient during the epidemic in liters	Consumption per 1 patient in 2019 in ml	Consumption per 1 patient in epidemic in ml	Increase in percentage
Surgery clinic	0.04	93	32	0.4	40	320	800
Internal Medicine and Cardiology clinic	0.07	204	70	0.34	70	340	486
Internal Medicine and Cardiology clinic	0.24	37	20	0.54	240	540	225
Internal Medicine and Cardiology clinic	0.07	257	80	0.31	70	310	443
Child health clinic	0.06	35	20	0.57	60	570	950
Anesthesiology and Intensive care clinic	0.26	54	30	0.55	260	550	211

advantages as well as disadvantages of this method have been broadly discussed in the literature. The advantages consist in relatively simple data collection as well as a lower number of staff members being involved in the monitoring resulting in lower costs. The disadvantage consists in measurement inaccuracies as *e.g.* cases of disinfectant spills or cleaning agents being used by the patients are not accounted for. Despite the above, the disinfectant consumption rate is often associated with the hand hygiene behavior rate; according to some authors, it is a priority method which should be considered more important than direct observation [16-19]. As the result of the educational program being implemented in the hospital, the compliance with the hand hygiene guidelines has improved significantly. The program was based on worksite training, poster campaign, observational studies, disinfectant consumption monitoring and promotion of hand disinfectant use. Of note is the fact that hygiene consultants used UV lamps to better visualize potential risks during the workshop training. In relation to the low compliance with the hand hygiene principles as defined by the "Five Moments for Hand Hygiene", particularly in relation to the contact with patient's surroundings (only 22% of proper behaviors as determined during the initial audit), an assumption was made that the personnel was unaware of the risk of pathogen transmission in cases when no direct contact with the patient has occurred. Thanks to the use of UV lamps, employees could better see that the patient's surroundings (bed, pajamas, personal items) are a reservoir of pathogens which are easily transmitted onto professionals' hands even when the patient is

absent, and therefore, that appropriate hygiene measures should be taken after touching such items. As shown by this example, it is rational to include various techniques for better visualization of the pathogen transmission stages in educational materials as this may result in higher compliance of hygiene principles by the health care staff [20]. In the course of our study, we observed that hand hygiene behaviors were significantly more common after touching the patient than before touching the patient (60 vs 54% at day 0 and 95 vs 80% at day 365). Whitby et al. highlighted that health care workers are more likely to comply with hygiene principles when self-preservation imperative is involved, *i.e.* when they perceive their hands to be contaminated and have the potential for transmitting the infection to employees themselves as well as those close to them (*i.e.* after touching the patient or their biological material) [8]. Therefore, promotion of attitudes stressing the personnel's responsibility for the patients' health, including legal liability in case of any claims from patients having acquired nosocomial infection, is very important. According to many authors, nurses are more aware of the problem as compared to physicians [21, 22]. Boscard et al. suggest that the motivation behind hand hygiene compliance in nurses consists in their concern for the safety of themselves as well as their close ones, since nurses are aware of risks associated with the failure to comply with the procedures [23]. Regardless of the monitoring method, appropriate reporting of results, and feedback on observation and disinfectant consumption results should be an important educational as well as motivational component of the hand hygiene

program [24]. In our experience gained during implementation of the monitoring program at the Medcover Hospital, direct observation and feedback was the most effective measurement method. Although an improvement was achieved, there is no certainty as to how long the new compliance rates would hold after intervention is discontinued. This would require further observations and development of efficient methods for the strengthening of behavior patterns. Many authors have highlighted that numerous health care professionals have problems with complying to hand hygiene principles. The reported causes of such a non-compliance include heavy workload and non-availability of disinfectants as well as insufficient number of protective gloves [25]. These, however, are not the only causes: problems with availability of protective gloves or disinfectants had never been encountered at Medcover Hospital, suggesting a significant importance of the “human factor”, the lack of appropriate procedures, education, and hygiene monitoring. According to WHO recommendations, hand cleansing or disinfection should be performed at the point of care, *i.e.* at a place where the three elements: the patient, the health care professional, and a medical procedure, exist concurrently. Hand cleansing and disinfection agents should be readily available at points of care so that health care professionals do not have to leave the patient zone [10]. On the basis of these recommendations, hand disinfectant holders were placed on patient beds in the Medcover Hospital. Studies confirmed that disinfecting hands using an alcohol-based rub is more efficient than washing while being easy to implement and inexpensive. According to calculations, prevention of 8 cases of hospital-acquired pneumonia would compensate the annual cost of hand disinfection agents [26]. As shown by such calculations, implementation of hand hygiene programs leads to measurable therapeutic and economic benefits [27]. Most employees of the Medcover Hospital changed their behavioral habits and the compliance rate has increased significantly as the result of increased use of hand disinfectants from 49% at the initial audit to 81% at day 180 and 77% at day 365. A significant increase in the tested parameters was observed in the semiannual audit, followed by a slight decrease in the final audit. Our results correspond to those obtained in other studies as medical personnel appears to be somewhat bored with the hand hygiene campaigns. It might show that the best method for the improvement in hand hygiene consists in placing hand cleansing instructions at the key points of care [9]. According to Pittet et al. [28], best results are achieved when education is combined with hand hygiene reminders such as posters, brochures, memes, etc. Although posters are considered to be somewhat outdated as an educational tool, they may provide useful reminder when placed at the point of care. The importance of posters developed using the social marketing concept was demonstrated by Forrester in Canada [29] as well as by successful national campaigns in Australia and Europe.

Implementation of current graphical trends and aggressive content increases the impact of this type of media [30, 31]. Introduction of hand hygiene programs for medical personnel at health care institutions is of high importance in the prevention of infections. As shown by Pittet et al., implementation of these recommendations in the University Hospital In Geneva reduced the nosocomial infection rate from 16.9 to 9.9% [32, 33]. Rosenthal et al. showed that the improvement in hand safety contributed to a significant reduction in the rate of nosocomial infections (from 47.55 to 27.93 per 1,000 patient/day) [34]. Multi-aspect campaigns unambiguously increase the hand hygiene compliance rates. During a 2-year campaign carried out by the WHO in 8 regions of the world (2004-2006), the mean compliance rate increased from 39.6 to 56.9%; notably, the impact of the intervention was higher in the developing countries where the access to knowledge and protection measures was more limited [35]. However, it must be noted that compliance with high hygienic standards is also associated with the institutional structure of the health care system which differs in different countries. Epidemiological studies revealed a correlation between infection rates and the low number of personnel in relation to the high number of patients. As the result of the number of patients or physicians being too low, hand hygiene behaviors are reduced or even absent between provision of consecutive patients [36, 37]. Without appropriate employment rates, it would be very difficult to expect an improvement in the quality of services and maintenance of high hygienic standards. Considering the dwindling number of applicants for health care jobs in Poland as well as the aging of the society and health care professionals combined with economically-driven emigration, maintenance of high treatment standards may become increasingly difficult in near future. Notably, the degree of hand hygiene program implementation is associated with the quality of epidemiological process monitoring. As shown by the studies, appropriate number of epidemiologists is required in relation to the number of hospital beds [7]. According to the common consensus, the appropriate rate is 1:250; however, as demonstrated by Delphi [38], a ratio of 0.8-1/100 might be required for an improvement to be observed. In Poland, the ratio has been statutorily established at 1:200; many hospitals, however, fail to comply with this requirement. In our study, the organizational culture and safety of health care was shown to be the weakest link of the Multi-aspect Strategy for Hand Hygiene (55 points). This result is not satisfactory since the support from health care administration and local governments is crucial for hand hygiene being considered a priority for patient safety and for educational programs being continued [39]. According to the self-assessment survey administered at the Medcover Hospital, the advancement of the hand hygiene program was “intermediate” at the beginning and closer to “advanced” at the end showing that hygiene practices

improved significantly. The measures are being continued to date. The compliance with hand hygiene principles at the Medicover Hospital in “non-pandemic period” was pretty good; it was higher than at numerous sites in developed countries assessed in the similar manner. We expect, that further improvements will be still possible, particularly by increasing institutional safety, continuing the educational measures and optimizing the epidemiological personnel employment ratios. We estimate that particular attention must be paid to measures related to the organizational culture promoting health care safety. This element is particularly difficult to change as it is related to the culture of work modeled by the management staff who must acquire, strengthen, and implement new knowledge in their own behaviors before implementing efficient methods to promote, strengthen, and enforce hand hygiene behaviors at all levels of subordinate personnel. Changes in organizational culture are considered to take longer and require significant time and resources; they become visible in longer time frames, and they require continuous monitoring and strengthening. However, they are an efficient way for promoting appropriate hygiene habits in large health care institutions (hospitals, health care networks). We were not expecting that other factor can change totally hospital staff behaviors. Continuation of the study of hygiene practices related to hand washing after the outbreak of the COVID-19 epidemic provided completely new observations of behavior among medical staff. Measurements of the use of liquid soap and hand disinfectant carried out at that time showed more than 550-fold increase in consumption.

The results of this part of the study indicate the accompanying component of the psychosocial factor promoting protective behavior during the pandemic. Similar observations were made during the Severe Acute Respiratory Syndrome (SARS) epidemic in 2003, it was recorded that with an increased number of cases of infection, care for hand hygiene increases significantly [40]. Perception of threat is a subjective phenomenon, even pragmatic than based on experience, Leppin et al. referred to this as a cognitive-emotional phenomenon [41]. Greater levels of anxiety may be associated with significant behavioral changes, e.g. more frequent washing, disinfecting hands to protect against infection, its complications and potential death. Recent studies by the National Health Commission of China in Chinese hospitals in February 2020 estimated the transmission of infection between COVID-19 patients and medical personnel to be 3.8%. Guo et al. they compared the COVID-19 pandemic with the Middle East Respiratory Syndrome (MERS) epidemic in Saudi Arabia in 2012 and SARS in South Korea in 2015. Outbreaks were concentrated in hospitals and the percentage of infections among healthcare professionals ranged between 33-42%. Unfortunately, the transmission risk factor has not been clearly defined [42]. Current research confirms that widely available detergents, including soap, are a reliable and cheap form of minimization of viral transmission between patients and others peoples including medical staff. Other

compounds with proven effectiveness in preventing hand-transmitted infections are disinfectant based on alcohol. Current quality requirements of disinfectants indicate that the concentration of alcohol having proven antiviral efficacy in the prevention of COVID-19 is 62-71% [43]. Hand washing still remains the most effective form of prevention of transmission infectious respiratory diseases including COVID-19 [44]. Our study had a certain limitation consisting in randomization being impossible due to the single-site, all-hospital character of the intervention. Due to the multimodality of the campaign, it is difficult to pinpoint the most effective element of the strategy. However, our results suggest that long-term, planned epidemiological activity promoting proper behaviors and habits in relation to hand hygiene may significantly increase the indices of epidemiological safety in hospital treatment.

Conclusions

Providing education to healthcare professionals in relation to proper hand hygiene during providing care to the patients is the most important element of multimodal interventional strategies aimed at hand hygiene improvement. The First Global Patient Safety Challenge “Clean Care is a Safer Care” has acquired its desired effect; however, long-term educational measures are required to maintain and further increase the quality of services and patient safety. COVID-19 pandemic dramatically increase accuracy of proper hand hygiene procedures and consumption of disinfectant agents.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MK developed the original idea. RD, MA, BW, TP carried out the literature search. MK, RD, MA collected the data. MK carried out the statistical analysis. MK, BW drafted the manuscript. All authors have read and approved the latest version of the manuscript for publication.

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RESEARCH ARTICLE

Characteristics, management and outcomes of critically ill COVID-19 patients admitted to ICU in hospitals in Bangladesh: a retrospective study

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Keywords

Bangladesh • COVID-19 • Critical care • Epidemiology • Clinical characteristics • Comorbidities • Managements

Summary

Objectives. This study aimed to analyze the epidemiological and clinical characteristics of COVID-19 cases and investigate risk factors including comorbidities and age in relation with the clinical aftermath of COVID-19 in ICU admitted cases in Bangladesh.

Methods. In this retrospective study, epidemiological and clinical characteristics, complications, laboratory results, and clinical management of the patients were studied from data obtained from 168 individuals diagnosed with an advanced prognosis of COVID-19 admitted in two hospitals in Bangladesh.

Results. Individuals in the study sample contracted COVID-19 through community transmission. 56.5% (n = 95) cases died in intensive care units (ICU) during the study period. The median age was 56 years and 79.2% (n = 134) were male. Typical clinical manifestation included Acute respiratory distress syndrome

(ARDS) related complications (79.2%), fever (54.2%) and cough (25.6%) while diabetes mellitus (52.4%), hypertension (41.1%) and heart diseases (16.7%) were the conventional comorbidities. Clinical outcomes were detrimental due to comorbidities rather than age and comorbid individuals over 50 were at more risk. In the sample, oxygen saturation was low (< 95% SpO₂) in 135 patients (80.4%) and 158 (93.4%) patients received supplemental oxygen. Identical biochemical parameters were found in both deceased and surviving cases. Administration of antiviral drug Remdesivir and the glucocorticoid, Dexamethasone increased the proportion of surviving patients slightly.

Conclusions. Susceptibility to developing critical illness due to COVID-19 was found more in comorbid males. These atypical patients require more clinical attention from the prospect of controlling mortality rate in Bangladesh.

Introduction

The Coronavirus Disease 2019 (COVID-19), came into limelight in early December 2019, when some cases of pneumonia were reported in Wuhan, Hubei, China; whose cause following laboratory assessment, was found to be a novel strain of virus belonging to the Coronavirus family and was labelled SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) [1]. The spread of the infection is a rising, rapidly advancing circumstance and due to this whirlwind rate of spread, COVID-19 has been pronounced as a global pandemic by the WHO since March 11, 2020. As of 23rd September, more than 31.7 million positive cases of COVID-19 have been reported in 217 countries and territories with more than 975,315 deaths. COVID-19 targets the respiratory tract of humans and has similar clinical symptoms to SARS-CoV and MERS-CoV [2-4]. Typical symptoms experienced by COVID-19 positive individuals include fever, dry cough, fatigue, headache,

vomiting, diarrhoea, shortness of breath, myalgia, acute respiratory distress syndrome (ARDS) related symptoms and shock [5-9]. Previous studies reported that the patients who need intensive care tend to be older in age and male, and about 40% have comorbid conditions, including diabetes, cardiac diseases, hypertension, asthma and other chronic illnesses such as liver or kidney disease [10, 11]. According to the World Health Organization, about 5% COVID-19 patients, who are severe or critically ill require admission to an intensive care unit (ICU) [12]. However, shortages of standard healthcare resources, especially ICU supports are causing the high mortality rate of critically ill patients.

The COVID-19 pandemic has imposed an enormous burden and massive challenges to the health care system, especially ICUs, across developed, developing and underdeveloped countries. Likewise, Bangladesh also falls in the category of unfortified countries due to its high population and poor health care system [13]. In Bangladesh, current

median age is 26.7 years and mortality rate is 5.52 [14]. Moreover, life expectancy is 73.4 years and a total of 7% of the country's population are senior citizens [14, 15]. Most of these senior citizens, as well as middle-aged people in the country, have comorbidities, such as diabetes (9.7%), asthma (5.2%), hypertension (20%), cardiac disease (4.5%) and chronic pulmonary disease (11.9%), and around 1.3 to 1.5 million cancer patients in the country are vulnerable to COVID-19 [16-19]. All of these people, who belong to a vulnerable group, may require immediate hospitalisation and intensive care if they contract COVID-19 [11]. Compared to the eight worst affected countries, Bangladesh has the lowest number of COVID-19 ICU beds per 10,000 inhabitants (Supplementary Fig. 1). How the health management system with its poor and limited resources is responding to and tackling critical COVID-19 patients is a matter of inordinate concern. Therefore, it is important for health and government authorities to have information on the clinical features and outcomes of COVID-19 in critically ill cases for them to address the necessities of ICU facilities and prepare for a possible second wave of COVID-19 in Bangladesh. In China, India, Greece and the U.S., similar epidemiological studies have already been conducted sampling COVID-19 patients admitted in the ICU, in order to distinguish COVID-19's clinical implications on patients who had to be admitted in the ICU. Insights obtained from these studies can assist experts to further pinpoint exact management and follow-up medical routines [20-23]. Therefore, this study aims to investigate the epidemiological and clinical features, disease severity, treatment and clinical outcomes of critical COVID-19 cases in Bangladesh with the goal of portraying a bigger picture of severe clinical manifestations of COVID-19 so that the malleability Bangladesh's health care system can be modified in terms of tackling COVID-19.

Methods

PATIENTS AND DATA COLLECTION

This study's sample comprises 168 COVID-19 patients with definite outcomes who were admitted to Chittagong General Hospital and Chittagong Medical College Hospital (COVID-19 unit) between 1st April 2020 and 7th August 2020. The Chittagong General Hospital and Chittagong Medical College Hospital (COVID-19 unit) are specialised hospitals that have been authorised for managing most of the critical COVID-19 patients in the country's economic hub, namely Chattogram city. The epidemiological and demographic data for this study were obtained from the inpatients' files. Approval of this study was provided by the Institutional Review Board (IRB) of Chattogram General Hospital Ethics Committee. In terms of data collection and usage, patients and in some cases, their next of kin (first degree relatives) gave their accord.

THE CRITERIA FOR ICU ADMISSION

Management of all the COVID-19 patients admitted in the ICU were implemented according to the regulations set

nationally for COVID-19 management in Bangladesh [24]. Based on clinical symptoms, patients were divided into mild, moderate, severe and critical groups. Most of the severe or critical patients and few moderate ill patients were admitted to the ICU. Those in the severe group have respiratory distress, i.e. a respiratory rate of ≥ 30 beats per minute in a resting state and an oxygen saturation of $\leq 92\%$ SpO₂, and those in the critical group experience respiratory failure, Sepsis and shock, thus requiring mechanical ventilation, as well as the combined failure of other organs, which require ICU monitoring and treatment. In both the hospitals combined during the study duration, a total of 1,835 COVID-19 patients were admitted. Of these 1,835 patients, 168 (9.16%) had to be admitted in the ICU and 95 of these 168 ICU patients died. Among the patients who survived, 55.9% (94/168) were in critical condition, 39.9% (67/168) were in severe condition and other 4.2% (7/168) were in moderate condition. The coordinative physicians were accountable for collecting this data from the patients. ARDS was defined according to the Berlin definition [25], and shock was defined according to the sepsis-3 criteria [26].

RT-PCR ASSAY FOR COVID-19

Whether the cases of the sample were positive with COVID-19 was confirmed via a real-time reverse transcription polymerase chain reaction (RT-PCR) assay of respiratory tract samples. Throat swabs were collected and maintained in the viral transport medium. The laboratory test assays for COVID-19 were conducted according to standards set by the World Health Organisation's (WHO). Upper and lower respiratory tract specimens were collected in order to extract SARS-CoV-2 RNA. The RNA was obtained and further tested by means of RT-PCR using the same method that was described previously [20].

STATISTICAL ANALYSIS AND PLOTTING

Descriptive statistical analyses were performed to express categorical variables with numbers and proportions. These were then compared using a chi-square test. P values of less than or equal to 0.05 (two-sided) were considered statistically significant. R-script and GraphPad Prism version 7.04 was used to perform all of the statistical analyses and the figure plotting. Patients with at least one type of comorbidity were considered comorbid, and those with no comorbidity were considered non-comorbid patients.

Results

CLINICAL FEATURES, EPIDEMIOLOGICAL FEATURES AND VITAL SIGNS EXAMINATION

Among the 168 COVID-19 patients admitted in the ICU with a confirmed outcome, 95 (56.5%) of the severely ill patients died in the ICU and the remaining 73 patients (43.5%) were transferred to the isolation ward following improvement (Tab. I). Although 66.7% of the patients were over 50 years old, the highest proportion (28.6%)

Tab. I. Demographic and baseline features of COVID-19 ICU patients.

Variable	All patients (%)	Dead (%)	Alive (%)	Pearson's χ^2	P-value
Age (n = 168; dead = 95; alive = 73)					
11-20	2/168 (1.2%)	2/95 (2.1%)	0/73 (0.0%)	14.7	0.03
21-30	11/168 (6.5%)	4/95 (4.2%)	7/73 (9.6%)		
31-40	14/168 (8.3%)	4/95 (4.2%)	10/73 (13.7%)		
41-50	29/168 (17.3%)	13/95 (13.7%)	16/73 (21.9%)		
51-60	48/168 (28.6%)	34/95 (35.8%)	14/73 (19.1%)		
61-70	36/168 (21.4%)	20/95 (21%)	16/73 (21.9%)		
71-80	22/168 (13.1%)	15/95 (15.8%)	7/73 (9.6%)		
80+	6/168 (3.6%)	3/95 (3.1%)	3/73 (4.1%)		
Sex (n = 168; dead = 95; alive = 73)					
Male	134/168 (79.8%)	75/95 (78.9%)	59/73 (80.8%)	0.09	0.76
Female	34/168 (20.2%)	20/95 (21.0%)	14/73 (19.1%)		
Dwelling place (n = 168; dead = 95; alive = 73)					
Urban	110/168 (65.5%)	62/95 (65.3%)	48/73 (65.6%)	0.00	0.95
Rural	58/168 (34.5%)	33/95 (34.4%)	25/73 (34.2%)		
No	12/168 (7.1%)	9/95 (9.5%)	3/73 (4.1%)		
Comorbidities (n = 168; dead = 95; alive = 73)					
Diabetes	88/168 (52.4%)	53/95 (55.8%)	35/73 (47.9%)	1.02	0.31
Hypertension	69/168 (41.1%)	41/95 (43.2%)	28/73 (38.4%)	0.39	0.53
Heart diseases	28/168 (16.7%)	23/95 (24.2%)	5/73 (6.8%)	8.96	0.00
Other chronic diseases	16/168 (9.5%)	12/95 (12.6%)	4/73 (5.5%)	2.45	0.12
Asthma	15/168 (8.9%)	3/95 (3.2%)	12/73 (16.4%)	8.95	0.00
Kidney diseases	5/168 (3.0%)	3/95 (3.2%)	2/73 (2.7%)	0.02	0.87
Common symptoms during hospital admission (n = 168; dead = 95; alive = 73)					
ARDS related	133/168 (79.2%)	81/95 (85.3%)	52/73 (71.2%)	4.93	0.03
Fever	91/168 (54.2%)	50/95 (52.6%)	41/73 (56.2%)	0.21	0.65
Others	43/168 (25.6%)	25/95 (26.3%)	18/73 (24.7%)	0.06	0.81
Cough	43/168 (25.6%)	26/95 (27.4%)	17/73 (23.3%)	0.36	0.55
Sore throat	10/168 (6.0%)	5/95 (5.3%)	5/73 (6.8%)	0.19	0.67
Hypertension	5/168 (3.0%)	3/95 (3.2%)	2/73 (2.7%)	0.02	0.87
Diarrhoea	4/168 (2.4%)	2/95 (2.1%)	2/73 (2.7%)	0.07	0.79
Vomiting	4/168 (2.4%)	4/95 (4.2%)	0/73 (0.0%)	3.15	0.08

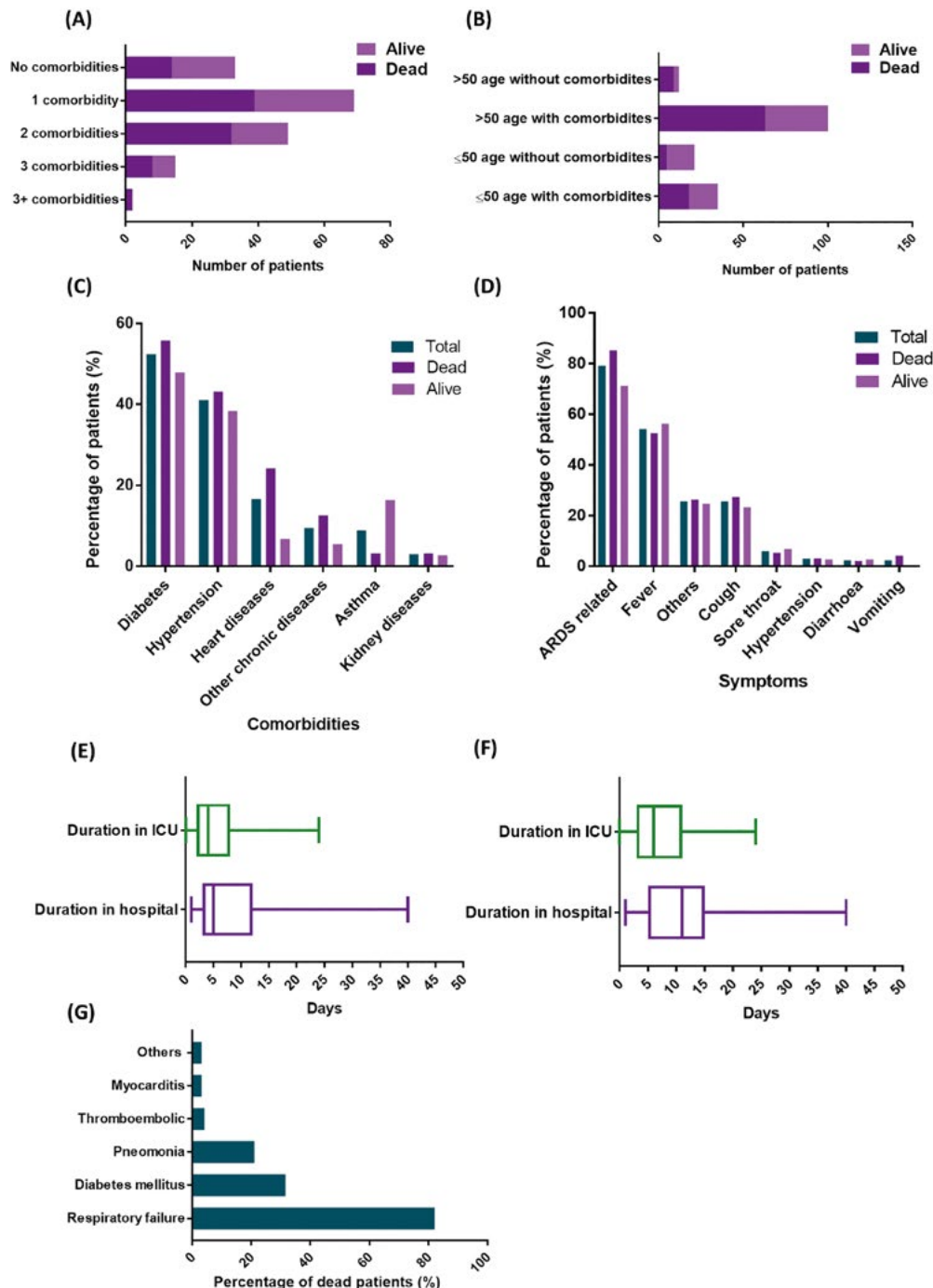
n: number of patients.

was between 51 and 60 years old. The proportion of male patients (79.8%) was more than female patients (20.2%). The COVID-19 individuals were into diverse professions and while the 10 (6.0%) of the patients had direct involvement in the healthcare system, most of the patients were from urban areas (65.5%). Persistence of a comorbidity was directly proportional to the state of being admitted in the ICU. As shown in Figure 1A, the proportion of deceased patients was relatively low in the group without comorbidities. Interestingly, the patients who were over 50 years old and had comorbidities comprise 66.3% of the total deaths, with the number of deaths being seven times the number of deaths in the group without comorbidities (Fig. 1B). About 82.1% (138/168) of patients had at least one coexisting chronic illness, predominantly diabetes (52.4%), hypertension (41.1%) or heart disease (16.7%) (Tab. I). The prevalence of diabetes, hypertension and heart disease in deceased patients was slightly higher (Fig. 1C). Interestingly, patients with asthma survived well compared to other comorbidities. The most common symptoms

experienced by patients were ARDS (133/168; 79.2%), fever (91/168; 54.2%) and coughing (43/168; 25.6%) (Fig. 1D). The median length of hospital stay was five days, and the median length of ICU stay was four days (Fig. 1E). The average duration of stay in the ICU was higher in surviving patients. In surviving patients, the median length of hospital stay was eleven days, and the median length of ICU stay was six days (Fig. 1F). In case of the deceased population of this study, respiratory failure (78/95; 82.1%), diabetes mellitus related complications (30/95; 31.6%), pneumonia (20/95; 21.0%), thromboembolic (4/95; 4.2%) and myocarditis (3/95; 7.4%) were found to be the most prevalent causes of death (Fig. 1G).

The body temperatures for all individuals in the study sample (Tab. II) were measured, and this ranged from 98°F to 102+°F. The vital signs at admission to the ICU were moderate fever $\geq 99^\circ\text{F}$ for 40 patients (71.1%), heart rate ≥ 100 beats per minute for 85 patients (51%) and a respiratory rate of ≥ 25 breaths per minute in 56% of the recorded patients (Tab. II). The patients who

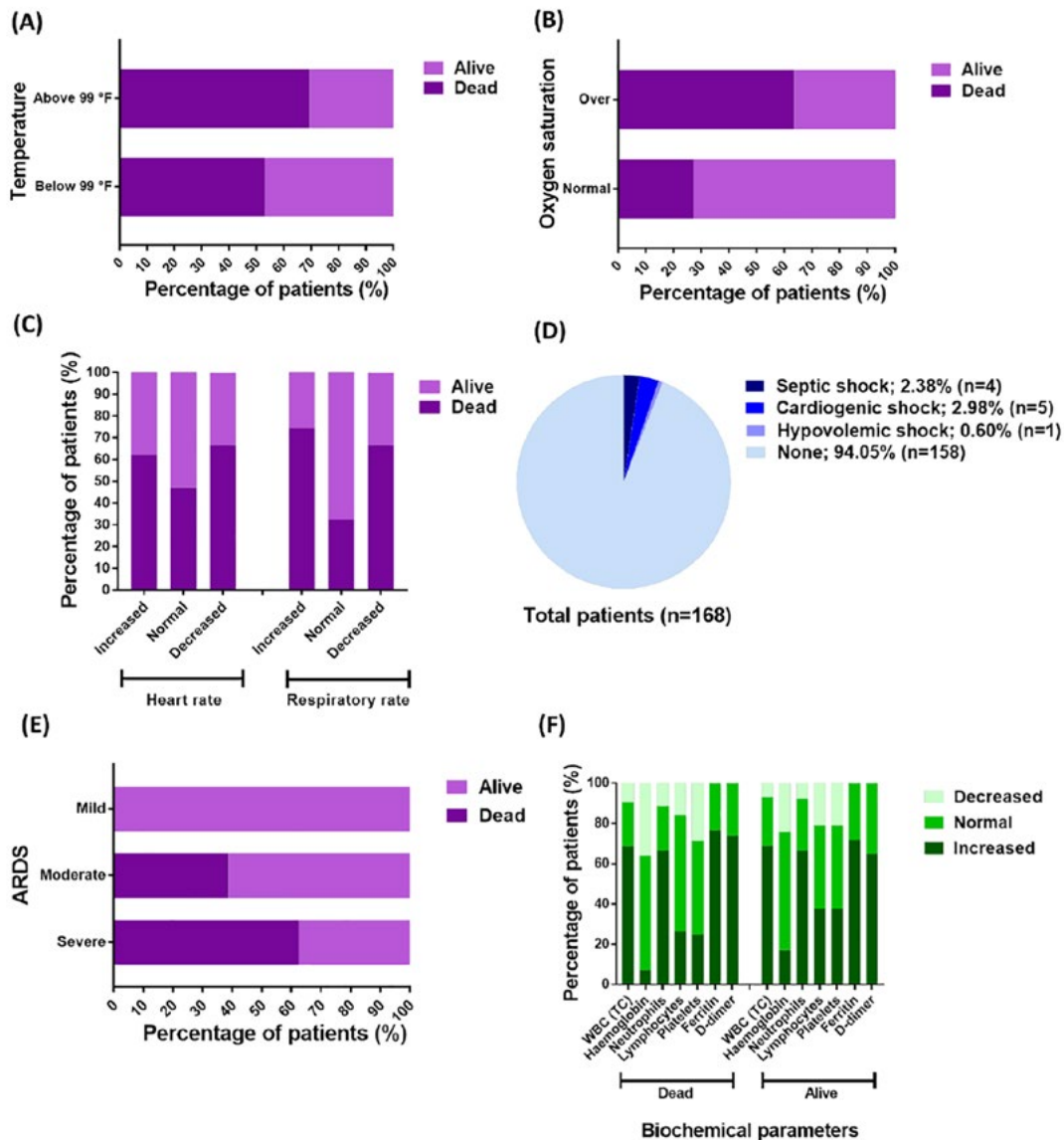
Fig. 1. The clinical features of Bangladeshi patients infected with COVID-19 admitted to the ICU. (A) Frequency of number of comorbidities in patients admitted to the ICU; (B) Relationship between age and comorbidities and its frequency in patients; (C) Percentage of the occurrence of different comorbidities in total, dead and alive patients; (D) Percentage of the occurrence of different symptoms in total, dead and alive patients; (E) Boxplot of the number of days in the ICU and hospital for patients admitted to the ICU, with the boxes spanning the 25 to 75 percentiles and the horizontal lines in the boxes representing the medians; (F) Boxplot of the number of days in the ICU and hospital for survived patients admitted to the ICU, with the boxes spanning the 25 to 75 percentiles and the horizontal lines in the boxes representing the medians; (G) Distribution of the reasons for death. ARDS: acute respiratory distress syndrome; ICU: intensive care unit.



had a moderate or high fever ($\geq 99^{\circ}\text{F}$) tended to have a higher mortality rate than those with a mild or no fever (Fig. 2A). Oxygen saturation was low ($< 5\%$ SpO₂) in 135 patients (80.4%) and the mortality rate of these patients was relatively high (Fig. 2B). The death rate of patients who had an abnormal heart rate and respiratory rate was higher (Fig. 2C). Shock occurred in 10 patients

(5.9%), including cardiogenic shock in 5 patients (2.9%) and septic shock in 4 patients (2.4%) (Fig. 2D). Of all 168 ICU patients, seven (4.2%) were classified as having a hypertensive crisis. Unfortunately, none of these patients survived. ARDS occurred in 167 (99.4%) patients, with 31 patients (18.5%) having moderate ARDS, three patients (1.8%) having mild ARDS and

Fig. 2. Vital signs, risk factors and laboratory findings. (A) Distribution of the clinical outcomes (dead or alive) of the patients in the no or low fever ($\leq 99^{\circ}\text{F}$) group compared to those in the moderate or high fever ($> 99^{\circ}\text{F}$) group; (B) Distribution of the clinical outcomes (dead or alive) of the patients in the normal oxygen saturation ($\geq 95\%$ SpO₂) group compared to those in the low oxygen saturation ($< 95\%$ SpO₂) group; (C) Distribution of dead and alive patients according to their heart rate and respiratory rate, namely whether it was increased, normal or decreased, with the normal reference values being a heart rate of 60 to 100 beats per minute and a respiratory rate of 12 to 20 breaths per minute; (D) Pie chart of the occurrence of septic shock, cardiogenic shock and hypovolemic shock; (E) Distribution of the clinical outcomes (dead or alive) of patients in the mild, moderate and severe ARDS groups; (F) Biochemical parameters of COVID-19 patients admitted to the ICU, with the normal reference values being: normal range of WBC of $4\text{--}10 \times 10^9$ per L, normal range of haemoglobin of 130–175 g per L, normal range of neutrophils of $1.8\text{--}6.3 \times 10^9$ per L, normal range of lymphocytes of $1.1\text{--}3.2 \times 10^9$ per L, normal range of platelets of $125\text{--}350 \times 10^9$ per L, D-dimer $< 0.5 \mu\text{g/mL}$, Ferritin $< 500 \mu\text{g/L}$. ARDS: acute respiratory distress syndrome; F: Fahrenheit; ICU: intensive care unit; L: litre; TC: total count; WBC: white blood cell.



133 patients (79%) experiencing severe ARDS. Eighty three out of the 133 severe ARDS patients (62.4%) died (Fig. 2E).

LABORATORY FINDINGS

The laboratory findings of the patients upon admission to the ICU are shown in Figure 2 and Table III. Statistical analysis was only conducted on the patients whose laboratory results were available. Elevated levels of White Blood Cell (WBC) and Neutrophils were identified in 68.9% (42/61), and 66.7% (44/64) patients, respectively. For 71 patients who underwent tests on

D-dimer, an excessive level was identified from 49 (69.0%) patients, with the level higher than 5 mg/L in 15 (21.1%) patients. Out of the 69 patients who had tests of Ferritin, elevated levels of Ferritin were identified in 53 (76.8%) patients (Tab. III). The biochemical parameters of the survived and non-survived patients were also compared, and it was found that they were essentially identical (Figure 2F).

MANAGEMENT AND MEDICATIONS

Oxygen therapy was administered in accordance with the patients' oxygen saturation. Over 90% of the

Tab. II. Vital signs at ICU admission of COVID-19 patients.

Variable	All patients (%)	Dead (%)	Alive (%)	Pearson's χ^2	P-value
Temperature (°F) (n = 168; dead = 95; alive = 73)					
< 98.0	5/168 (3.0%)	4/95 (4.2%)	1/73 (1.4%)	7.38	0.19
98 to 99	127/168 (75.6%)	66/95 (69.5%)	61/73 (83.5%)		
99.1 to 100	31/168 (18.4%)	21/95 (22.1%)	10/73 (13.7%)		
100.1 to 102	3/168 (1.8%)	2/95 (2.1%)	1/73 (1.4%)		
102+	2/168 (1.2%)	2/95 (2.1%)	0/73 (0.0%)		
Heart rate (normal: 60 to 100 beats per minute) (n = 168; dead = 95; alive = 73)					
Increased	85/168 (50.6%)	53/95 (55.8%)	32/73 (43.8%)	4.28	0.12
Normal	68/168 (40.5%)	32/95 (33.7%)	36/73 (49.3%)		
Decreased	15/168 (8.9%)	10/95 (10.5%)	5/73 (6.9%)		
Respiratory rate (normal: 12 to 20 breaths per minute) (n = 168; dead = 95; alive = 73)					
Increased	51/91 (56.0%)	38/53 (71.7%)	13/38 (34.2%)	15.09	0.00
Normal	34/91 (37.4%)	11/53 (20.8%)	23/38 (60.5%)		
Decreased	6/91 (6.6%)	4/53 (7.5%)	2/38 (5.3%)		
Blood pressure (systolic) (normal range: 90 to 120 mmHg) (n = 168; dead = 95; alive = 73)					
Hypertensive crisis	7/168 (4.2%)	7/95 (7.4%)	0/73 (0.0%)	7.42	0.06
Increased	78/168 (46.4%)	39/95 (41.0%)	39/73 (53.4%)		
Normal	50/168 (29.7%)	28/95 (29.5%)	22/73 (30.1%)		
Decreased	33/168 (19.7%)	21/95 (22.1%)	12/73 (16.5%)		
Blood pressure (diastolic) (normal range: 60 to 80 mmHg) (n = 168; dead = 95; alive = 73)					
Hypertensive crisis	7/168 (4.2%)	7/95 (7.3%)	0/73 (0.0%)	18.97	0.00
Increased	40/168 (23.8%)	22/95 (23.2%)	18/73 (24.7%)		
Normal	100/168 (59.5%)	47/95 (49.5%)	53/73 (72.6%)		
Decreased	21/168 (12.5%)	19/95 (20.0%)	2/73 (2.7%)		
Saturation of O2 (SpO2%) (normal range: 95 to 100) (n = 168; dead = 95; alive = 73)					
95 to 100	33/168 (19.6%)	9/95 (9.5%)	24/73 (32.8%)	33.88	1.813e-05
90 to 94	25/168 (14.8%)	7/95 (7.4%)	18/73 (24.6%)		
85 to 89	34/168 (20.2%)	26/95 (27.3%)	8/73 (11.0%)		
75 to 84	23/168 (13.8%)	15/95 (15.8%)	8/73 (11.0%)		
65 to 74	19/168 (11.3%)	11/95 (11.6%)	8/73 (11.0%)		
55 to 64	19/168 (11.3%)	16/95 (16.8%)	3/73 (4.1%)		
< 55	15/168 (9.0%)	11/95 (11.6%)	4/73 (5.5%)		
Acute respiratory distress syndrome (ARDS) (n = 168; dead = 95; alive = 73)					
Severe	133/168 (79.2%)	83/95 (87.4%)	50/73 (68.5%)	9.79	0.00
Moderate	31/168 (18.5%)	12/95 (12.6%)	19/73 (26.0%)		
Mild	3/168 (1.7%)	0/95 (0.0%)	3/73 (4.1%)		
None	1/168 (0.6%)	0/95 (0.0%)	1/73 (1.4%)		

* Number of patients with available information; ICU: Intensive care unit; n: number of patients.

patients who were admitted to the ICU (158/168; 93.6%) required oxygen during the disease. Of the 158 patients with available information, 64.8% (103/159) received oxygen support via a mask, and 25.2% (40/159) received oxygen support via a high flow nasal cannula.

Prone positioning was implemented to enhance oxygenation and improve lung recruitability in some patients with severe ARDS (151/168; 89.9%) (Tab. IV). Convalescent plasma (CP) was transfused into eight patients. However, only three of these eight patients survived after the convalescent plasma transfusion. As for the medications administered, 94 patients (56.0%) received antiviral agents, 164 patients (97.6%) received antimicrobial agents, 126 patients (75.0%) received an anti-allergic drug, 149 patients (88.7%) received anti-inflammatory drugs and 145 patients (86.3%) received vitamin and mineral supplements. Favipiravir (71/168; 42.3%) and Remdesivir (31/168; 18.4%) were

the most commonly used antiviral drugs among the ICU patients. However, the proportion of surviving patients was greater in the Remdesivir cohort than the Favipiravir cohort (Fig. 3A). Additionally, Methylprednisolone (97/168; 57.7%) and Dexamethasone (40/168; 23.8%) were the two most used glucocorticoids (Fig. 3A). Meropenem (126/168; 76.2%) was the most commonly used antibiotic, followed by Ceftriaxone (50/168; 29.8%), Azithromycin (33/168; 19.4%) and Moxifloxacin (33/168; 19.4%) (Fig. 3A). As shown in Figure 3B, the proportion of survived patients was slightly higher with the use of Meropenem, as well as Remdesivir and Dexamethasone, than with the use of Favipiravir or Methylprednisolone. Six patients were treated with Remdesivir and Dexamethasone and only one of them died. The vitamin C, vitamin D and zinc supplements that were commonly used did not show any improved clinical outcomes (Fig. 3C).

Tab. III. Laboratory findings of patients with COVID-19 in ICUs.

Variable	All patients (%)	Dead (%)	Alive (%)	Pearson's χ^2	P-value
White blood cell count (× 10 ⁹ per L; normal range 4-10) (n* = 61; dead* = 32; alive* = 29)					
Increased	42/61 (68.9%)	22/32 (68.8%)	20/29 (69.0%)	0.15	0.93
Normal	14/61 (23.0%)	7/32 (21.9%)	7/29 (24.1%)		
Decreased	5/61 (8.2%)	3/32 (9.4%)	2/29 (6.9%)		
Haemoglobin (g/L; normal range 130-175) (n* = 57; dead* = 28; alive* = 29)					
Increased	7/57 (12.3%)	2/28 (7.1%)	5/29 (17.2%)	1.82	0.40
Normal	33/57 (57.9%)	16/28 (57.1%)	17/29 (58.6%)		
Decreased	17/57 (29.8%)	10/28 (35.7%)	7/29 (24.1%)		
Neutrophils (× 10 ⁹ per L; normal range 1.8-6.3) (n* = 66; dead* = 27; alive* = 39)					
Increased	44/66 (66.7%)	18/27 (66.7%)	26/39 (66.7%)	0.28	0.87
Normal	16/66 (24.2%)	6/27 (22.2%)	10/39 (25.6%)		
Decreased	6/66 (9.1%)	3/27 (11.1%)	3/39 (7.7%)		
Lymphocytes (× 10 ⁹ per L; normal range 1.1-3.2) (n* = 48; dead* = 19; alive* = 29)					
Increased	16/48 (33.3%)	5/19 (26.3%)	11/29 (37.9%)	1.27	0.53
Normal	23/48 (47.9%)	11/19 (57.9%)	12/29 (41.4%)		
Decreased	9/48 (18.8%)	3/19 (15.8%)	6/29 (20.7%)		
Platelets (× 10 ⁹ per L; normal range 125-350) (n* = 57; dead* = 28; alive* = 29)					
Increased	18/57 (31.6%)	7/28 (25.0%)	11/29 (37.9%)	1.20	0.55
Normal	25/57 (43.9%)	13/28 (46.4%)	12/29 (41.4%)		
Decreased	14/57 (24.6%)	8/28 (28.6%)	6/29 (20.7%)		
D-dimer (mg/L; normal range < 0.5) (n* = 71; dead* = 31; alive* = 40)					
Normal	22/71 (31.0%)	8/31 (25.8%)	14/40 (35.0%)	2.4	0.48
> 0.5 to ≤ 5	34/71 (47.9%)	16/31 (51.6%)	18/40 (45.0%)		
> 5 to ≤ 10	11/71 (15.5%)	4/31 (12.9%)	7/40 (17.5%)		
> 10	4/71 (5.6%)	3/31 (9.7%)	1/40 (2.5%)		
Ferritin concentration (µg/L; normal range < 500) (n* = 69; dead* = 30; alive* = 39)					
Normal	16/69 (23.2%)	7/30 (23.3%)	9/39 (28.1%)	1.65	0.80
≥ 500 to < 1,000	25/69 (36.2%)	13/30 (43.3%)	12/39 (30.8%)		
≥ 1,000 to < 1,500	13/69 (18.8%)	5/30 (16.7%)	8/39 (20.5%)		
≥ 1,500 to < 2,000	11/69 (15.9%)	4/30 (13.3%)	7/39 (17.9%)		
≥ 2,000	4/69 (5.8%)	1/30 (3.3%)	3/39 (7.7%)		

* Number of patients with available information; ICU: Intensive care unit; n: number of patients.

Discussion

On 22nd September 2020, COVID-19 cases in Bangladesh totalled to 352,178, with 260,790 recovered cases and 5,007 deaths. The information on the clinical characteristics of COVID-19 individuals having an advanced and deleterious prognosis of COVID-19 is still scarce although the positive cases are nowhere near decreasing. The median age of the critical COVID-19 patients of the sample in this study (56 years) is lower than that of Italy, the United States of America (USA), Greece and China [22, 27-29]. However, the gender propensity of this study's patients (mostly men) is consistent with that of COVID-19 patients in ICUs in Italy, USA and China [27-29]. The management of patients with several comorbidities is challenging due to their frailty and increased risk of mortality, which is amplified when these comorbid individuals are diagnosed with COVID-19. The current study has found that older (≥ 50) Bangladeshi male patients with previous comorbidities, such as diabetes, hypertension and heart diseases, are profoundly susceptible to COVID-19, which is comparative to the pattern that has been revealed in China, Italy and New York [8, 27, 29, 30].

In Bangladesh, most people diagnosed with diabetes are from urban areas, and the prevalence of diabetes is highest among those aged from 55 to 59 years [31]. The presence of comorbidity might explain COVID-19's severity in Bangladeshi patients aged 51 to 60 years.

Another finding from this study was that patients with asthma survived well compared to other comorbidities. As with other viruses, SARS-CoV-2 triggers asthma exacerbations, which is why asthma is listed as a risk factor for COVID-19 related morbidity. However, this study's finding is consistent with that of Leonardo Antonicelli et al. (2020), who found that asthma seems to play a minimal role in clinical severity [32]. ARDS (79.2%) was found to be the most prominent symptom within the study sample upon admission to the ICU, and this was also reflected in patients described in reports from China, USA and Europe [8, 27, 28]. Other noteworthy symptoms are fever (8.40%) and coughing (7.70%), and the results obtained by this study align with the trends concerning high prevalence seen in other countries [27-29]. Intestinal signs and symptoms, such as diarrhoea, were rarely developed by the patients in this study.

Tab. IV. Managements of patients with COVID-19 in ICUs.

Variable	All patients (%)	Dead (%)	Alive (%)	Pearson's χ^2	P-value
Respiratory support (n* = 159; dead* = 86; alive* = 73)					
Oxygen delivery by mask	103/159 (64.8%)	50/86 (58.1%)	53/73 (72.6%)	8.69	0.03
High-flow nasal cannula	40/159 (25.2%)	28/86 (32.6%)	12/73 (16.4%)		
Oxygen delivery by nasal cannula	12/159 (7.5%)	5/86 (5.8%)	7/73 (9.6%)		
Non-invasive mechanical ventilation	3/159 (1.9%)	3/86 (3.5%)	0/73 (0.0%)		
Invasive mechanical ventilation	0/159 (0.0%)	0/86 (0.0%)	0/73 (0.0%)		
Extracorporeal membrane oxygenation (ECMO)	0/159 (0.0%)	0/86 (0.0%)	0/73 (0.0%)		
None	1/159 (0.6%)	0/86 (0.0%)	1/73 (1.4%)		
Oxygen supply (n* = 159; dead* = 86; alive* = 73)					
< 2 L min ⁻¹	2/159 (1.3%)	0/86 (0.0%)	2/73 (2.7%)	132.32	2.2e-16
> 2 to < 5 L min ⁻¹	17/159 (10.7%)	9/86 (10.5%)	8/73 (11.0%)		
> 5 to < 10 L min ⁻¹	34/159 (21.4%)	17/86 (19.8%)	17/73 (23.3%)		
> 10 to < 20 L min ⁻¹	97/159 (61%)	53/86 (61.6%)	44/73 (60.3%)		
> 20 to < 30 L min ⁻¹	1/159 (0.6%)	1/86 (1.2%)	0/73 (0.0%)		
> 30 to < 50 L min ⁻¹	5/159 (3.1%)	5/86 (5.8%)	0/73 (0.0%)		
> 50 to < 70 L min ⁻¹	2/159 (1.3%)	1/86 (1.2%)	1/73 (1.4%)		
> 70 L min ⁻¹	0/159 (0.0%)	0/86 (0.0%)	0/73 (0.0%)		
None	1/159 (0.6%)	0/86 (0.0%)	1/73 (1.4%)		
Prone position (n = 168; dead = 95; alive = 73)					
Yes	151/168 (89.9%)	86/95 (90.5%)	65/73 (89.0%)	0.10	0.75
No	17/168 (10.1%)	9/95 (9.5%)	8/73 (11.0%)		
Plasma transfusion (n = 168; dead = 95; alive = 73)					
Yes	8/168 (4.8%)	5/95 (5.3%)	3/73 (4.1%)	0.12	0.73
No	160/168 (95.2%)	90/95 (94.7%)	70/73 (95.9%)		
Antivirus drugs (n = 168; dead = 95; alive = 73)					
Yes	94/168 (56.0%)	56/95 (58.9%)	38/73 (52.1%)	0.80	0.37
No	74/168 (44.0%)	39/95 (41.1%)	35/73 (47.9%)		
Antibacterial drugs (n = 168; dead = 95; alive = 73)					
Yes	164/168 (97.6%)	95/95 (100.0%)	69/73 (94.5%)	5.33	0.02
No	4/168 (2.4%)	0/95 (0.0%)	4/73 (5.5%)		
Anti-allergic drugs (n = 168; dead = 95; alive = 73)					
Yes	126/168 (75.0%)	69/95 (72.6%)	57/73 (78.1%)	0.65	0.42
No	42/168 (25.0%)	26/95 (27.4%)	16/73 (21.9%)		
Antiemetic drugs (n = 168; dead = 95; alive = 73)					
Yes	12/168 (7.1%)	7/95 (7.4%)	5/73 (6.8%)	0.02	0.90
No	156/168 (92.9%)	88/95 (92.6%)	68/73 (93.2%)		
Vitamin and mineral supplements (n = 168; dead = 95; alive = 73)					
Yes	145/168 (86.3%)	90/95 (94.7%)	55/73 (75.3%)	13.14	0.00
No	23/168 (13.7%)	5/95 (5.3%)	18/73 (24.7%)		
Hypertension related drugs (n = 168; dead = 95; alive = 73)					
Yes	65/168 (38.7%)	38/95 (40.0%)	27/73 (37.0%)	0.16	0.70
No	103/168 (61.3%)	57/95 (60.0%)	46/73 (63.0%)		
Atypical neuroleptic/Anti-psychotic drugs (n = 168; dead = 95; alive = 73)					
Yes	6/168 (3.6%)	5/95 (5.3%)	1/73 (1.4%)	1.82	0.18
No	162/168 (96.4%)	90/95 (94.7%)	72/73 (98.6%)		
Anti-inflammatory drugs (n = 168; dead = 95; alive = 73)					
Yes	149/168 (88.7%)	87/95 (91.6%)	62/73 (84.9%)	1.82	0.18
No	19/168 (11.3%)	8/95 (8.4%)	11/73 (15.1%)		
Sedatives (n = 168; dead = 95; alive = 73)					
Yes	14/168 (8.3%)	6/95 (6.3%)	8/73 (11.0%)	1.17	0.28
No	154/168 (91.7%)	89/95 (93.7%)	65/73 (89.9%)		
Heart disease related drugs (n = 168; dead = 95; alive = 73)					
Yes	18/168 (10.7%)	10/95 (10.5%)	8/73 (11.0%)	0.01	0.93
No	150/168 (89.3%)	85/95 (89.5%)	65/73 (89.0%)		

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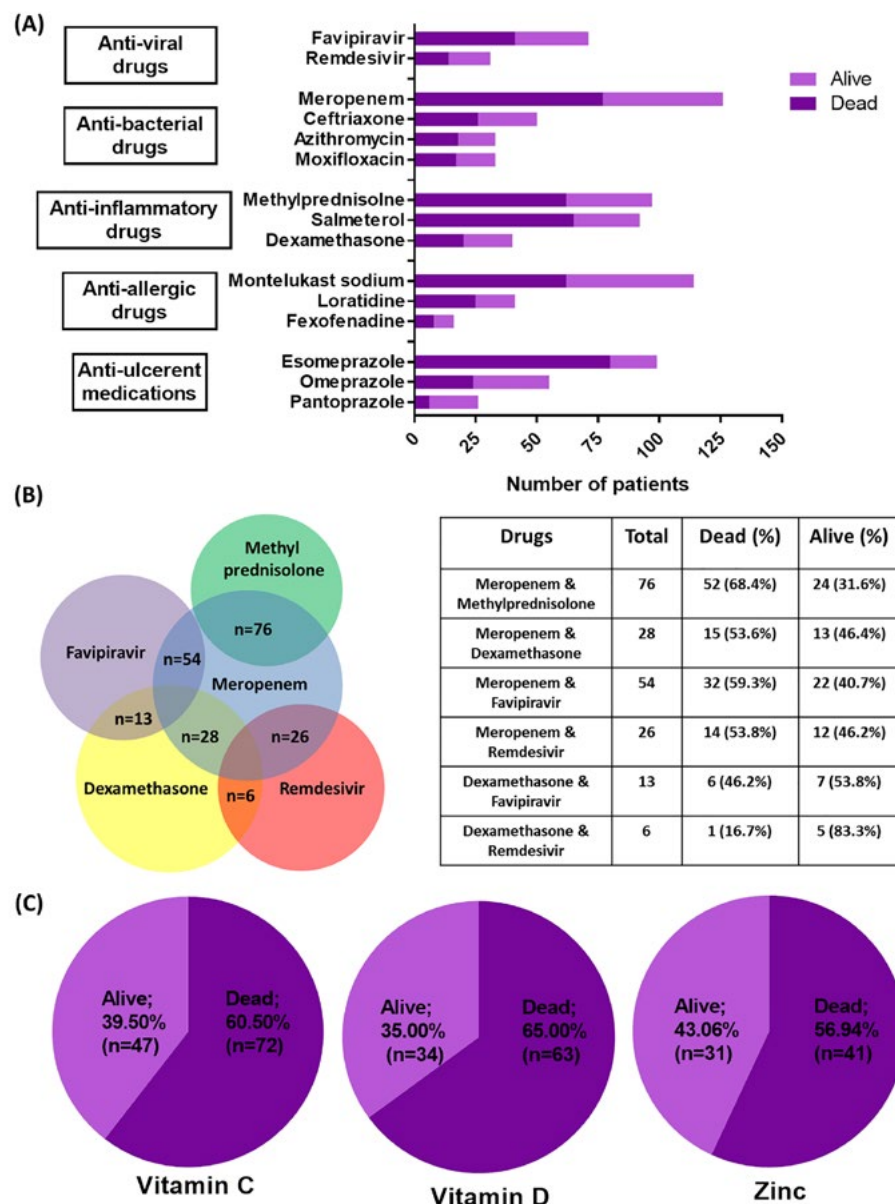
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Tab. IV. Managements of patients with COVID-19 in ICUs.

Variable	All patients (%)	Dead (%)	Alive (%)	Pearson's χ^2	P-value
Bronchodilator (n = 168; dead = 95; alive = 73)					
Yes	130/168 (77.4%)	76/95 (80.0%)	54/73 (74.0%)	0.86	0.35
No	38/168 (22.6%)	19/95 (20.0%)	19/73 (26.0%)		
Anti-ulcerent medications (n = 168; dead = 95; alive = 73)					
Yes	143/168 (85.1%)	81/95 (85.3%)	62/73 (84.9%)	0.00	0.95
No	25/168 (14.9%)	14/95 (14.7%)	11/73 (15.1%)		
Thyroid and hormone-related drugs (n = 168; dead = 95; alive = 73)					
Yes	5/168 (3.0%)	2/95 (2.1%)	3/73 (4.1%)	0.57	0.45
No	163/168 (97.0%)	93/95 (97.9%)	70/73 (95.9%)		

* Number of patients with available information; ICU: Intensive care unit; n: number of patients.

Fig. 3. Drugs, vitamins and electrolytes commonly administered to COVID-19 patients in the ICU. (A) Different generics of the drugs administered to COVID-19 patients in the ICU; (B) Venn diagram of drug combinations for the commonly used antibiotic, Meropenem with two antiviral drugs and two glucocorticoids, with the antiviral drugs being Favipiravir and Remdesivir and the glucocorticoids being Methylprednisolone and Dexamethasone and the proportions of dead and alive patients in each overlapped drug group being shown as a percentage; (C) Pie chart illustrating the numerical proportion of dead and alive patients who took Vitamin C, Vitamin D and Zinc supplements.



Majority of the study population had to rely upon supplemental oxygen while being cared for in the ICU. The cause of their inclination towards supplemental oxygen was severe to moderate ARDS which was indicated by their low oxygen saturation levels. In cases with depleting oxygen saturation, Oxygen therapy by high-flow nasal cannula (HFNC) and mechanical ventilators provide higher efficacy in the matter of additional oxygen support [33, 34]. However, given the spike in COVID-19 cases, the demand of HFNC has increased substantially because HFNC has been found to improve therapy by reducing the requirement of invasive ventilation [33]. Unfortunately, during the initial stages of this study HFNC could not be provided to the participating population and ventilators were limited as well which deprived patients of the support of mechanical ventilation when needed. This scarcity of proper ventilation might explain the prevalence of a high mortality rate in patients with a moderate to high fever and a low oxygen saturation.

Therapeutic plasma exchange has been recommended as a treatment measure for patients with severe COVID-19; however, this study found that therapeutic plasma exchange had no significant impact on the improvement of critically ill patients. According to a recent study, therapeutic plasma exchange can be effective in critically ill patients if it can be applied within the first week of symptom onset [35]. Unfortunately, most of the patients in the current study were admitted to the ICU in a critical condition due to the lack of available ICU beds. Therefore, it may have been too late for convalescent plasma therapy to have an effective impact.

To the extent of the author's knowledge, so far, this study is the only study on the medicine administered to critically ill COVID-19 patients in Bangladesh. Currently, there is no recommended treatment for COVID-19 infection in careful supportive care [36]. In this study, 97.6% of patients received antibacterial agents, 56% received antiviral therapy and 88.7% received anti-inflammatory drugs. Even though the antiviral drug Favipiravir was the mostly used antiviral drug, the survival rate was higher among the patients who had been given Remdesivir. Favipiravir concentrations become lower in critically ill patients than in healthy subjects, which might be one reason why Favipiravir is less effective [37]. Several countries, such as Japan, Taiwan and USA, and the European Union (EU) suggest the conditional use of Remdesivir to treat critical patients [38, 39]. Therefore, Remdesivir can be a better choice over Favipiravir in providing aid to COVID-19 individuals.

A recent report suggests that glucocorticoids may also minimize severe clinical outcomes in critical COVID-19 patients with ARDS [40]. The current study finds that Dexamethasone has comparatively better clinical outcomes than Methylprednisolone. According to a large clinical trial conducted in the United Kingdom (UK), Dexamethasone reduced deaths by about one-third in critical COVID-19 patients who were on ventilator support [41]. In this study, only one out of six patients who were treated with both Remdesivir and Dexamethasone died. However, further studies with larger sample sizes are

required to evaluate the effectiveness of the combined use of Remdesivir and Dexamethasone.

Although the findings of this study were significant, limitations were also in order. Firstly, laboratory data collection to conduct a broad and extensive study was inevitably challenging as the laboratory results were not systematically collected. Secondly, the evaluated data was extracted retrospectively from patients' medical files and not all laboratory tests were conducted on all patients. Thirdly, because of the study's objective to identify the critical care needs of patients with the greatest severity of illness, the sample size is small. Therefore, more thorough assessment of comorbidities in larger samples of critical Bangladeshi patients with COVID-19 and future studies are required. Despite these limitations, this study represented the largest cohort of critically ill COVID-19 patients from Bangladesh reported to date.

Conclusions

To summarize, parallel to the data obtained from studies conducted in other countries, there is an elevated prevalence of comorbidities, such as diabetes, hypertension and heart diseases, in a profuse number of COVID-19 patients with critical expositions who are hospitalised in Bangladesh. Since this cohort is more vulnerable in terms of COVID-19 related morbidity and mortality, besides implementing an effective policy for the prevention and control of the disease in general, the authorities should pay more attention to these atypical patients. In conclusion, the findings reported here provide important context for effective strategies for the provision of comprehensive health care to critically ill COVID-19 patients. However, future studies with larger sample sizes are needed in order to assess the risk factors and associated clinical outcomes in a broader sense.

Abbreviations

ARDS: acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; RT-PCR: Real-time reverse transcription polymerase chain reaction; USA: United States of America; UK: United Kingdom; WHO: World Health Organization.

Code availability

The source code and pipeline to reproduce our analyses can be accessed at https://github.com/sharifshohan/Cross_Sectional_Study_Bangladesh.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

AS, MMA, HMM, AP and TUQ: Study design. SN, ASA, AUC, HK, TR and PD: Literature review, Data collection. MUSS, HMM and AS: Data analysis, Visualization. SN, HMM and AS: Manuscript writing, Editing. All authors reviewed and approved the final manuscript paper; approved the final version and agreed to be accountable for the work.

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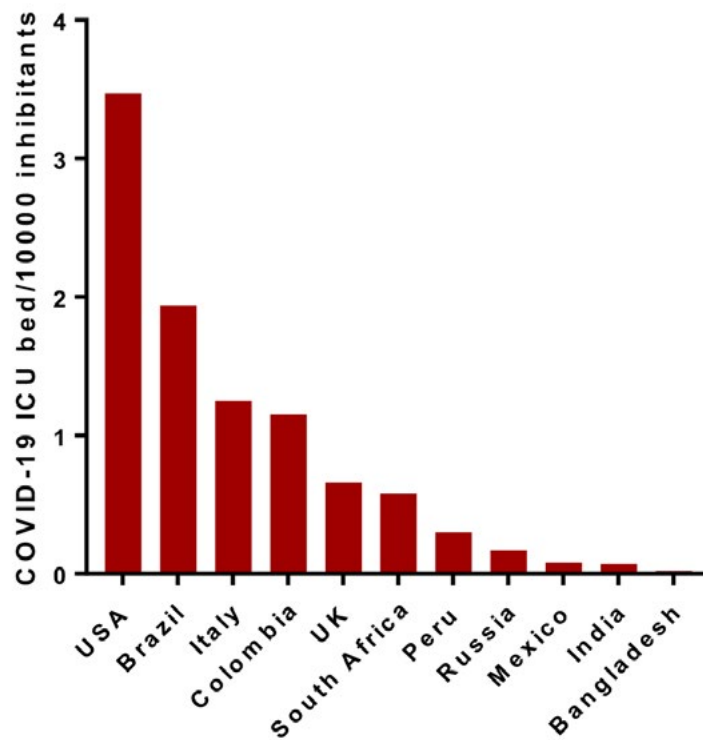
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Supplementary data

Supplementary Fig. 1. The number of COVID-19 ICU beds available for every 10,000 inhabitants of Bangladesh and other countries worse affected by COVID-19. USA, United States of America; UK, United Kingdom [9, 14, 42-47].



LETTER TO THE EDITOR

Vaccination: a question of social responsibility

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Keywords

Vaccines • Vaccination • Health • Hesitancy

Dear Sir,

Vaccines and vaccination have been on the media coverage for decades with credits and discredit. Polemics are jeopardizing some of the significant achievements in healthcare. Non-motivated vaccine hesitancy, delay, and vaccine refusal are dominating healthcare front news with a dramatic increase of exanthemata in the last few years across the globe. Vaccine hesitancy may be due to safety concerns, low confidence in vaccines, and adequacy of specific recommendations. Physicians, parents, and anti-vaxxers are not able to communicate correctly, and miscommunication has been amplified during the current COVID-19 pandemic. An increase of such preventable diseases in countries where these diseases seemed to be contained has characterized the headlines of both social media and professional platforms [1-3]. The argumentation that our immune system can fight preventable diseases is affected by the relatively weaker immune response of the current children compared with children of more than a hundred years ago. Family physicians have a responsibility to explain to parents that vaccines not only benefit their children but other children as well, particularly when traveling in developing countries.

COVID-19 disease, the infectious disease caused by SARS-CoV-2, is a pandemic that has reached all continents and caused numerous deaths worldwide, and the vaccine roll out is on progress [4]. With diverse vaccine candidates, the anti-vaxxers have populated many blogs and websites, raising the shield against potential vaccines and recruiting several political figures at their rallies. However, the misconception that vaccines are generally unsafe is growing and merges with anti-masks protests. The key is that several steps need to be reached before a vaccine can be distributed to the general population. There is collective amnesia that has allowed for the rise of the anti-vaccine movement, whose careless followers believe vaccines are to line the pockets of Big Pharma. The amnesia involves the ignorance that the smallpox vaccine was so prodigiously successful at eradicating the disease that it no longer is habitually given. Although fraudulent data are still populating West and East websites raising conspiracy theories, the efficacy of vaccines is consolidated in the scientific

literature. Yet, specific risk factors have been identified in University students with the tendency of believing in conspiracy theories in coping with stress [5, 6]. It has been estimated that the polio vaccine has saved 10 million people from paralysis only since 1988. It prevented 500,000 deaths, and a global vaccination campaign for measles that began in 2000 prevented an expected 23 million deaths by 2018.

In the United States and Canada, influenza season usually occurs in the winter, and numerous strategies are being explored to prevent the spread of influenza and minimize the risk of severe complications related to this infection. Influenza and COVID-19 infections may devastate our health care systems. If, during non-epidemic years, approximately 100,000 persons are admitted to the hospital as a result of influenza infection each year in the United States or Canada, the number of admissions to the hospital more than doubles during epidemic years [7]. Since the beginning of the COVID-19 pandemic, the notion that people wearing face masks may protect both themselves and others has been heavily politicized [8]. Anti-facemasks may become the forerunners of the anti-SARS-CoV-2 vaccine protesters in the nearest future. The emphasis on individual freedom and distrust for institutional authority share a comparison to vaccines. Some people may have medical, mental health, or even communication issues that are legitimate reasons to be exempt from wearing a mask. Still, most of the people should obey public health principles for the benefit of all community [8].

We want to emphasize that vaccination is not only a personal choice, but an issue of social responsibility, international development, and institutional commitment that need to be expressed with integrity. One of the ten risks to global public health is vaccine hesitancy, according to the World Health Organization (WHO) [9]. Social responsibility is an ethical context where either an organization or an individual must act for the benefit of society. In this context, social responsibility has a task to allow an individual or a governmental or nongovernmental organization to perform in the best interests of the community at large. In the setting of individual social responsibility, it is mandatory for advocating political or social issues that can help others, e.g., advocating for policies

targeting domestic and family violence in post-conflict communities. In this context, an egocentric view of parents choosing their children not to be vaccinated without consistent data should be considered irresponsible from a social point of view. In an international context, countries, and societies have different degrees of development related to their pre- and post-colonial history, culture, and interaction with neighbors. Several countries struggle in post-colonial history because they need fields of development that may engage their populations with international expansion. The recent rise of measles in Madagascar means bringing this country several years back to the colonial era with a dreadful increased rate of morbidity and mortality.

The International Covenant on Economic, Social, and Cultural Rights (ICESCR) provides that all individuals are entitled to the gratification of the highest attainable standard of physical and mental health [10]. In the framework of epidemics and the current pandemic, our social commitment will be crucial in the 21st century. There will not be any victory for healthcare if dialog and empathy are not strengthened.

Abbreviations

WHO: Health Organization.

ICESCR: International Covenant on Economic, Social, and Cultural Rights.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Both authors conceptualized the study, collected data, drafted the initial manuscript, and revised the final manuscript. Both authors performed the quality control check and are responsible for the content of this manuscript. Both authors meet the ICMJE requirements for authorship.

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RESEARCH ARTICLE

Assessment of hygienic conditions of recreational facility restrooms: an integrated approach

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Keywords

Air sampling • Bioaerosol • *Legionella* spp. • *Pseudomonas aeruginosa* • Recreational facility restrooms

Summary

Introduction. Microbiological quality of recreational environments included restrooms, is generally assessed by water and surface monitoring. In this study, an environmental monitoring, conducted in spring, of swimming pool restrooms of a recreation center located in the Marche region has been carried out. Seven water samples and seven surface swabs were collected. Moreover, six air samples have been included. The aim of this study was to evaluate if air microbiological monitoring, along with molecular detection in real-time PCR, could give additional useful information about the hygienic conditions of the facility.

Methods. Heterotrophic Plate Count (HPC) both at 22°C (psychrophilic) and 37°C (mesophilic) was determined by separate cultures in all samples. The presence of *Legionella pneumophila* and *Pseudomonas aeruginosa* was evaluated by both culture and real-time PCR.

Results. The analysis of shower water recorded a HPC load of mesophilic bacteria (37°C) more than 10-fold higher in men restroom, respect to women's one (> 100 vs < 10 CFU/ml), while in air samples was between < 100 and > 500. Concerning pathogen presence, both species *Legionella pneumophila* and *Pseudomonas aeruginosa* were detected only in men restroom, but in different sample types by using different methods (culture and real-time PCR).

Conclusions. Air sampling may offer the advantage of giving more representative data about microbial presence in restrooms, including bacterial species transmitted through aerosol, like *Legionella*. Moreover, the concurrent use of molecular and microbiological detection in an integrated approach could offer the advantage of greater sensitivity.

Introduction

In recreational facilities, like swimming pools, people can get exposed to pathogens and this may constitute a public health problem; restrooms may represent a potential at-risk environment. The risk of acquiring infections in swimming pools is often associated with microbial contamination of water and inadequate disinfection. Additionally, direct contact with contaminated surfaces and inhalation of air are also potential routes of exposure to pathogens [1].

Legionella pneumophila (*L. pneumophila*) has been recovered from a wide range of artificial water systems including hot water supplies, cooling towers, whirlpools spa but it is also a common inhabitant of natural water [2].

Legionella spp. grows best in warm water, and many legionnaire disease outbreaks are associated with hot water systems [3, 4].

In public swimming pools, especially in the dressing room areas, *L. pneumophila* can spread through shower aerosols produced from contaminated water sources and aerosols can be inhaled [5].

Pseudomonas aeruginosa (*P. aeruginosa*) is also a common environmental bacterium that forms biofilms on wet surfaces [6]. It can also be found in groundwater

and drinking water systems [7]. The bacterium is one of the most common causes of opportunistic human infections.

P. aeruginosa is responsible of many episodes of infections associated with attendance at swimming pools. Moreover, *Legionella* spp. and *Pseudomonas* spp. can also resist stressful environmental conditions, like water chlorination, because of their ability to enter into a viable but non-culturable (VBNC) state [8]. VBNC forms typically exhibit a low level of metabolic activity and fail to grow on standard medium, while they retain certain features of viable cells, such as cellular integrity and virulence [9]. Under favorable conditions they can resuscitate, recovering their cultivability and regaining pathogenic potential [10, 11].

Currently, there are several methods for *Legionella* spp. and *Pseudomonas* spp. detection and enumeration including: standard culture methods [12], PCR and real-time PCR [13, 14], also in its quantitative application [15]. Culture methods, using prescribed growth media and specific conditions, recover only culturable organisms [16]. Over the past ten years, molecular methods are used for the detection of airborne and waterborne microorganisms not growing on culture media.

Bioaerosols are among the less studied particles in the environment, due the lack of standardization in sampling procedures [17, 18]. Moreover, it has been showed that only a small proportion of the total bioaerosol burden is culturable [19].

Recommendations for the control and prevention of legionellosis [20] do not include air sampling. However, this kind of sampling has been used by other authors, in combination with water systems surveillance, for the detection of *L. pneumophila* [21] and *P. aeruginosa* [22]. Airborne *L. pneumophila* may be collected by agar impaction, filtration and liquid impingement. Agar impaction samplers should be used for short sampling times to avoid cell desiccation stress. However, in case of low bacterial concentration, false negative results can occur. To date, numerous liquid-and filter-based samplers have been used for detecting airborne *Legionella* [21]. Liquid-based sampling methods have been described as the best sampling methods to obtain culturable *L. pneumophila* [21, 23], while filtration sampling (gelatine filters) is adequate for capturing total cells. Indeed, collection with liquid impingement relieves the dehydration stress, although a major drawback with conventional impingers is the violent bubbling producing cell damage and reduction of microbial recovery. Some of these problems have been attenuated by swirling aerosol collectors, combining impingement and centrifugal motions to preserve cultivability [24]. The presence of *L. pneumophila* [25] and *P. aeruginosa* [13, 26] in recreational centers has been investigated by several authors by the examination of water through filtration membranes. In our knowledge, other sampling methods for the detection of the above-mentioned pathogens in sport-related environments, included restrooms, are lacking.

Therefore, the aim of this study was to evaluate if air microbiological monitoring, performed through a swirling aerosol collector (Coriolis), could give additional useful information about the hygienic conditions of recreational facility restrooms.

This pilot study aims to propose a new integrated approach, comprising standard microbiological methods and real-time PCR, for the detection of *L. pneumophila* and *P. aeruginosa* and the determination of the Heterotrophic Plate Count (HPC) in recreational facility restrooms, analyzing a complete panel of environmental matrices: water, surfaces and air.

This may offer the advantage of giving more representative data about microbial presence, including also bacterial species known to be transmitted through aerosol. Moreover, the concurrent use of molecular and microbiological detection could give greater sensitivity, especially with VBNC forms possibly originated from disinfection.

Methods

A total of 20 samples were collected from restrooms of one recreational swimming pool, between June and

August 2018. This recreational swimming pool is in the Marche Region, Central Italy.

WATER SAMPLES

Each hot water sample, collected from sink taps and showers in men and women restrooms, was placed in 1 L sterile bottles, containing 10% sodium thiosulfate to neutralize any residual chlorine. Although all samples were collected by turning on the tap hot water, the temperature not exceeded 32°C. Samples were transported to the laboratory in a thermally insulated box and analysed immediately.

Legionella sampling and analysis was performed in accordance with Italian Guidelines [20] and the standard method ISO11731:2017 [27]. Briefly, 1 L of water was filtered through a membrane (0.2 µm, 47 mm diameter; Millipore, Billerica, MA, USA) of cellulose nitrate. Each membrane was put in a tube containing 5 ml of original water sample, shaken and then held at 50°C for 30 min. An aliquot of 0.5 ml was spread on *Legionella* CYE supplemented with *Legionella* BCYE growth supplement (Oxoid Ltd., Hampshire, UK) and incubated for 24 h at 37°C with 2.5% CO₂ for 10 days. Suspected colonies were counted and then confirmed by real-time PCR, as described below.

Isolation and identification of *P. aeruginosa* was performed according to the standardized procedure UNI EN ISO 16266:2008 [12]. Briefly, 100 ml of each water sample was filtered with a cellulose ester membrane (0.45 µm porosity, 47 mm diameter; Millipore), which was then placed onto a *Pseudomonas* Agar with *Pseudomonas* CN Supplement (PACN) (Oxoid) plate. PACN plates were incubated at 35 ± 1°C for 44 ± 4 h before the counting of colonies. Blue/ green pyocyanin-producing colonies were counted as confirmed *P. aeruginosa* according to UNI EN ISO 16266:2008 [12]. Fluorescent non-pyocyanin-producing or reddish-brown colonies were recorded as presumptive *P. aeruginosa* and subjected to confirmation tests according to UNI EN ISO 16266:2008 [12].

The Heterotrophic Plate Count (HPC) at 22°C and 37°C was determined by the pour plate method, using standard Plate Count Agar (PCA, Oxoid) [28]. The plates were incubated at 37°C for 40-48 h and at 22°C for 64-72 h. The results were expressed in colony forming units (CFU)/ml.

AIR SAMPLES

Air contamination in recreational facility restrooms was assessed by a wet cyclone technology (Coriolis® µ Exonder, Borgo Ticino, NO, Italy). The Coriolis cyclone sampler was adjusted to sample 3,000 L of air (300 L/min for a period of 10 min). Airborne bacteria were collected in Coriolis® µ sterile cones filled with 15 ml phosphate buffered saline (PBS) + 0.005% Tween 80. HPC were conducted on PCA. 100 µl of sample were placed on the plates and incubated at 22 and 37°C. Next, the number of bacterial colonies was counted and recalculated as CFU per m³ (CFU/m³). The liquid material was filtered

through 0.2 µm cellulose ester membranes of 47 mm diameter (Millipore). For isolation of *Pseudomonas*, filter was placed on *Pseudomonas* Agar Base with CN (Oxoid) and incubated at $35 \pm 1^\circ\text{C}$ for 44 ± 4 h. For isolation of *Legionella*, filter was placed on *Legionella* CYE Agar Base supplemented with *Legionella* BCYE growth supplement (Oxoid) and incubated for 24 h and 10 days, checking the plates at intervals of 2-4 days, at 2.5% CO₂ at 37°C .

A second series of samples was analyzed in parallel by real-time PCR, as described below.

SWAB SAMPLES

Bacterial microbiota present on the surface of the shower head (inside and out) was collected using sterile non adsorbent cotton swabs rubbed on a 10 x 10 cm² area, covering the entire surface by moving the swab back and forth across the surface horizontal and vertical strokes; then resuspended in 5 ml of physiological solution (0.9%, w/v, NaCl). For microbiological analyses, sample volumes of 0.1 mL were spread over the surface of PCA, PACN and *Legionella* CYE Agar Base supplemented with *Legionella* BCYE growth supplement. All plates were incubated for optimal temperature and time as per water analysis and after incubation the number of colonies was counted and was expressed as the number of CFU per cm² (CFU/cm²).

PCR TESTING

Molecular detection in real-time PCR of *P. aeruginosa* and *L. pneumophila* was performed in water, air and swab samples. Sample analysis was performed according to Schiavano et al. [29] for *P. aeruginosa* and with the DI-Check *Legionella pneumophila* kit (Diateva, Fano, Italy) for *L. pneumophila*.

Results

Concerning pathogen presence, both species were detected only in men restroom. *P. aeruginosa* was found in shower water and air samples by microbiological method and in shower swab surfaces by real-time PCR, while *L. pneumophila* was detected at a very low level in the external surface of shower heads with the real-time PCR, namely 4 and 7 genomic units (GU)/PCR, approximately corresponding to 160-280 GU in the sampled surfaces (Tab. I).

The analysis of shower water recorded a HPC load of mesophilic bacteria (37°C) more than 10-fold higher in men restroom, respect to women's one (Tab. II). These values are in accordance with those reported by [30, 31]. Similarly, in air samples the HPC load of psychrophilic flora (22°C) was higher in men restroom respect to women's one (Tab. II).

Discussion

Detection of microbial contamination in environmental matrices in recreational environments is important for

safeguarding the state of hygiene and the health of pool users. The HPC at 22 and 37°C is a mandatory criterium to assess water potability, according to law provisions in Italy [32] and can be considered an indicator of hygiene. It is currently used to determine air quality in indoor environments, including recreational facilities [33].

In this study two different incubation temperatures were used to quantify the presence of mesophilic and psychrophilic species in water. According to the microbiological classification of air quality in non-industrial environments provided by the European Collaborative Action [34], a level of psychrophilic flora < 100 CFU/m³, which was found in women restrooms, corresponds to the category of "low contamination", while an HPC load > 500, as that recorded in men restrooms, can be included in the "high contamination" category. Microbial pollution is a key element of indoor air pollution. It is caused by hundreds of species of bacteria and fungi, filamentous fungi (mold), growing indoors when sufficient moisture is available [35].

HPC are not considered an indicator of health risk. But, the *Legionella* presence in water appears to be in relationship with load and generic water quality parameters, i.e. HPC at 22°C and HPC at 37°C [36]. It is important to consider that the presence of these mesophilic and psychrophilic bacteria could be correlated with the colonization of water system by *Legionella* [37]. In our study, the water samples were collected from the hot water tap because numerous scientific evidences thought the hot water distribution system to be the most frequent source of cases or outbreaks of legionella in hotels, schools, sport facilities, offices and private residences [38].

In recreational facilities, the potential risk of infection with *Legionella* could be associated with the inhalation of aerosols containing the bacteria, in particular the aerosols created in the showers [39].

Although the limited sampling number does not allow a statistical analysis of significance about the association of high levels of HPC at 37°C and pathogen presence, which is out of the scope of this study, results confirmed previously reported data [25]. The lack of positive results for *Legionella* with the standard microbiological method could be due to the presence of VBNC cells [9] or bacteria contained in amoebae [10]. Moreover, PCR positive samples in absence of isolation of living bacteria could be ascribed to the presence of dead microorganisms, i.e. inactivated by disinfection procedures. Nevertheless, in water and air monitoring, filter-concentration before culture could have improved sensitivity, in contrast to real-time PCR, in which only a fraction of the extracted sample was PCR-amplified.

The integrated approach used in the present study takes advantage from the examination of different types of matrices, not limiting to water samples. Indeed, for some pathogens like *L. pneumophila*, aerosol inhalation is the main pathway of exposure, thus air sampling may offer

Tab. I. Results of pathogen detection by microbiological and real-time PCR methods in samples from men restrooms.

Sample type		Microbiological methods		Real-time PCR	
		<i>P. aeruginosa</i> UNI EN ISO 16266:2008	<i>L. pneumophila</i> UNI EN ISO 11731:2017	<i>P. aeruginosa</i>	<i>L. pneumophila</i>
Water	Shower water	+	-	-	-
	Tap water	-	-	-	-
Air	Air	+	-	-	-
Surfaces	Shower head (inside)	-	-	+	-
	Shower head (out)	-	-	+	+

* Values are: 4 and 7 GU/PCR, in the first and second sample, respectively.

Tab. II. Results of HPC load in men and women restrooms.

Location	Sample type		HPC*	
			22°C	37°C
Men restroom	Water	Shower water	< 10	> 100
		Tap water	< 10	< 10
	Air	Aerosol	> 500	> 300
	Surfaces	Shower head (inside)	n.c.	n.c.
		Shower head (out)	n.c.	n.c.
Women restroom	Water	Shower water	< 10	< 10
		Tap water	< 10	< 10
	Air	Aerosol	< 100	> 300
	Surfaces	Shower head (inside)	n.c.	n.c.
		Shower head (out)	n.c.	n.c.

n.c.: not counted. After incubation many colonies were confluent and this made counting impossible. * Values are reported as CFU/ml for water samples and CFU/m³ for air samples.

useful information about its presence and give a better knowledge about the microbiological quality of such environments. Moreover, the application of two kinds of methodologies, culture-based and real-time PCR, increased detection sensitivity, especially for surface analysis.

Conclusions

Microbiological monitoring of water, air and surface quality for the presence of important species, like *Legionella* spp. and *Pseudomonas* spp., is useful and crucial in order to determine the potential exposure of swimming pool users. The use of different sampling methods gave integrated information that allowed to highlight the contamination by pathogens on different matrices. The multipoint analysis approach used in this preliminary study, with the application of both culture and molecular methods, can increase the probability of a reliable detection. In conclusion, an accurate environmental monitoring of restrooms in recreational pool facilities including air, along with the application of good hygienic practices, can be of main importance to prevent or reduce the exposition of pool users to microbiological risks.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization and data curation: SGF and GA; Formal analysis: SGF, GA and GBr; Methodology: SGF, GA and CV; Supervision: SGF, GA and GBr; Validation: SGF, GA, VC and GBr; Writing original draft: SGF and GA; Writing, review & editing: SGF, GA, GBr, GB and CV.

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RESEARCH ARTICLE

Sleep duration and its relationship with school performance in Iranian adolescents

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Keywords

Sleep duration • School performance • Adolescents

Summary

Background. *Inadequate or poor sleep quality is common problems in adolescent that affect on their learning, memory and school performance. The present study aimed to determine the association between sleep hours and academic performance in young adults.*

Methods. *This cross-sectional study was designed as a descriptive-analytic study. Samples of adolescents of 14-18 years old in Qazvin city were enrolled. The Pediatric sleep questionnaire and BEARS questionnaire used for all students to screen comprehensively major sleeps problems in them. Chi-square test, t-test, analysis of variance (ANOVA), and correlation were performed to determine the relationship between the data ($P < 0.001$).*

Results. *Between 653 adolescents, 40% were male and 60% were female. Sleep duration, sleep onset delay, sleep insufficient, rate*

of oversleeping and academic performance had a direct relationship with gender ($P < 0.001$). The sleep duration, rate of oversleeping and academic performance were significantly higher in boys, sleep onset delay and sleep insufficient was significantly higher in girls. Time of falling sleep at weekend nights and weekday nights have positively correlation with age ($P < 0.001$). Also, a significant relationship between students' sleep hours with academic performance was shown ($P < 0.001$).

Conclusions. *The overall result was that sleep duration, sleep onset delay, sleep insufficient and rate of oversleeping of students in this study had a significant influence on academic performance. Students without difficulty in falling asleep had good academic performance in compared to students with difficulty in falling asleep.*

Introduction

Sleep is a periodic and natural state of human which during that body and mind is at rest, the eyes usually close and consciousness is partially or completely reduced [1]. Body movements reduce during sleep and body does not respond to external stimuli. Almost a third of humans' life is spent in sleep [2, 3]. Sleep is a biological behavior of human that regulation of it is based on a complex biological pattern in the brain. In most cases, disruption of the sleep cycle is an early sign of physical and mental illnesses [4]. Good quality of sleep is necessary to perform routine daily function including metabolic activities, hormonal processes, and proper regulation of appetite [5, 6]. Chronic sleep deprivation induces many detrimental effects of physical health including impaired carbohydrate metabolism, increase risk of diabetes, and dysfunction of appetite regulation hormones such as leptin and ghrelin. In some documents suggested that development of obesity and diabetes in elder people is due to poor quality of sleep in this group [7]. It is important that inadequate sleep (insufficient quantity or poor quality of sleep) is epidemic in our

modern societies, and many people suffer from it [8-10]. Empirical evidence has shown that children need an average of 9 hours of sleep at night. According to the researches, 45% of them sleep less than 8 hours at night [10, 11]. Sleep problems affect the academic performance of students [12-14]. Obtaining adequate sleep is essential for good performance of children in school. Inadequate or poor sleep qualities are common problems in adolescent that effect on their learning, memory and school performance [12]. Other studies have shown that insufficient sleep, fragmentation of sleep and sleeping late have detrimental effects of academic performance of teenagers [13-15]. In a study in America, which was performed between 88 students, it was proved that better quality, longer duration, and greater consistency of sleep were correlated with the better grades in the lessons [16]. In a research in Pakistan, 64.24% of students with global Pittsburgh sleep quality index (PSQI) score ≥ 5 have poor sleep quality. The mean grade point average (GPA) of poor sleepers was 2.92 ± 1.09 which was significantly lower than that of good sleepers. Poor sleep quality had a negative impact on the academic performance and adequate sleep had a positive impact on the refresh

of students every day; adequate sleep helps them in learning and memory processing [5]. In Iran, study of 407 students found that 9.1, 36.1, 39.3 and 13.5% of them had excellent, good, satisfactory and poor daily sleep quality. In this research, appropriate sleep duration and adequate sleep period had a positive effect on the academic performance including educational achievement, high scores in the exams and freshness in the classroom [17]. Given the importance of sleep for students, the present study aimed to determine the association between sleep hours and academic performance in young adults.

Materials and methods

STUDY DESIGN

This cross-sectional study was designed as a descriptive-analytic study. A sample of adolescents of 14-17 years of age in the first, second and third degree of high school (two schools were chosen, randomly) in Qazvin city were enrolled. Sample size was calculated with considering 8% precision, 95% confidence interval and 80% power about 700 students. Participants were selected using cluster sampling, so that 700 students were chosen from 10 schools in 5 different parts of city (two schools were selected from each area of city). Pre-university students were excluded from study because of the stress due to university entrance exam and its effects on sleep pattern. After selecting the desired school, some students were selected randomly from them.

STUDY TOOL

Study's questionnaires were distributed among them. Data collection tools were two questionnaires which their validity and reliability has been confirmed in previous studies. The Pediatric Sleep Questionnaire consist 22 questions was designed to evaluate sleep problems in children. Its sensitivity and specificity have a range between 0.81 to 0.85, and 0.87, respectively compared to polysomnographic results. Also, Cronbach's alpha coefficient of questionnaire was 0.77 in this study for PSQ. Also, the BEARS questionnaire developed by Owen used for all students to screen comprehensively major sleeps problems in them. Five sleep domain evaluated by this questionnaire including bedtime problems, excessive daytime sleepiness, awakening during the night, regularity and duration of sleep, and snoring. Previously, Mohammadi and colleague were assessed validity and reliability of Persian version of this questionnaire. The BEARS internal consistency in our study was high with a Cronbach's alpha of 0.79. A total of 700 questionnaires were distributed. Twenty of questionnaires were excluded because of the incomplete filling of the questions. Also, 27 of students were excluded due to suffering from diseases that effect on their sleep parameters [18-21].

STATISTICAL ANALYSIS

Finally, data collected from 653 cases were confirmed for use in the analysis. Statistical package for social sciences (SPSS) version 16 was used for data analysis. Chi-square test, t-test, analysis of variance (ANOVA), and correlation were performed to determine the relationship between the data ($P < 0.001$).

Results

In this study, 653 adolescents 14-18 years were surveyed, of which 261 (40%) were male and 392 (60%) were female. Average age of our sample was 15.7 ± 0.9 . Education levels in students were as follow: 154 (23.6%) in the first year, 242 (37.1%) in the second year of high school and 257 (39.4%) in the third year of high school. Information on age, education grade, hours of sleep during the night, and delay amount in the sleep onset are mentioned (Tab. I). The average sleep duration was significantly higher in boys than girls ($P < 0.001$). The hours of starting sleep at night and waking in the morning was significantly different between boys and girls ($P < 0.05$). Sleep onset delay was significantly higher in girls than boys ($P < 0.001$).

Hours of sleep on weekdays and weekends between boys and girls were compared (Tab. II). Sleep duration was classified in three different categories (less than 7 hours, 7-9 hours, and more than 9 hours during night). Sleep insufficient was significantly higher in girls than boys ($P < 0.001$). In contrast, the rate of oversleeping was higher in boys. Also, hours of sleep on weekends were higher than weekdays. Pearson analysis showed that time of falling sleep at weekend nights ($p = 0.83$, $P = 0.03$) and weekday nights ($p = 0.14$, $P < 0.001$) have positively correlation with age.

Academic performance of students was divided into three categories based on their GPA. Students with GPA equal or less than 15 was classified in poor academic performance. Also, students with GPA between 15.01-17.99 and equal or more than 18 were classified as medium and good academic performance, respectively. Results showed that academic performance was significantly better in girls than boys (Tab. III).

Students who sufferings from difficulty to falling asleep have significantly lower academic performance ($P < 0.001$) (Tab. IV). Also, there was a significant relationship between students' sleep hours in weekends and weekdays with academic performance. The average hours of sleep among students with better academic performance was less than students with medium and poor academic performance ($P < 0.001$). The amount of delay in falling asleep was more in students who had lower academic performance ($P = 0.002$) and total sleep time during weekend ($P < 0.001$) and weekdays ($P < 0.001$) were significantly higher in students with better academic performance (Tab. V).

Tab. I. The baseline characteristics and sleep-wake schedule in male and female students.

Baseline characteristics	Girls	Boys	Total	P-value
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
Age	15.76 (1.00)	15.70 (0.97)	15.73 (0.99)	0.44
GPA	17.09 (1.63)	16.64 (1.85)	16.91 (1.73)	0.001
Hours of falling asleep at night during weekend	24.88 (1.16)	24.54 (1.25)	24.75 (1.21)	< 0.001
Hours of falling asleep at night during weekdays	24.00 (0.95)	23.73 (0.97)	23.89 (0.97)	< 0.001
Hours of waking up at morning during weekend	9.60 (1.71)	9.35 (1.32)	9.50 (1.57)	0.038
Hours of waking up at morning during weekdays	6.31 (0.60)	6.70 (0.34)	6.46 (0.55)	< 0.001
Total sleep time during weekend	10.29 (1.89)	10.60 (1.75)	10.42 (1.84)	0.034
Total sleep time during weekdays	8.17 (1.68)	8.79 (1.46)	8.42 (1.62)	< 0.001
Latency to falling asleep (min)	41.44 (40.87)	29.75 (26.22)	36.77 (36.17)	< 0.001

Tab. II. Frequency of male and female students in terms of sleep duration on weekends and weekdays.

Sleep duration	Gender	Less than 7 hours Number (percent)	7-9 hours Number (percent)	More than 9 hours Number (percent)	P-value
Total sleep duration on weekends	Boys	6 (2.3)	165 (63.2)	90 (34.5)	< 0.001
	Girls	60 (15.3)	246 (62.8)	86 (21.9)	
	Total	66 (10.1)	411 (62.9)	176 (27)	
Total sleep duration on weekdays	Boys	4 (1.5)	46 (17.6)	211 (80.8)	< 0.007
	Girls	12 (3.1)	106 (27)	274 (69.9)	
	Total	16 (2.5)	152 (23.3)	485 (74.3)	

Tab. III. Comparison academic performance and difficulty in falling asleep in male and female students.

Variables	Boys Number (percent)	Girls Number (percent)	Total Number (percent)	P-value
Academic performance				0.03
Good (≥ 18)	76 (29.1)	138 (35.2)	214 (32.8)	
Medium (15.01-17.99)	124 (47.5)	193 (49.2)	317 (48.5)	
Poor (≤ 15)	61 (23.4)	61 (15.6)	122 (18.7)	
	Boys Number (percent)	Girls Number (percent)	Total Number (percent)	0.13
Difficulty in falling asleep				
Yes	61 (23.4)	108 (27.6)	169 (25.9)	
No	200 (76.6)	284 (72.4)	484 (74.1)	

Tab. IV. Relationship between difficulty in falling asleep and academic performance.

Academic performance	Difficulty in falling asleep		P-value
	Yes Number (percent)	No Number (percent)	
Good (≥ 18)	30 (14)	184 (86)	< 0.001
Moderate (15.01-17.99)	99 (31.2)	218 (68.8)	
Poor (≤ 15)	40 (32.8)	82 (67.2)	

Tab. V. Relationship between total sleep-wake schedule, and delay to falling asleep with students' academic performance

Sleep-wake schedule	(years ≤ 15) N = 122 Mean \pm SD*	(years 15.01-17.99) N = 317 Mean \pm SD	(years ≥ 18) N = 214 Mean \pm SD	P-value
Hours of falling asleep at night during weekend	25.17 (1.37)	25.10 (1.38)	25.20 (1.45)	0.69
Hours of falling asleep at night during weekdays	23.66 (1.13)	23.57 (1.21)	23.86 (1.12)	0.02
Hours of waking up at morning during weekend	10.50 (1.77)	10.43 (1.61)	10.12 (1.62)	0.055
Hours of waking up at morning during weekdays	6.68 (0.57)	6.57 (0.64)	6.52 (0.55)	0.083
Total sleep time during weekend	10.86 (2.01)	10.54 (1.79)	9.97 (1.72)	< 0.001
Total sleep time during weekdays	8.91 (1.65)	8.44 (1.68)	8.11 (1.45)	< 0.001
Latency to falling asleep (min)	41.75 (41.30)	39.55 (36.51)	29.80 (31.38)	0.002

Mean \pm SD*; mean \pm standard deviation (SD).

Discussion

In this study, the mean total sleep duration was 42.8 hours during weekdays, and this amount was significantly lower in girls than boys. Also, a significant difference found between boys and girls in terms of the time to go to bed and waking up in the morning. Another result showed that the average number of sleep hours was lower in students who had better academic performance than students with average and poor academic performance. According to the center for disease control and prevention (CDC) in America, the optimal duration of sleep recommended for teenagers are more than 8.5 hours at night [19]. In our sample, duration of sleep for 24 hours was 8.42 ± 1.6 and 10.4 ± 1.8 for weekdays and weekends, respectively. Total duration of sleep was more in boys than girls, and girls went later to sleep than boys at both of the weekends and weekdays. In a study in America the average length of sleep on the weekend was about 9 hours in boys and girls. But, this amount was reduced to 7.1 hours for boys and 5.2 hours for girls during weekdays. These results were different from current study that in our study students' sleep duration on weekend was 5.1 hours more than American teenagers. Also, the duration of sleep in weekdays was lower for both American girls and boys about 2.1 and 1.8 hours, respectively. So, in total during the whole week, Iranian teenagers slept more than American teenagers. In this study, there was not significant correlation between age and sleep duration. Total sleep duration decreases with increasing age [19]. In another study in Canada, it was found that seventy percent of students aged 14 to 18 years old sleep less than 8.5 hours during the night [10]. In this study, sixty percent of students reported that they sleep less than 8.5 hours during night at weekdays. Also, we found a wide gap in sleep duration between weekends and weekdays (Yo-yo sleeping), so that our samples slept two hours more in weekends compared to weekdays. These results show that students' sleep was not enough during weekdays, therefore they sleep more in weekends to compensate their sleep insufficiency. This large difference will cause a negative impact on students' performance in school [20]. This amounts in studies conducted in other countries is as follow: America 2.1 hours [19], Taiwan 1 hour [21], China 2.5 hours [22], and Australia 16 minutes [20]. There was no difference in sleep duration between weekdays and weekend in Switzerland [23]. Current study showed that with increasing students' age, the time for going to bed were delayed. Similar results were obtained in other studies to confirm our results [21, 24]. In this study, total sleep duration was more in boys than girls in all days of the week. Similar results were obtained in a study conducted in Taiwan [21], but a survey in Australia showed that teenager girls sleep more than boys [20]. Recent findings have shown that sleep is important for the proper function of learning and memory [13, 25]. The possibility of delay in sleep onset increases with the onset of puberty that can lead to daytime sleepiness and negative effects on academic performance in students.

A study in America showed that delay in sleep initiation more than 30 minutes for more than one night during the week has a significant association with increased rates of academic failure in students [26]. In another study conducted in China, the average delay in starting sleep was 30 minutes in students [27]. This amount was calculated in the present study 36.77 minutes. A review study in 2010 showed that increasing hours of sleep is associated with better academic performance in students [12]. But in our study, students who have fewer hours of sleep during night had better academic performance. On the other hand, another study did not report a significant relationship between sleep duration and academic performance in students [28]. In a study in Iran, 102 students completed PSQI. Based on the results there was no significant difference between students with high grades and those with low grades. But there were moderate and sometimes severe sleep disturbances in both groups. Also, there was no significant difference between sleep quality and academic achievement [29]. In another hand, in our results significant difference between sleep quality and academic performances between students was existed. A research between 341 selected students in Iran showed that 59.1% of them had poor sleep quality. Also, there was a significant negative relationship between sleep quality with academic interaction and academic vitality. There was a significant positive relationship between academic motivations with academic vitality. Also, a significant difference between male and female students in academic vitality was observed [30]. Different reasons such as level of family income, family size, intake of supplements and vitamins, social media dependency, addiction to social networks and social issues can affect the academic success in the different students [29, 31]. Improve adolescent sleep including delaying school start times, providing sleep education, and utilizing light therapy to improve the health, wellbeing and academic performance of sleepy teenagers are in the programs of researchers in this field in different countries [30]. The results from this study indicated that sleeping time in Iranian students is more than students in other countries. In this study, sleep duration, sleep onset delay, sleep insufficient and rate of oversleeping was associated with better academic performance in students. Also, difficulty in falling asleep was associated with weaker academic performance. The overall result was that in students without difficulty in falling asleep, a positive influence on the academic performance was observed.

Conclusions

The result of this study showed that some of sleep characteristics such as sleep duration, sleep onset delay, sleep insufficient and rate of oversleeping of students could be a significant influence on adolescents' academic performance. Further studies are needed to objectively determine the effect of sleep variables on adolescents' performance.

LIMITATIONS

First, the design is cross sectional. Therefore, it may be difficult to confirm a cause-effect relationship. Moreover, the selected students were found randomly. Also, findings may not be applicable to all students in other geographical locations.

Ethical statement

All recruiters agreed. Participation in the study was voluntary and participants were told that they could withdraw from the study at any time. The information obtained from the participants in this study has been kept confidential. Also, the participants were not exposed to any kind of injury. The study was approved by the Ethics Committee of the Qazvin University of Medical Sciences. Thesis code: 952

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors had same share in collecting data for the study, contributing to the study design and sampling methodology, analyzed the data and presented its findings. All authors read and approved the last version.

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RESEARCH ARTICLE

The prevalence of preventive behaviors and associated factors during the early phase of the COVID-19 pandemic among Iranian People: Application of a Health Belief Model

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Keywords

Coronavirus disease 2019 • Preventive behaviors • Health belief model • Cross-sectional • Iran

Summary

Introduction. *Coronavirus disease 2019 (COVID-19) has developed into a severe public health concern. The present study was aimed to evaluate the related preventive behaviors to COVID-19, and associated factors among Iranians based on the constructs of the Health Belief Model (HBM).*

Methods. *This cross-sectional study was conducted between March and April 2020 among Iranians. Data of 1,020 people were collected by a self-administered questionnaire based on the constructs of HBM and also a demographics questionnaire. Simple and multivariable linear regression models were used to determine the predictors of preventive behaviors concerning COVID-19. A P-value of less than 0.05 was considered significant.*

Results. *The mean score of preventive behaviors concerning COVID-19 was 4.27 (standard deviation = 0.60). 40.6% (95% CI: 38.6-43.7%), and 56.5% (95% CI: 53.4-59.5%) of the participants exhibited a high, and moderate level of preventive behaviors, respectively.*

75.1% of the participants would always/often wear face masks out home or in crowded places. The most common preventive behaviors were using of personal belongings in the workplace or at home (96.1%) and staying at home except for very necessary or for work (92.9%). Results showed that all six HBM constructs, i.e., perceived susceptibility ($B = 0.07$, $P < 0.001$), perceived severity ($B = 0.08$, $P < 0.001$), perceived benefits ($B = 0.25$, $P < 0.001$), perceived barriers ($B = -0.12$, $P = 0.001$), cues to action ($B = 0.07$, $P < 0.001$), and self-efficacy ($B = 0.26$, $P < 0.001$) were significant predictors of related preventive behaviors to COVID-19. Female gender was another predictor of preventive behaviors ($B = 0.18$, $P < 0.001$).

Conclusions. *This study demonstrated the effectiveness of HBM constructs in predicting COVID-19 preventive behaviors. Therefore, the model as a framework for designing training programs for improving health behaviors among Iranians during the COVID-19 pandemic seems to be helpful.*

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a novel member of the Coronavirus family. It may affect humans by developing multiple symptoms such as pneumonia, fever, trouble breathing, and lung infection [1]. The virus was first observed in December 2019 in Wuhan, China, and has been officially named as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) [2]. According to the WHO announcement, by 12 May 2020, more than 4 million positive cases had affected 215 countries, regions or regions, and 285,000 deaths were reported [3]. The possible ways for transmission of SARS-CoV-2 are droplets from the patient's mouth or nose, contact, contaminated surfaces (fomites), and the fecal-oral route [4, 5]. Currently, there is no vaccination or effective antiviral therapy for the COVID-19. Therefore, personal hygiene behaviors such as wearing face masks, hand hygiene, and social distancing, which is proven are

effective in infection control [6, 7], is the best way to minimize the risk of transmitting the disease.

Health education interventions that supported by theory-based research could be helpful during the COVID-19 pandemic to motivate people to engage in preventive behaviors. The health belief model (HBM) is a conceptual model that is widely applied to explain and predict preventive health behaviors [8]. According to this model, people need to feel a real risk (perceived susceptibility) and also to have an extensive perception of the risk depth and seriousness of it (perceived severity) to adopt preventive behaviors. Also, when they feel that trying to change their behavior has many benefits (perceived benefits) and can overcome barriers to healthy behaviors (perceived barriers), there is more possibility that they are inclined to admit them. Moreover, the confidence level of a person from his/her capacity to perform a behavior (self-efficacy) is an influencing factor that can lead one toward that. Cues to action, such as advice from others, are another stimulus to decide to admit a health recommendation [9].

Exploring the prevalence of preventive behaviors and associated factors during a pandemic can help officials promote public health measures that improve the health behaviors rate in the general population. This study was aimed to evaluate the related preventive behaviors to COVID-19 and associated factors among Iranians based on the constructs of HBM.

Methods

STUDY DESIGN, PARTICIPANTS, AND SAMPLING STRATEGY

This was a cross-sectional study that was conducted on Iranian people. Subjects were selected by convenience sampling between March and April 2020, by sending an invitation along with the web page link of the online questionnaires through social networks (such as WhatsApp and Telegram). The inclusion criteria were the willingness to participate in the study, living in Iran, and the age of 15 years old or older. The sample size was determined as 1,004 individuals assume a small effect size of 0.11, 90% power, and a 95% confidence interval (CI), and a possible loss rate of 10%.

MEASURES

Demographic

The demographic questionnaire included several items about age, gender, educational level, marital status, income, underlying medical condition, physical exercise, and smoking.

The HBM-based scale

The HBM scale was designed based on six constructs based on the Likert scale, including perceived susceptibility, perceived severity, perceived benefit, perceived barrier, cues to action, and self-efficacy [10, 11]. The mean score was obtained for all subscales of the HBM scale by summing the answers and then dividing by the number of items. The mean scores of each subscale were also categorized into none/very low, low, moderate, and high based on the quartiles of the distribution of the scores. Further details of the HBM subscales were as follows:

- Perceived susceptibility toward COVID-19.
It was measured by six items (e.g., “There is a possibility that I will be infected with COVID-19” based on a 7-point Likert scale (1 = “strongly disagree”, 2 = “disagree”, 3 = “somewhat disagree”, 4 = “neither agree nor disagree”, 5 = “somewhat agree”, 6 = “agree”, 7 = “strongly agree”). Three negative items were rated in reverse. A higher total score would represent higher perceived susceptibility to COVID-19 by respondents.
- Perceived severity toward COVID-19.
Eight items were designed to measure perceived severity toward COVID-19 (e.g., “COVID 19 may lead to me be hospitalized”) based on 7-point Likert scales (1 as “strongly disagree” to 7 as

“strongly agree”). Higher scores would represent that respondents perceive more severe adverse consequences of COVID-19.

- Perceived benefits of related preventive behaviors to COVID-19.

Twelve items (e.g., “I could prevent COVID-19 by wearing facemasks in busy environments”) were designed to indicate the degree of agreement of the benefits of preventive behaviors in preventing contracting and spreading COVID-19 based on a 7-point Likert scale (1 as “strongly disagree” to 7 as “strongly agree”). Higher scores would indicate that respondents perceive more benefits in related preventive behaviors to COVID-19.

- Perceived barriers of related preventive behaviors to COVID-19.

Respondents were asked to rate the degree of difficulties in performing relate the preventive behaviors to COVID-19 based on a 7-point Likert scale (1 as “strongly disagree” to 7 as “strongly agree”). To this purpose, twelve items (e.g., “Face mask use makes me feel suffocated”) were designed. Higher scores of these items indicate respondents perceive more barriers in performing related preventive behaviors to COVID-19.

- Cues to action in preventive behaviors to COVID-19.
It was measured by five items (e.g., “I have watched programs about COVID-19 on various TV channels”) based on a 5-point Likert scale (1 as “strongly disagree” to 5 as “strongly agree”). A higher score would represent more cues to perform relate preventive behaviors to COVID-19.

- Perceived self-efficacy in performing related preventive behaviors to COVID-19.

Twelve items (e.g., “I can prevent COVID-19 by following health principles”) were designed to indicate the degree of self-efficacy in performing related preventive behaviors to COVID-19 based on a 5-point Likert scale (1 as “strongly disagree” to 5 as “strongly agree”). Higher scores would suggest more self-efficacy.

The scale of preventive behaviors concerning COVID-19

Twelve items were designed to measure preventive behaviors related to COVID-19 (e.g., “I wear a face mask when I leave home or in crowded places”). These items rated based on a 5-point Likert scale (1 = “never”, 2 = “rarely”, 3 = “sometimes”, 4 = “often”, and 5 = “always”). The answers were then summed and divided by the numbers of items to obtain the mean score and then categorized into none/very low, low, moderate, and high level based on the quartiles of the response distribution. Higher scores would suggest more performing preventive behaviors concerning COVID-19.

Validity and reliability of the scales

The content validity of the scales was assessed using the content validity ratio (CVR), and content validity index (CVI) based on the opinions of a team of experts

consisting of seven health education and promotion specialists and three infectious disease specialists. The last version of the scales was completed by adding experts' suggestions. The reliability of the scales was measured using Chronbach's alpha coefficient based on a pilot sample of 30 participants. For the HBM model constructs the Chronbach's alpha were as follows: perceived susceptibility ($\alpha = 0.66$); perceived severity ($\alpha = 0.74$), perceived benefit ($\alpha = 0.92$), perceived barrier ($\alpha = 0.79$), cues to action ($\alpha = 0.92$), and perceived self-efficacy ($\alpha = 0.92$). Chronbach's alpha for the scale of preventive behavior concerning the COVID-19 was 0.89.

ETHICAL CONSIDERATIONS

Study approval was obtained from the Ethics Committee of the Gonabad University of Medical Sciences (Ethical Code No: IR.GMU.REC.1399.002). The relevant descriptions of the research and its objectives were inserted at the outset of the online questionnaire. All participants completed the electronic questionnaires anonymously and with informed consent.

STATISTICAL ANALYSIS

Statistical analyses in this study were conducted using SPSS 16.0 software. Descriptive statistics for individual characteristics, the HBM constructs, and the preventive behaviors of respondents were generated using frequency (percent) for qualitative variables and mean [standard deviation (SD)] for quantitative variables. Univariate analysis was conducted by simple linear regression and variables with $P < 0.15$ were entered into a multivariable linear regression. We considered this selection criterion to avoid missing the variables that are not quite significant in the univariable model but may gain significance in a multivariable model by taking into account other variables [12, 13]. The multivariable linear regression model was used to investigate the efficacy of HBM in predicting related preventive behaviors to COVID-19 by controlling the effects of individuals' characteristics. A $P < 0.05$ was considered significant in the multivariable linear regression.

Results

INDIVIDUAL CHARACTERISTIC OF THE PARTICIPANT

A total of 1020 Iranian people participated in the study. The mean age of the participants was 38.5 (SD = 12.7), varying between 16 and 75 years old. Other characteristics of the participant have shown in Table I.

PREVENTIVE BEHAVIORS CONCERNING COVID-19

The mean score of preventive behaviors concerning COVID-19 was 4.27 (SD = 0.60). 40.6% (95% CI: 38.6-43.7%), and 56.5% (95% CI: 53.4-59.5%) of the participants exhibited a high, and moderate level of preventive behaviors, respectively. Table II summarizes the prevalence of related preventive behaviors to

COVID-19 among respondents. Overall, 75.1% of the participants would always/often wear face masks when leaving home or in crowded places to prevent contracting and spreading COVID-19. The most common preventive behaviors were using of personal belongings in the workplace or at home (96.1%) and staying at home except for very necessary or for work (92.9%).

TESTING THE HEALTH BELIEF MODEL

The mean score of the HBM constructs have shown in Table III. Perceived susceptibility, perceived benefits, and cues to action scores of most of the respondents were at a moderate or high level. The self-efficacy of most of the respondents about COVID-19 was at a high level. In comparison, perceived barriers scores of most of the respondents were at a very low or low level. The most common obstacles in performing preventive behaviors during COVID-19 were dryness, or soreness of the hand skin in case of repeated washing (74.2%), fake, rare, or costly disinfectants such as alcohol (72.4%), sweating the hands due to wearing gloves (53.4%), and the sensation of suffocation when using face masks (46.1%). Individual factors of gender, age, educational level, marital status, smoking, and physical exercise level had a $P < 0.15$ in the simple linear regression, and therefore entered multivariable linear regression model to control for their effects.

Tab. I. Characteristics of the participants.

Variable	N.	%
Gender		
Female	606	59.4
Male	414	40.6
Educational level		
High school or less	240	23.5
College	780	76.5
Marital status		
Married	718	70.4
Single/ divorced/ widowed	302	29.6
Income		
Low	176	17.3
Moderate	764	74.9
Good	80	7.8
Occupation		
Employee	370	36.3
Student	182	17.8
Retired	120	11.8
Housewife	163	16.5
Other	180	17.6
Underlying medical condition		
Yes	144	14.1
No	876	85.9
Smoking cigarettes/hookah		
Yes	138	13.5
No	882	86.5
Physical exercise level		
None/mild	692	67.8
Moderate and higher	328	32.2

Tab. II. Frequency distribution of preventive behaviors during the COVID-19 pandemic.

Preventive behaviors	Never/rarely N (%)	Sometimes N (%)	Often N (%)	Always N (%)
1. I wear a mask when I leave home and in crowded places	116 (11.3)	138 (13.5)	364 (35.7)	402 (39.4)
2. I regularly disinfect items such as mobile phones, tablets, keyboards, etc	22 (2.1)	118 (11.6)	380 (37.3)	500 (49.0)
3. I use my personal belongings at work or home	20 (2.0)	20 (2.0)	126 (12.4)	854 (83.7)
4. I heat the bread before eating it	82 (8.0)	104 (10.2)	342 (33.5)	492 (48.2)
5. I hold as far as possible a distance of at least two meters from other people	82 (8.0)	204 (20.0)	326 (32.0)	408 (40.0)
6. I wash my hands at least 20 seconds with soap and water	48 (4.7)	104 (10.2)	290 (28.4)	578 (56.7)
7. I avoid eating uncooked foods, and I cook them well to ensure their health	28 (2.8)	106 (10.4)	322 (31.6)	564 (55.3)
8. I wear gloves when I go out	116 (11.3)	142 (13.9)	382 (37.5)	380 (37.3)
9. I regularly disinfect all of the house's handles and surfaces	60 (5.9)	194 (19.0)	386 (37.8)	380 (37.3)
10. I'm not going to meet relatives' homes to prevent the spread of COVID-19	68 (6.7)	86 (8.4)	324 (31.8)	542 (53.1)
11. As much as possible, I leave home only in very necessary or for work	24 (2.4)	48 (4.7)	258 (25.4)	690 (67.6)
12. Before consumption, I wash and disinfect fruits and vegetables	48 (4.7)	92 (9.0)	310 (30.4)	570 (55.9)

Tab. III. Mean, standard deviation, and level of HBM constructs during the COVID-19 pandemic.

Variables	Mean (SD)	Level, n (%)		
		Very low/Low	Moderate	High
Perceived susceptibility	5.16 (0.86)	128 (12.6)	746 (73.1)	146 (14.3)
Perceived severity	4.03 (1.09)	544 (53.3)	428 (42.0)	48 (4.7)
Perceived benefits	5.93 (0.80)	24 (2.4)	522 (51.1)	474 (46.5)
Perceived barriers	3.36 (1.01)	758 (74.3)	250 (24.5)	12 (1.2)
Self-efficacy	4.61 (0.53)	16(1.6)	286 (28.0)	718 (70.4)
Cues to action	3.56 (0.81)	300 (29.4)	584 (57.3)	136 (13.3)

SD: Standard Deviation.

The results of multivariable linear regression showed that all the six HBM constructs were statistically significant in the prediction of COVID-19 associated preventive behaviors, after controlling the effects of individual characteristics. In summary, perceived susceptibility ($B = 0.07$, $P < 0.001$), perceived severity ($B = 0.08$, $P < 0.001$), perceived benefits ($B = 0.25$, $P < 0.001$), perceived barriers ($B = -0.12$, $P = 0.001$),

cues to action ($B = 0.07$, $P < 0.001$), and self-efficacy ($B = 0.26$, $P < 0.001$) were significant predictors of related preventive behaviors to COVID-19. Also, the results showed that respondents with gender female ($B = 0.19$, $P < 0.001$) would more obey preventative behaviors (Tab. IV). The multivariable linear model's adjusted R-squared coefficient value was 0.511. In other words, 51.1% of the preventive behavior variation was

Tab. IV. Associated factors with preventive behaviors during the COVID-19 outbreak based on HBM constructs and individual characteristics.

Predictors	Simple linear regression					Multiple linear regression				
	B	Beta	SE	t	P	B	Beta	SE	t	P
Age	0.005	0.10	0.001	3.24	0.001 ⁺	0.001	0.03	0.001	1.22	0.222
Gender: female ^a	0.33	0.27	0.04	8.78	< 0.001 ⁺	0.18	0.15	0.03	6.22	< 0.001
Educational level: college ^b	0.15	0.11	0.04	3.36	0.001 ⁺	0.05	0.03	0.03	1.58	0.115
Marital status: married ^c	0.18	0.14	0.04	4.37	< 0.001 ⁺	-0.05	-0.04	0.03	-1.56	0.119
Smoking cigarettes/hookah: yes ^d	0.25	0.14	0.06	4.57	< 0.001 ⁺	-0.04	-0.03	0.04	-1.03	0.303
Physical exercise level: moderate and higher ^e	0.07	0.06	0.04	1.83	0.06 ⁺	0.01	0.01	0.03	0.45	0.656
Income: low ^f	0.06	0.04	0.05	1.12	0.265	-	-	-	-	-
Underlying medical condition: yes ^d	0.07	0.04	0.05	1.34	0.180	-	-	-	-	-
Perceived susceptibility	0.16	0.23	0.02	7.63	< 0.001 ⁺	0.07	0.10	0.02	4.31	< 0.001
Perceived severity	0.07	0.12	0.02	3.91	< 0.001 ⁺	0.08	0.14	0.01	5.78	< 0.001
Perceived benefits	0.44	0.58	0.02	22.58	< 0.001 ⁺	0.25	0.33	0.02	11.97	< 0.001
Perceived barriers	-0.24	-0.40	0.02	-13.86	< 0.001 ⁺	-0.12	-0.20	0.01	-7.74	< 0.001
Self-efficacy	0.66	0.58	0.03	22.63	< 0.001 ⁺	0.26	0.23	0.03	7.68	< 0.001
Cues to action	0.22	0.30	0.02	10.00	< 0.001 ⁺	0.07	0.09	0.02	3.64	< 0.001

B: unstandardized coefficient; Beta: standardized coefficient; SE: Standard Error; ⁺: $P < 0.15$; ^a reference category: Male; ^b reference category: high school and less; ^c reference category: single/widowed/divorced; ^d reference category: no; ^e reference category: none/mild; ^f reference category: moderate or above.

explained by the multivariable model's independent variables [$F(12, 1,007) = 89.57, P < 0.001$].

Discussion

This study was aimed to evaluate the preventive behaviours related to COVID-19, and associated factors based on the theoretical framework of HBM among Iranians.

Our findings showed that most of all respondents adopted related preventive behaviors to COVID-19 (e.g., wearing face masks, stay-at-home, and avoiding unnecessary commuting out), which was in line with the results of the study by Kwok et al., in Hong Kong during the early phase of COVID-19 pandemic [14].

The findings of the current study showed the HBM's usefulness in identifying the determinants of related preventive behaviors to COVID-19 among Iranians, which was in line with similar studies. For instance, in one study by Tang et al., on Chinese adults in Hong Kong, during the severe acute respiratory syndrome (SARS) outbreak, the efficiency of the HBM in predicting the practice of face mask-wearing was revealed [15]. Another study by Najimi et al., among Iranian high school students indicated the efficacy of the HBM in improving preventive behaviors of influenza A [9]. Similarly, in one study by Tan et al., the adequacy of HBM for explaining the use of personal protection equipment among family physicians in Singapore during the SARS outbreak was verified [16].

The present study found that the perceived benefits were the first important factor in determining the preventive behaviors linked to COVID-19, which is consistent with the findings of previous similar studies [17-19]. This finding indicates that if people perceive the positive aspects of preventive behaviors in the deal with COVID-19, it is more likely to push them towards changing behaviors and adopting healthy practices in society by reducing the barriers.

The results of our study indicated that raising the level of self-efficacy is a significant factor to have more preventive behaviors. Previous research also reported self-efficacy as an influential element in determining health behaviors [20-22]. People with a higher level of self-efficacy have higher motivation and greater awareness of environmental opportunities. They increase their efforts in the event of a failure [22, 23].

Our findings revealed that perceived barriers have a significant negative correlation with the preventive behaviors related to COVID-19. This result is consistent with the results from the study by Coe et al., which found that people with lower scores on the perceived barriers are more likely to conduct the H1N1 vaccine [24]. In this study, the most common obstacles in performing preventive behaviors during COVID-19 were as follows: dryness or soreness of the hand skin in case of repeated washing, fake, rare, or costly disinfectants such as alcohol, sweating the hands due to wearing gloves, and the sensation of suffocation when using face masks. Therefore, to improve preventive behaviors during

the COVID-19 epidemic, it is necessary to reduce the current barriers and present the appropriate approaches to overcome them. These study results indicated that perceived severity, perceived susceptibility, and cues to action were the next influential factors amongst the HBM's constructs in determining preventive behaviors. A previous study during the early Hong Kong SARS epidemic also showed that perceived susceptibility, perceived benefits, and cues to action were significant predictors of wearing face masks [15]. Similarly, in a study, on a Hispanic population in Northern Manhattan, it is revealed that higher scores of perceived severity concerned with influenza were associated with more usage of face masks [25].

The study results showed that perceived susceptibility, perceived benefits, and self-efficacy of most of the respondents about COVID-19 were at a high level. These suggest that most respondents believed they were at high risk of contracting COVID-19. They were also conscious of the effectiveness of preventive behaviors in preventing COVID-19 from spreading. Moreover, they had a high perceived of their capability to successfully implementation of preventive health behaviors. In comparison, perceived barriers scores of the respondents were at an average level. Thus, reducing the factors that potentially prevent individuals from adopting health behaviors to avoid COVID-19 spread is demanded. Besides, perceived severity and cues to action scores were at average levels. COVID-19 is a novel disease and may be occurred asymptomatic in some cases. Therefore most people may imagine it like simple flu. According to these results, giving more information to people to understand the depth of the risk of COVID-19 through mass media and government is crucial to stimulate individuals to admit health recommendations.

There is some evidence on the associations between individuals' demographic characteristics and their preventive behavioral practices [15, 18, 26]. Based on the results of the present study, women would more obey preventative behaviors.

This study had some limitations. First, it was a web-based survey, and due to the non-random sampling procedure, which was unavoidable to prevent infection with COVID-19, there were concerns concerning the sample representative. Second, self-reported questionnaires in this sample could be a further source of bias. Third, the causal relationships could not be determined due to the cross-sectionalism of the study design.

Notwithstanding, these limitations, this research presented valuable information on influencing factors on the preventive behaviors concerning COVID-19 that could be used to increase the efficacy of interventions against the spread of COVID-19.

In this study, we solely focused on the HBM constructs as potential predictors of COVID-19 preventive behaviors. Psychological factors or emotional responses to COVID-19 could affect health behaviors [15, 27, 28]. Therefore, we suggest further researches to investigate the effect of them in predicting preventive behaviors during COVID-19.

Conclusions

There were high levels of related preventive behaviors to COVID-19 among the respondents. Women would more obey preventative behaviors. This study provided evidence on the efficacy of HBM in predicting related preventive behaviors to COVID-19 among Iranians.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

ADN contributed to the design, concepts of the work, data acquisition, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. FM contributed to the design, analysis, interpretation, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. NY contributed to the design, concepts of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SJ contributed to the design, concepts of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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RESEARCH ARTICLE

Association between oral health-related quality of life and general health among dental patients: a cross-sectional study

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Keywords

Oral health • Quality of life • SDG1 • SDG3 • SDG4 • SDG5 • Blood pressure • Blood glucose • Body mass index

Summary

Globally, the prevalence of chronic diseases is increasing significantly, causing deterioration of oral and general health and therefore quality of life. The present study was designed to assess the relationship between oral health-related quality of life and general health of dental patients. The study is part of the University's plan to achieve the United Nations Sustainable Development Goals number 1, 3, 4 and 5. Dental school students' satisfaction with their early engagement in clinical activities and research work was also evaluated. A convenience sample of 600 subjects attending dental clinics aged ≥ 18 years of both sexes was included in the study. Second-year dental students conducted the study under the supervision of public health staff members over two successive academic years (2015–2016 and 2016–2017). Oral health-related quality of life was assessed using the Dental Impact on Daily Liv-

ing (DIDL) questionnaire. Blood pressure, random blood glucose level, body mass index, and waist circumference were measured as indicators of general health. There were statistically significant inverse correlations between DIDL scores and both mean blood pressure ($r = -0.215$, $p < 0.001$) and mean blood glucose level ($r = -0.272$, $p < 0.001$). Non-significant inverse correlations were observed between DIDL scores and both body mass index ($r = -0.062$, $p = 0.131$) and waist circumference ($r = -0.040$, $p = 0.340$). Students' satisfaction scores with research activities were high, ranging from 75.9% to 78%. Dentists must raise patients' awareness about the importance of oral health and its impact on their quality of life and general health. Participation of dental students in dental research is encouraged even in their early academic years.

Introduction

The importance of quality of life has increased lately as it became one of the outcome measures of research on chronic diseases, oral disease, and other medical conditions. The evaluation of this measure focuses on the importance of functional, social, and psychological outcomes of patients [1]. It is evident that worldwide, the global disease burden is currently shifting from communicable to non-communicable diseases (NCDs), which include cardiovascular disease, diabetes, cancer, and respiratory diseases [2]. In African nations, oral diseases were prioritized as an additional NCD because many risk factors of most common NCDs are also risk factors for oral diseases [3]. Hypertension, diabetes, and obesity are all examples of chronic medical conditions that affect oral health, in addition to their characteristic general health effects; oral conditions resulting from these diseases usually have a negative impact on patients' quality of life [1, 4]. The oral cavity is involved in many essential social functions, such as nutrition, speech, and appearance. Impairments on any level may interfere with a person's quality of life and well-being [5]. The reported shortage of measures of oral health in terms of quality of life had led to the development of the Dental Impact on Daily Living (DIDL) questionnaire by Leao and Sheiham to fill this gap [6]. The questionnaire

includes items such as appearance, pain, comfort, eating restrictions, and general performance. The DIDL instrument has been confirmed to differentiate between subjective impacts on different social classes, groups, and sexes [6, 7].

Hypertension is one of the common general health conditions that have a negative impact on oral health, and this may be related to the cumulative effect of heart disease and periodontal disease, which share common risk factors [8, 9]. Common adverse effects of antihypertensive drugs are xerostomia and gingival hyperplasia [10]. The use of thiazide diuretics can result in erosions, ulcerations of buccal mucosa, and lichenoid reactions, which cause oral pain and discomfort and have a significant negative effect on oral health and hence the quality of life [11, 12]. According to the National Hypertension Project, the prevalence of hypertension has reached 35.5% among men and 34.5% among women in 2008. Globally, the number of persons affected by hypertension continues to increase as a result of aging and the increase in populations [13].

Diabetes is also one of the most common general health conditions that affect oral health, especially if poorly controlled [14]. It is expected to be the seventh leading cause of death in 2030. For instance, in Egypt, the prevalence of diabetes among adults aged 20–79 years was approximately 15.6% in 2015 [15]. The

most prevalent oral condition associated with diabetes mellitus is periodontal disease [16], which results in loss of teeth due to loss of both periodontal attachment and alveolar bone [17]. Furthermore, peripheral neuropathy that occurs in patients with diabetes negatively affects smell and taste functions [18, 19]. Those problems, together with a high caries index and reduced salivary production, significantly worsen quality of life in patients with diabetes [20-22].

The prevalence of obesity has increased internationally over the last decades, and obesity was considered by the World Health Organization as a global epidemic in the 1990s [23]. Studies have shown that poor oral health in obese people that resulted in periodontal disease, teeth loss, and inflammation might be the intermediate factor between obesity and poor dental outcomes [23-25]. Body Mass Index (BMI) is a general measure of obesity (calculated as weight in kilograms divided by height in meters squared) [26]. Increased BMI was associated with poor oral health-related quality of life in adolescents as these individuals were less proficient in performing vigorous physical and self-care activities; therefore, obesity could have an effect on oral health in everyday life [27, 28].

Therefore, in the present study, blood pressure, blood glucose level, and BMI were measured, and the results were assessed with regard to Oral Health-Related Quality Of Life (OHR-QOL) among dental patients. In addition, second-year dental students participated in this research as part of their dental public health curriculum to obtain early experience in communication with patients.

Methods

This cross-sectional study was conducted with a convenience sample of 600 dental patients through two academic years (2015-2016 and 2016-2017). The study was conducted at the Dental Clinics Complex of the Faculty of Oral and Dental Medicine - Misr International University. Participants answered a modified Arabic version of a validated DIDL questionnaire [7] and were screened for blood pressure level, blood glucose level, and BMI.

PARTICIPANTS

According to a pilot study results in which the correlation between DIDL score and blood pressure was the primary outcome, the predicted minimum sample size (n) was 527 subjects. The sample size was increased to 600 subjects to ensure participation of every second-year dental student in the study. Sample size calculation was performed using IBM® SPSS® Sample Power® Release 3.0.1 (IBM Corporation, Armonk, NY, USA).

Healthy or medically compromised dental patients aged ≥ 18 years of both sexes were included. Completely edentulous subjects were excluded because the DIDL questionnaire is designed for edentulous subjects. Pregnant subjects were excluded because pregnancy may be associated with hypertension or other medical problems. Subjects with mental or psychological

problems were excluded because their psychological status might affect their answers to the questionnaire.

According to the code of ethics of the World Medical Association (Declaration of Helsinki); each student provided his or her patient with a full verbal explanation of the study objectives and procedures, including how the patient would be screened for hypertension, diabetes, and BMI. Subjects then provided written consent for participation. Subjects who declined to participate in the study or who quit the study at any time were excluded without any effect on their regular treatment at the university clinics.

QUESTIONNAIRE

Before the study, the questionnaire was pilot-tested by two dental public health staff members on 60 randomly selected dental patients. Face validity was evaluated to assess the understanding and completion time of the questionnaire. Three questions in the DIDL questionnaire about the association between oral health and romantic aspects of life were excluded because of cultural trends. The results of the pilot study were not included in the final results.

The questionnaire was divided into four sections. The first section was about demographics, and participants provided data about their age, sex, education level, residence, occupation, and social status. The second section concerned general health and included six questions on a nominal scale about any medications or any health problems, including hypertension, diabetes, and history of surgeries, as well as participants' attitudes toward regular measurement of blood pressure and blood glucose level. The third section concerned oral health behavior and included seven questions about tooth brushing frequency, brushing tools, types of the toothbrush, use of other oral hygiene aids, partial denture cleansing (if applicable), and frequency and reasons for visiting a dentist. The fourth section included the DIDL questionnaire, which comprised 33 questions assessing OHR-QOL in the preceding 3 months. The questionnaire has five dimensions: appearance, pain, oral comfort, general performance, and eating and chewing. Responses to the questionnaire are recorded on 3-point Likert scales. To give a weight to each dimension, the summed response of that dimension is divided by the total possible scale score; then, the dimensional weight is multiplied by the summed dimension responses to provide the dimension score. The sum of all the five weighted dimension scores is the total DIDL score. The responses are categorized as "dissatisfied," "relatively satisfied," and "satisfied" [7].

TRAINING OF STUDENTS

Dental Dentistry students received training sessions during the dental public health course. The sessions included instructions on how to lead an interviewer-administered questionnaire and how to record blood pressure, blood glucose level, body weight, height, and waist circumference. Training sessions were conducted by dental public health staff members and five calibrated physicians. Cronbach's alpha values for inter-examiner reliability of the five physicians were 0.792 for systolic

blood pressure measurements and 0.771 for diastolic blood pressure measurements [29].

RECORDED MEASUREMENTS

All measurements were performed by second-year dental students, under complete supervision of the main investigators, dental public health staff members, and resident physicians.

Blood pressure

Blood pressure was measured in mmHg using mercurial sphygmomanometers and stethoscope (Shanghai Medical Instruments Ltd., Shanghai, China). The most recent guidelines for blood pressure reference range were used in the study: Normal blood pressure was < 120/80 mm Hg; elevated blood pressure was defined as a systolic value between 120 and 129 mm Hg and a diastolic value of < 80 mm Hg; stage 1 hypertension was defined as a systolic value between 130 and 139 mm Hg or a diastolic value between 80 and 89 mm Hg; stage 2 hypertension was defined as a systolic value of at least 140 mm Hg or a diastolic value of at least 90 mm Hg; and hypertensive crisis was defined as a systolic value of > 180 mm Hg or a diastolic value of > 120 mm Hg. Patients in hypertensive crisis were also those who needed prompt changes in medication if there were no other indications of problems or immediate hospitalization if there were signs of organ damage [30]. Blood pressure was measured in the right upper arm using a blood pressure monitor. The subject was asked to sit down for at least 5 min before blood pressure was measured [31]. The measurement was repeated after at least 5 min by the resident physician to confirm the student's reading.

Blood glucose level

To assess blood glucose level, a finger-tip blood sample was obtained with AccuChek Performa glucose meter (Roche Diabetes Care, Inc., Basel, Switzerland) in mg/dL. The reference range was a random plasma glucose level of ≥ 200 mg/dL (at any time of the day regardless of when the most recent meal was eaten) [32]. Trained nurses were assigned to perform the needle prick with disposable needles, and the students recorded the readings with the complete aseptic procedures.

Body mass index and waist circumference

To assess BMI, subjects were weighed with a lever-actuated balance to the nearest 0.1 kg (TBF-300, Tanita Corporation, Tokyo, Japan). Standing height was measured with a wall-mounted stadiometer with a range of 60-207 cm (Leicester Height Meter; Child Growth Foundation, London, UK). BMI was then calculated as the body weight in kilograms divided by the square of the height in meters [33]. Waist circumference in centimeters was measured with plastic measuring tape above the iliac crest level while the subject was at minimal respiration. Assessment of BMI and waist circumference was performed in accordance with the World Health Organization's classification of obesity [34].

Patients with critical blood pressure, blood glucose levels, or BMI values were informed about their condition and referred to the resident physician.

Oral health awareness

During the study, a brief educational session was given to the patients with the aim of increasing oral health awareness. The students also distributed oral health educational materials in the form of brochures or posters to help the patients retain the information.

MEASURING STUDENTS' SATISFACTION

At the final dental public health examination, a specially designed self-administered questionnaire in the format of 5-point Likert scales was distributed to assess the degree of the students' satisfaction with the study procedures, including the usefulness of their interview with the patients, whether participation in such a study inspired them to take part in upcoming research, and suggestions for improving future dental students' research.

Results

This study was conducted on 600 patients, of whom 379 (63.2%) were male and 221 (36.8%) were female. Their mean age was 42.6 years (standard deviation, 12.4 years); the youngest was 18 years old and the oldest was 77 years old (95% confidence interval, 41.6 to 43.6). Educational levels and occupations of the participants are depicted in Figures 1 and 2.

Fig. 1. Pie chart representing distribution of educational levels of study participants.

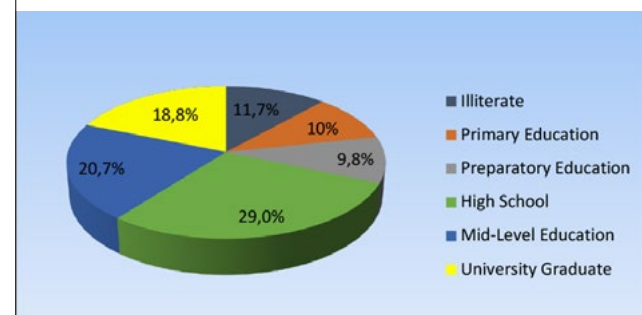
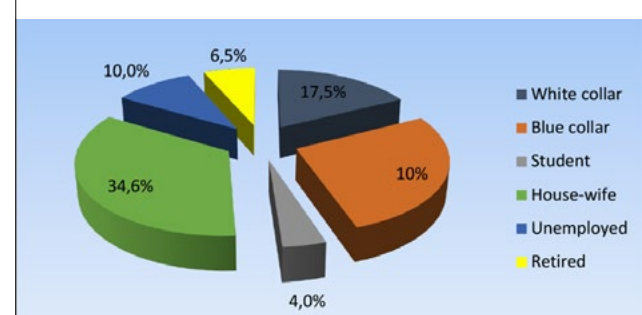


Fig. 2. Pie chart representing distribution of occupations of study participants.



RELIABILITY OF MEASUREMENTS

The agreement between blood pressure measurements obtained by the students and those obtained by the physicians was assessed using Cronbach's alpha reliability coefficient. The results showed very good agreement (Cronbach's alpha, 0.815; intra-class correlation coefficient, 0.774).

GENERAL HEALTH

Responses to questions regarding general health are presented in Table I. General health measurements performed by second-year dental students are presented in Table II. The state of blood pressure among subjects is listed in Table III. Random blood glucose levels of subjects are listed in Table IV. BMIs and waist circumferences of subjects are listed in Table V. Responses to the DIDL questionnaire are listed in Table VI.

ASSOCIATION BETWEEN DIDL SCORES AND GENERAL HEALTH MEASUREMENTS

An ordinal regression model was constructed with sociodemographic data and general health

measurements as independent variables and DIDL scores as the dependent variable. Regression results revealed that none of the sociodemographic characteristics had an effect on the DIDL scores. There were statistically significant inverse correlations between DIDL scores and both mean blood pressure ($r = -0.215$, $P < 0.001$) and blood glucose level ($r = -0.272$, $P < 0.001$). There were nonsignificant inverse correlations between DIDL scores and both BMI ($r = -0.062$, $P = 0.131$) and waist circumference ($r = -0.040$, $P = 0.340$). Students' satisfaction scores are illustrated in Figure 3.

Tab. II. General health measurements performed by second-year dental students.

Measurement	Mean	SD	95% confidence interval	
			Lower limit	Upper limit
Height (cm)	165	13.7	163.8	166.2
Weight (kg)	81.9	18.6	80.3	83.6
BMI (kg/m ²)	30.1	7.8	29.4	30.8
Waist circumference (cm)	105.2	24.7	103.1	107.3
Mean blood pressure (mm Hg)	104.8	14.3	103.7	106
Blood glucose level (g/dL)	108.7	43.7	105.1	112.3

BMI: body mass index; SD: standard deviation.

Tab. I. Responses to general health questions.

Question	N	%
Are you diabetic?		
Yes	45/600	7.5
No	526/600	87.7
Don't know	29/600	4.8
<i>If yes, what type of medication do you use?</i>		
Tablets	34/45	75.6
Insulin injection	5/45	11.1
Others	6/45	13.3
Don't know	0/45	0
<i>If yes, do you use your medication regularly?</i>	43/45	95.6
Are you a hypertensive patient?		
Yes	96/600	16
No	427/600	71.2
Don't know	77/600	12.8
<i>If yes, do you use your medication regularly?</i>	39/96	40.6
Do you assess your blood pressure and/or blood glucose level regularly?		
Yes	176/600	29.3
No	424/600	70.7
Do you use any regular medication?		
Yes	125/600	20.8
No	475/600	79.2
Do you suffer from any kidney or liver problems?		
Yes	77/600	12.8
No	484/600	80.7
Don't know	39/600	6.5
Have you undergone any surgery before?		
Yes	332/600	55.3
No	268/600	44.7

Tab. III. Blood pressure categories among hypertensive subjects, normotensive subjects, and subjects who did not know they had hypertension.

Blood pressure	Hypertensive patients		Normotensive patients		Patients who did not know their blood pressure status	
	N	%	N	%	N	%
Normal	11	11.5	93	21.8	14	18.2
Elevated	4	4.2	22	5.2	1	1.3
Stage 1 hypertension	29	30.2	148	34.7	28	36.4
Stage 2 hypertension	46	47.9	157	36.8	32	41.6
Hypertensive crisis	6	6.3	7	1.6	2	2.6
Total	96	16	427	71.2	77	12.8

Tab. IV. Blood glucose categories among diabetic subjects, normal subjects, and subjects who did not know they had diabetes.

Diabetes category	Normal patients		Patients with diabetes		Patients who did not know their blood glucose status	
	N	%	N	%	N	%
Normal	519	98.7	28	62.2	25	86.2
Diabetes	7	1.3	17	37.8	4	13.8
Total	526	87.7	45	7.5	29	4.8

Tab. V. Body mass index (BMI) and waist circumference of subjects.

BMI categories	N	%
<i>Underweight (< 18.5 kg/m²)</i>	15/600	2.5
<i>Normal (18.5 to 24.9 kg/m²)</i>	134/600	22.3
<i>Pre-obese Preobese (25 to 29.9 kg/m²)</i>	174/600	29.0
<i>Obese class 1 (30 to 34.9 kg/m²)</i>	161/600	26.8
<i>Obese class 2 (35 to 39.9 kg/m²)</i>	66/600	11.0
<i>Obese class 3 (≥ 40 kg/m²)</i>	50/600	8.3
Waist circumference categories		
Above action level 1		
Female	53/221	24
Male	120/379	31.7
Total	173/600	28.8
Above action level 2		
Female	168/221	76
Male	259/379	68.3
Total	427/600	71.2

Waist circumference above action level 1: patients should lose weight, increase physical activity and give up smoking; waist circumference above action level 2: patients should seek advice from health professionals for weight management.

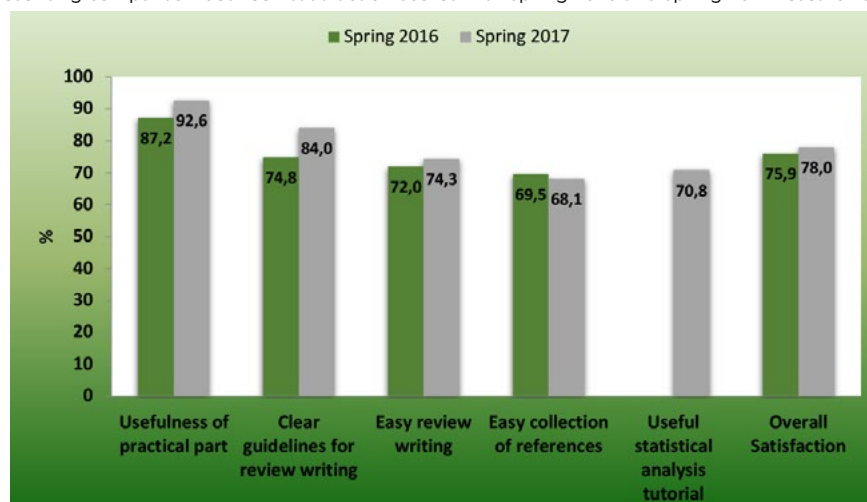
Tab. VI. Scores on Dental Impact on Daily Living (DIDL) questionnaire.

DIDL dimensions	Dissatisfied		Relatively satisfied		Satisfied	
	N	%	N	%	N	%
Appearance	301	50.2	102	17	194	32.3
Pain	433	72.2	112	18.7	194	32.3
Oral comfort	311	51.8	148	24.7	138	23
General performance	417	69.5	52	8.7	127	21.2
Eating and chewing	337	56.2	57	9.5	203	33.8

Discussion

The aims of this study were to encourage dental students to participate in research work, improve their practical

skills in measuring blood pressure and blood glucose level, and improve communication skills with patients through the interviewer-led questionnaire. In addition, the results were beneficial to the participants involved in the study as each subject received educational materials regarding oral and general health and were informed about their current overall health status. We included subjects with various educational levels and occupations to increase the validity of the study. The DIDL questionnaire was used because it is simple, clear, valid, and reliable. It can be filled out in a short time by patients with various educational and social levels [7]. Blood pressure measurements recorded by the students showed good to very good interobserver agreement with those recorded by the physicians, which indicates that the training of students before the practical part of the study was efficient. Concerning the responses of the patients to the questions about general health, the results showed that 7.5% of participants were diabetic and 16% were hypertensive. Although the majority of patients with diabetes used their medications regularly, fewer than half of the hypertensive patients used their medications regularly. Moreover, only 29.3% of the participants underwent regular assessment of blood pressure and blood glucose level. Of interest was that almost half of patients who reported being hypertensive had stage 2 hypertension, wherein only a few of patients who reported having normal blood pressure and the majority of subjects who did not know whether they were hypertensive, blood pressure categories ranged from elevated blood pressure to hypertensive crisis. Also, the results showed that 13.8% of subjects did not know whether they had diabetes although the random recordings of blood glucose levels indicated that they were elevated; 1.3% of subjects who reported having normal blood glucose levels actually had high random blood glucose levels. These findings are consistent with those of Williams et al., who mentioned that approximately 5% of dental patients have diabetes [35].

Fig. 3. Bar chart representing comparison between satisfaction scores with Spring 2016 and Spring 2017 research activities.

The abovementioned results revealed that many dental patients were unaware of the importance of regular assessment of their blood pressure and blood glucose level and that the dentist could be the first medical professional to discover that a patient has inadequately controlled diabetes or hypertension. Several authors reported similar results and found that patients' general condition was correlated with their oral health [7, 32]. Therefore, screening of blood pressure and blood glucose level should be included in the routine dental examination, whether in private practice or in public and governmental clinics. With regard to general health measurements and descriptive statistics for BMI categories, the results showed that the most common BMI categorization was pre-obese, followed by obese class 1 and normal weight. Obese classes 2 and 3 were less prevalent. The least prevalent BMI category was underweight, which characterized 2.5% of the study sample. With regard to waist circumference categories, the majority of subjects were categorized as action level 2. This category included a higher proportion of women than of men. In contrast, subjects categorized as action level 1 were men. Rosli et al. (2019) [36] showed that the mean BMI was 26.3 kg/m² (standard deviation: 4.6) in a sample in which the majority of the respondents were overweight and obese and only 3.9% were underweight. Chan et al. (2017) [24] combined overweight and obese adults into one group; they found that of 17, 261 respondents, approximately half were overweight/obese, which may be consistent with the results of this study. With regard to the DIDL questionnaire, the results showed that the dissatisfaction was high (among more than half of subjects) regarding all dimensions of the questionnaire; the area of the most dissatisfaction was pain, and satisfaction was highest for eating and chewing. This information is valuable with regard to the increased functional and emotional effects of pain from teeth and oral sores and their impact on psychological and physical functioning, as well as health behavior [34]. The statistically significant inverse correlations in the present study between DIDL scores and both blood pressure and blood glucose level mean that chronic diseases, especially hypertension and diabetes, had a negative impact on OHR-QOL as measured by the DIDL questionnaire. This may be attributed to decreased awareness of patients with diabetes and hypertension about the potential impact of poor oral health on their general health. These findings were in agreement with the results of other studies that highlighted the need of patients with high blood glucose levels to be informed about the effect of high blood glucose level on oral health [37-39]. Dentists have an important role in increasing awareness about the importance of maintaining good oral hygiene in patients with diabetes and hypertension. The statistically significant inverse correlation between DIDL scores and hypertension may be related to the cumulative effect of heart disease and periodontal disease, which share common risk factors [5]. It may also be attributed to the effect of antihypertensive drugs on gingival condition and salivary flow as such drugs may cause enlargement of gingiva, dry mouth, alteration in taste sensation, pain, and swelling in salivary glands [40]. The non-significant inverse correlation between DIDL

scores and both BMI and waist circumference may be consistent with the findings of Rosli et al. [35], who showed that the association of oral health and quality of life with impact of nutritional status is related merely to the risk of nutritional deficiency and not to the actual BMI score. In contrast to other studies' findings of a correlation between OHR-QOL and the anthropometric measurements, waist circumference and DIDL scores were significantly inversely correlated, which indicates that high waist circumference might adversely affect OHR-QOL [41]. Overall, students were satisfied with the research activities. The increase in students' satisfaction scores throughout the research period indicates success of the corrective action plan that was based upon the students' and supervisors' comments about the research in its first year.

The present study complies with the University's plan to achieve the United Nations Sustainable Development Goals (SDGs). SDG1 (No Poverty) is achieved through free of charge dental treatment for all people without discrimination. SDG3 (Good Health and Well-Being) is achieved in the present study by assessment of the general health of people and educating them regarding general and dental health. The engagement of students in research at an early stage of their education is within SDG4 (Quality Education) and finally both genders are treated and educated equally which fulfills SDG5 (Gender Equality) [42].

LIMITATIONS

The present study was cross-sectional; thus, it could not demonstrate causal relationships. The sampling method used was convenience sampling, and this enabled easy enrollment of participants; however, it did not reflect the entire population; so, the generalizability of the results is limited. The findings related to oral health knowledge, attitude, and behavior depended on self-reported data, and the rates of oral health behavior may have been biased through over- and under-reporting.

Conclusions

Within the limitations of this study, it could be concluded that patients with diabetes and hypertension have lower levels of OHR-QOL. Dentists must raise patients' awareness about the importance of oral health in their general health and quality of life. Participation of dental students in dental research should be encouraged even in their early academic years. Early contact between dental students and patients is advised to improve communication skills of students.

Ethical committee approval

Ethical approval was obtained from the Institutional Review Board (IRB #1617-031).

Data statement

The authors state that data are available when requested.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

MMF was the study director, participated in conduction of the research, wrote the introduction, methodology and discussion sections; AS sections; AS participated in conduction of the research, wrote the introduction, methodology and discussion sections; KK participated in conduction of the research, wrote the results and discussion sections.

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RESEARCH ARTICLE

Personal hygiene in schools: retrospective survey in the northern part of Côte d'Ivoire

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Keywords

Personal hygiene • Primary school students • North Côte D'Ivoire

Summary

Introduction. *Students' personal hygiene helps maintain health and promote good academic performance. When health facilities are insufficient, this hygiene can be difficult to achieve. We wanted to analyse the determinants of personal hygiene in schools in the northern region of Côte d'Ivoire.*

Methods. *The retrospective cross-sectional study brings together data on 2,035 schoolchildren recruited from thirty schools in northern Côte d'Ivoire. Indexes on personal hygiene were constructed and analysed in comparison to the socio-demographic characteristics of students, homes and schools. They were analysed with R Software version 1.1.463, the χ^2 test and a logistic regression model.*

Results. *Overall, the majority of students had good personal hygiene (82.75%) with an average personal hygiene score of 4.74 ± 1.36 . The predictors of good personal hygiene among schoolchildren were female gender (OR = 1.5; 95% CI = 4.31-16.37), father's primary education level (OR = 1.55; 95% CI = 1.07-2.29), the father's income level above 60,000 FCFA (90 Euros) and modern housing (OR = 1.45; 95% CI = 1.05-2.03). However, the poor level of home sanitation resulted in poor personal hygiene among the students (OR = 0.34; 95% CI = 0.23-0.5).*

Conclusions. *Measures to raise the standard of living of families and the provision of sanitary facilities in homes becomes necessary in order to improve students personal hygiene.*

Introduction

Personal hygiene refers to the set of practices that help maintain good health and prevent the spread of diseases. This involves regular washing of the body, hands, trimming of the nails, washing clothes, washing the hair and brushing the teeth [1]. In schools, students spend most of their time closer to each other, resulting in rapid transmission of infections, due to their naturally weak immune system and lack of knowledge of basic hygiene practices [2, 3]. Hygiene therefore plays an essential role in the prevention of communicable diseases [4]. These pathologies are the cause of absenteeism (75% in Malaysia in 2019), resulting in working time loss for parents, significant medical expenses due to medical visits and antibiotic prescriptions [5]. More than 1.9 billion school days could be gained if the supply of drinking water, sanitation were achieved and the incidence of diarrhoeal diseases would be reduced [3, 6]. The provision of drinking water and sanitary facilities at schools contribute to improved personal hygiene with a positive impact on the health of students [7]. In Kenya, for example, diarrhoea cases were reduced by half in 2004 [8]. In Burkina Faso, in the study conducted by Erismann et al., the prevalence of helminthiasis was decreased in schools, from 11.4% in 2015 to 8.0% in 2016 [9]. The provision of facilities also encourages the improvement of good hygiene practices as noted

in the study by Chard et al. in 2014 in Laos, where we observed an increase in the number of students who used the toilet and washed their hands with soap after using the toilet [10]. However, these facilities are not always available at schools, especially in the underdeveloped countries. In 2018, only 51% of schools in these countries have access to adequate water supply and 45% had adequate sanitation [7]. However, the origins of many adult diseases have their roots from childhood health behaviour. School-aged children can learn specific health-promoting behaviours, even if they do not always understand the links between illness and behaviour [11]. Therefore, hygiene education in schools can promote behaviour that will improve students' academic performance by reducing the rate of morbidity and absenteeism [1, 4, 12]. Instilling good hygiene practices at a younger age could have a lasting impact on the health of schoolchildren [2, 13]. The factors associated with the personal hygiene of pupils are well elucidated in the literature [14-17], namely the inadequate and insufficient sanitation facilities in schools, the level of education of the father, the level of income of the father, access to drinking water, gender and class of students, cleanliness of toilets, lack of separated toilets only for girls and lack of soap and water in handwashing device.

Meanwhile in Côte d'Ivoire, these factors are little studied. It is with this in mind that we analysed the determinants of personal hygiene in the school

environment in the northern region of Côte d'Ivoire, based on a database on intestinal helminthiasis carried out in 2016 which made it possible to highlight the personal hygiene index [18, 19].

Material and methods

TYPE OF STUDY AND POPULATION

Between October 2016 and January 2017, a cross-sectional study was carried out in 4 departments in the northern area of Côte d'Ivoire, namely the departments of Tengrela, Boundiali, Ferkessedougou, Dabakala. The study examined elementary school children aged 5 to 15. All schoolchildren present during the survey period and who had lived in the north for more than 3 months were included. However, schoolchildren who had been dewormed 3 weeks before the start of the study were excluded.

Sampling

The educational departments of northern Côte d'Ivoire comprised 536 primary schools, with 81,041 schoolchildren enrolled in the period for the 2014-2015 school year [Department of Strategies, Planning and Statistics (DSPS, 2014-2015)]. To calculate the minimum number of schools and children to be included, the sample size was determined using Schwartz's formula with a theoretical prevalence of 50%, accuracy of 5%. The calculated sample was 384 students extrapolated to 510 students per region. The total enrollment was 2,040 schoolchildren.

In each region we have made the reasoned choice to take 60 classes, which brings us to an enrollment of 8.5 students per class, rounded off to 10 students per class. Each school has 6 classes, we have selected 10 schools per region.

Selection

Once in the classroom, the schoolchildren were randomly selected until they reached ten pupils.

COLLECTION OF DATA

Data were collected using a standardized questionnaire forms. These data related to age, sex, class, taking dewormer, the student housing environment (rural or urban), certain behaviors (for example, defecating habits, visiting rivers) and status. socio-economic status of the mother. The investigation included the functional signs related to various stages of schistosomiasis, such as itching, headache, stomach upset or diarrhea.

SAMPLE COLLECTION AND LABORATORY PROCEDURES

Faecal samples were taken from schoolchildren directly using the plastic pots and analyzed using the Kato-Katz method. A stool sample was taken for each child. This technique has been used to identify *S. mansoni* eggs and the presence of other helminths, including roundworms, whipworms, hookworms and *Taenia* sp. Thus a database on hookworms in schools conducted in the north of Côte d'Ivoire was set up. Our study was based on this database, which also contained variables on the personal hygiene of the student, the socio-demographic and environmental characteristics of the student, his family and the variables related to sanitation at school. Schools in the northern region of Côte d'Ivoire face a double challenge : insufficient access to drinking water and poor hygiene and sanitary conditions. Indeed, the average performance in mathematics and reading (-53.8 points and -34.9 points) in the Northern region are lower than the national averages in both subjects and irrespective of the level [20].

The data was exported to an Excel table for the construction of new variables.

VARIABLES

Dependent variable

The personal hygiene variable was constructed by referring to the personal hygiene index developed by Jeyakumar et al. [21]. The personal hygiene items (explained variable) consisted of four domains including hand hygiene, nail hygiene, wearing shoes, school excreta disposal. For hand hygiene, 3 criteria were retained, for nail hygiene and the wearing of shoes, these criteria were two in number and one criterion was retained for the elimination of excreta. The personal hygiene variable therefore included a total of 8 criteria (Tab. I). Hand hygiene was said to be good if the student always washed his hands before eating and after bowel movements, using soap and water. Nail hygiene was good if the student did not bite his or her nails and had clean nails. Foot hygiene was correct if the student had shoes that he always put on. Excreta disposal was correct if the student used the toilet. Each observation could get a score of 0 or 1. When the observed practice was positive, a score of 1 was assigned. The level of personal hygiene was therefore calculated by adding the scores. Thus, the total personal hygiene score was between 0 and 8. A poor personal hygiene practice corresponded to a score less than or equal to 3, a good personal hygiene practice to a score between 4 and 5 and a very good personal hygiene practice corresponded to a score between 6 and 8.

Tab. I. Indexes to assess personal hygiene.

Hand hygiene	Nail hygiene	Foot hygiene	Excreta elimination
Hand washing Always wash hands before eating and after toilet Use soap and water to wash hands	Have nails trimmed Have clean nails	Have shoes Wear shoes always	Use toilets
Possible score 0-3	Possible score 0-2	Possible score 0-2	Possible score 0-1

EXPLANATORY VARIABLES

The explanatory variables were the socio-demographic characteristics of the students, the area of residence, sanitation at school, the socio-economic characteristics of families and access to water and sanitation in households. The student's socio-demographic variables included age, gender, and educational attainment. The school sanitation was assessed on the basis of the answers to the existence of toilets in the school and the state of cleanliness of these toilets. The school sanitation was assessed on the basis of the answers to the existence of toilets in the school and the state of cleanliness of these toilets. Thus, the level of hygiene in the school was good when there was at least one toilet and when the facilities were clean.

The socio-demographic variables of the family consisted of the level of education of the father and the mother, the monthly income of the parents recoded into 2 salary levels with reference to the guaranteed minimum inter-professional wage (SMIG) in force in Côte d'Ivoire < 60,000 FCFA and \geq 60,000 FCFA or 90 Euros. The habitat type has been dichotomized into the modern type habitat and rural type habitat.

The household's water supply source was informed through the availability or not of drinking water at home. Access to good sanitation at home was treated like the disposal of excreta at school.

STATISTICAL ANALYSIS

The analysis of the data thus generated was carried out with R Software version 1.1.463.

Each variable was subjected to descriptive analysis. Associations between levels of personal hygiene and the variables studied were explored using the χ^2 test in univariate analyzes. A *p* value < 0.05 was considered indicative of a statistically significant association. Individuals with missing data for dependent variables were not retained for analysis. For multivariate analyzes, the analysis strategy was to include in the model all variables that had a *p*-value of less than 20% in univariate. This threshold has been favored so as not to immediately eliminate the important variables. Then, the variable which, at each step, provided the least information was removed from the model while checking that it was not a confounding factor (percentage of variation in odds ratio greater than 20-25%). This progressive elimination procedure was carried out until a model was obtained which consisted only of significant variables (*p*-values < 5%). Once the reduced model was obtained, relevant interaction terms were introduced and a top-down procedure was performed again to find out whether any interaction terms were significant (significance level set at 5%). The variables involved in a significant interaction were maintained in the model.

MISSING DATA

Pre-treatment

The pre-processing of the data consisted in listing the number of non-response by variable.

Data cleaning and missing data management. The non-response rates were estimated and were relatively low because only 5 (0.24%) children were concerned, which allowed us not to take them into account in our study and to have a correct database.

ETHICAL CONSIDERATIONS

The agreement of the head of the parasitology-mycology department of the Faculty of Pharmacy and Biological Sciences has been obtained for the use of the database. The original file was anonymous.

Results

SOCIODEMOGRAPHIC CHARACTERISTICS

Table II shows the socio-demographic characteristics of students, parents and households. There were 2,035 students with a sex ratio (M/F) of 1.24. There were practically the same number of pupils in the 3 levels CP, CE and CM (33%). The mean age was 9.2 (\pm 2.33) years. Most students attended schools with toilets (71.9%), however, 84% had poor sanitation in the schools. Most of the students had parents who were not educated, respectively 46% for fathers and 58% for mothers. More than half of the parents had a monthly income greater than or equal to the minimum wage (61% of fathers and 62% of mothers). Almost all of the students came from households where the parents lived as a couple (96.71%). Their housing was 68.55% rural. They had access to drinking water (97%) and a good level of sanitation (75%).

COMPONENTS OF PERSONAL HYGIENE

Analysis of personal hygiene in Table III shows that the components "hand hygiene", "foot hygiene" and "nail hygiene" were poor in 91, 72 and 67% of students, respectively. The most correct hygienic practice was the disposal of excreta (about 2 out of 3 students). Overall personal hygiene was good with an average score of 4.74 \pm 1.36. Thus, 8 out of 10 students had good personal hygiene.

UNIVARIATE ANALYSIS

The univariate analysis presented in Table IV revealed that personal hygiene was better in girls (*p* = 0.002), in students over 10 years old (*p* = 0.031) and when school sanitation was good (*p* < 0.001). Family characteristics related to personal hygiene were parents education level, level of their income above the minimum wage, modern housing and adequate sanitation (*p* < 0.001). When the household had access to good drinking water, the personal hygiene of the students was also better (*p* = 0.008).

MULTIVARIATE ANALYSIS

In the final logistic regression model, student sex, school and home sanitation, father's income and education level,

Tab. II. Socio-demographic characteristics of students in the north of Côte d'Ivoire (n = 2,035).

Socio-demographic characteristics	Frequency	Percentage
Students' characteristic		
Sex		
Male	1,128	55.43
Female	907	44.57
Age group (Years)		
< 10	1,094	53.76
≥ 10	941	46.24
Class		
CP	679	33.37
CE	679	33.37
CM	677	33.26
Schools characteristic		
Sanitation at school		
Poor	1,719	84.62
Good	313	15.38
Family characteristic		
Father's education level		
Illiterate	939	46.14
Primary school		21.28
Secondary school	382	18.77
Higher education	281	13.81
Mother's education level		
Illiterate	1,198	58.87
Primary school	439	21.57
Secondary school	319	15.68
Higher Education	79	3.88
Father's monthly income (FCFA)		
< 60 000	787	38.67
≥ 60 000	1,248	61.33
Mother's monthly income (FCFA)		
< 60 000	766	37.64
≥ 60 000	1,269	62.36
Matrimonial status		
Couple	1,968	96.71
Single parent	67	3.29
Portable water		
Yes	1975	97.05
No	60	2.95
Type of habitation		
Modern	640	31.45
Rural	1,395	68.55
Sanitation at home		
Yes	1,538	75.58
No	497	24.42

family home type were the predictors of good personal hygiene for students (Tab. V). Compared to boys, female students and those whose fathers received an elementary or secondary school education were 1.5 times more likely to have good personal hygiene. The same was true for modern-type housing compared to rural-type housing. The father's income level above the minimum wage doubled the student's probability of having good personal hygiene. Adequate sanitation at school was strongly associated with good student personal hygiene (8 times). Poor sanitation at home reduced by a third the probability of the student having good personal hygiene.

Discussion

This study took place in primary schools in northern Côte d'Ivoire with a sample of 2,035 students. Overall, in our study the majority of students had good personal hygiene (82%), as in the study conducted by Baba et al. in Nigeria, where 74% of school children had good personal hygiene [16]. This personal hygiene was associated with gender ($p = 0.002$) with girls being 1.5 times cleaner than boys. This trend has also been reported in studies by Motakpalli et al. and Sakar in India [4, 11]. Among the socio-demographic variables of the parents, the primary

Tab. III. Distribution of students according to the components of personal hygiene (n = 2,035).

Personal hygiene components	Frequency	Percentage
Hands hygiene		
Poor	1,856	91.2
Good	179	8.8
Nails hygiene		
Poor	1,363	66.98
Good	672	33.02
Foot hygiene		
Poor	1,468	72.14
Good	567	27.86
Excreta elimination		
Poor	673	33.07
Good	1,362	66.93
Global personal hygiene		
Poor	351	17.25
Good	1,091	53.61
Very good	593	29.14

and secondary education level of the father encouraged more than once a good personal hygiene in the pupils and personal hygiene improved with the advancement in the education level of the pupil and father. Rather, Lopez in 2007 noted that handwashing among students increased with mother's level of education [17]. Pupils whose fathers had a monthly income greater than or equal to 60,000 FCFA (90 Euros) were 2.36 times cleaner than those whose fathers earn a lower income ($p < 0.001$). This result could be explained by the fact that the father's income below the minimum wage is low, however several charges in the household fall on the father, namely sanitary products and sanitary facilities as well as access to potable drinking water which incur costs making this income very insufficient for household needs. These results are similar to those of Oga in 2004 in Agboville where the prevalence of intestinal helminthiasis decreased when the father's income increased [22].

In terms of the household and school environment, our study showed that children who lived in modern-type houses were 1.45 times cleaner than those in rural-type houses ($p < 0.001$). According to Bewa et al. (2016), in Benin, the type of housing was an indirect reflection of the economic level of the household [23]. In fact, in these households, children do not benefit from amenities such as drinking water supply and excreta disposal and may have difficulty practicing hygiene measures [24]. When schools had good sanitation, students were almost 8 times cleaner than those in schools with poor sanitation ($p < 0.001$). According to Koné in 2012, in Mali, such unsanitary conditions favour student absenteeism and the spread of diseases linked to faecal peril, in particular diarrheal diseases, typhoid fever and polio [25].

Among students aged 10 and above with poor home sanitation, personal hygiene was still 3.38 times more important. This could be related to the adaptability of children's development as they grow older. It has been reported that the ability to understand and apply basic personal hygiene advice would be improved in older

Tab. IV. Univariate analysis of factors associated with student personal hygiene.

Personal Hygiene	Bad	Good	P
Sex			
Female	130 (14.3)	777 (85,7)	0.002
Male	221 (19.6)	907 (80,4)	
Class			
CP	125 (18.4)	554 (81.6)	0.531
CE	117 (17.2)	562 (82.8)	
CM	109 (16.1)	568 (83.9)	
Age group (years)			
< 10	207 (18.9)	887 (81.1)	0.031
≥ 10	144 (15.3)	797 (84.7)	
Sanitation at school			
Good	10 (3.2)	304 (96.8)	< 0.001
Poor	341 (19.8)	1380 (80.2)	
Father's education level			
Illiterate	231 (24.6)	708 (75.4)	< 0.001
Primary school	75 (17.3)	358 (82.7)	
Secondary school	32 (8.4)	350 (91.6)	
Higher education	13 (4.6)	268 (95.4)	
Mother's education level			
Illiterate	272 (22.7)	926 (77.3)	< 0.001
Primary school	59 (13.4)	380 (86.6)	
Secondary school	18 (5.6)	301 (94.4)	
Higher education	2 (2.5)	77 (97.5)	
Father's income (FCFA)			
< 60,000	232 (29.5)	555 (70.5)	< 0.001
≥ 60,000	119 (9.5)	1,129 (90.5)	
Mother's income (FCFA)			
< 60,000	273 (21.5)	996 (78.5)	< 0.001
≥ 60,000	78 (10.2)	688 (89.8)	
Marital status			
Couple	335 (17.0)	1,633 (83.0)	0.144
Single parent	16 (23.9)	51 (76.1)	
Portable water			
No	18 (30)	42 (70)	0.008
Yes	333 (16.9)	1,642 (83.1)	
Type of home			
Modern	58 (9.1)	582 (90.9)	< 0.001
Rural	293 (21.0)	1,102 (79.0)	
Sanitation at school			
No	158 (31.8)	339 (68.2)	< 0.001
Yes	193 (12.5)	1,345 (87.5)	

children compared to younger children even if home sanitation was not adequate [16].

STUDY LIMITATIONS

This study highlights the level of hygiene of school children in the North as well as the risk factors. Outcomes should be considered cautiously as behaviours are self-reported. However, any bias in the responses can overestimate or underestimate the behaviours. The results of this study cannot be generalized to other hygiene practices in the country since the sampling is not representative of the country and it is a retrospective study.

Tab. V. Personal hygiene and predictive factors among students in the north of Côte d'Ivoire.

Variables	Personal hygiene		Adjusted OR (95% CI)	P-value
	Bad n (%)	Good n (%)		
<i>Students' characteristic</i>				
Sex				
Female	130 (14.3)	777 (85.7)	1.5 (1.16-1.94)	0.001
Male	221 (19.6)	907 (80.4)	1	-
Age group (years)				
< 10	207 (18.9)	887 (81.1)	1	-
≥ 10	144 (15.3)	797 (84.7)	0.79 (0.57-1.08)	0.152
<i>School characteristic</i>				
Sanitation at school				
Good	10 (3.2)	304 (96.8)	7.93 (4.31-16.37)	< 0.001
Poor	341 (19.8)	1380 (80.2)	1	-
<i>Family characteristic</i>				
Father's education level				
illiterate	231 (24.6)	708 (75.4)	1	-
Primary school	75 (17.3)	358 (82.7)	1.55(1.07-2.29)	0.021
Secondary school	32 (8.4)	350 (91.6)	1.84(1.02-3.38)	0.042
Higher education	13 (4.6)	268 (95.4)	1.95 (0.92-4.36)	0.089
Mother's education level				
illiterate	272 (22.7)	926 (77.3)	1	-
Primary school	59 (13.4)	380 (86.6)	0.96 (0.60-1.53)	0.877
Secondary school	18 (5.6)	301 (94.4)	1.90 (0.92-4)	0.085
Higher education	2 (2.5)	77 (97.5)	3.90 (0.99-26.08)	0.086
Father's Income (FCFA)				
< 60,000	232 (29.5)	555 (70.5)	1	-
≥ 60,000	119 (9.5)	1129 (90.5)	2.36 (1.59-3.54)	< 0.001
Mother's income (FCFA)				
< 60,000	273 (21.5)	996 (78.5)	1.37 (0.91-2.09)	0.129
≥ 60,000	78 (10.2)	688 (89.8)	1	-
Type of home				
Modern	58 (9.1)	582 (90.9)	1.45 (1.05-2.03)	0.025
Rural	293 (21.0)	1102 (79.0)	1	-
Sanitation at home				
No	158 (31.8)	339 (68.2)	0.34 (0.23-0.50)	< 0.001
Yes	193 (12.5)	1345 (87.5)	1	-
Age ≥ 10 years * Poor sanitation at home	-	-	3.38 (2-5.76)	< 0.001

Conclusions

The personal hygiene of pupils in northern Côte d'Ivoire was good. Thus girls had better hygiene than boys, children aged 10 and above were cleaner, the more higher the father's education level was, and the pupil's personal hygiene increased. Modern housing and sanitation at home and at school promoted good hygiene. Personal hygiene in students therefore requires the provision of health infrastructure both at home and at school, not to mention the training of students. This suggests an effective involvement of education authorities, the economy, without forgetting the participation of teachers, parents and students.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

SKJ: conception, design, data collection, supervision and writeup of the manuscript.

DAA: writing original draft.

KBP: data collection.

KJ : data analysis and interpretation.

TML, GBM[†], KKL: review.

All authors have read and agreed to the published version of the manuscript.

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RESEARCH ARTICLE

The influence of mindfulness-based stress reduction (MBSR) on stress, anxiety and depression due to unwanted pregnancy: a randomized clinical trial

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Keywords

Mindfulness-based stress reduction (MBSR) • Unintended pregnancy • Stress • Anxiety • Depression

Summary

Background. Individuals with unwanted pregnancies often experience high levels of anxiety, stress and depression that associated with maternal-neonatal outcomes. Mindfulness training is a safe and acceptable strategy to support mental health before parturition.

Purpose. The main objective of present study was to evaluate the influence of eight-week application of mindfulness-based stress reduction on stress, anxiety and depression caused by unplanned pregnancy.

Method. In this study, 60 women with unwanted pregnancy before 32 weeks of gestational age were selected and randomly divided into two groups. Intervention group received MBSR sessions, practice at home and the recorded sound. Mental health was evaluated before intervention and at the end of the eight sessions by standard

stress, anxiety and depression DASS-21 questionnaire. Data were analyzed using Chi-square, Mann-Whitney U and Wilcoxon tests.

Findings. In order to compare pre-test and post-test scores in each group, the Wilcoxon Test was used. The results revealed that the participants in the intervention group reported a significant decrease in mean scores of stress, anxiety and depression compared to baseline ($P = 0.0$). Whereas no significant decrease in mean stress, anxiety and depression score were found in control group. P-value was estimated to be 0.346, 0.212 and 0.343 respectively.

Conclusions. The mindfulness program has effectively reduced stress, anxiety and depression. Further research is needed to investigate the mechanisms and effects of mindfulness on maternal-neonatal outcomes.

Introduction

An unwanted pregnancy is unwanted or mistimed pregnancy. A mistimed pregnancy occurs in women who conceived sooner or later than the desire time. It happens in women who do not want any more children at the time of the conception [1].

Studies have shown that 49-51 percent of pregnancies in the United States of America are unwanted. Over time, the number of births due to requested pregnancy is decreased and births due to unwanted pregnancy are increased [2]. Unwanted pregnancy can lead to a wide range of physical and psychological consequences for mother and child and affects different aspects of social, economic and cultural health of the community [3, 4]. Women with unwanted pregnancies are most likely to receive inadequate pre-partum care and there were observed also high rates of alcohol consumption and smoking as well as premature labor as well as low birth weight and lactation among them [3, 5, 6]. In addition, the risk of physical and mental health problems increases among their children [3, 7, 8] which is one of

the global concerns due to its association with physical, mental, social and economic consequences [9]. Unwanted pregnancy is one of the most common and debilitating factors of women's mental health in fertility ages which, in turn, causes depression during pregnancy and after childbirth [10]. According to Abajobir et al. (2016), the prevalence of depression during pregnancy in women with unwanted pregnancies is twice [11]. Anxiety and depression are often experienced simultaneously [12, 13]. Anxiety appears to be influenced by emotion-oriented coping styles including emotional, selfish responds and fantasy reactions. Therefore, it is likely for consistent coping program such as mindfulness-based stress reduction program [MBSR] to reduce depression, anxiety and stress [13]. Early pregnancy depression in addition to predicate post-partum depression symptoms increases anxiety and stress in late pregnancy [14]. Based on the studies, unwanted pregnancy is associated with high levels of depression and perceived stress [15-18]. High stress level increases the risk of maternal mental health problems by mitigating coping skills [11]. In response to the stress levels, mindfulness

increasingly focuses on mental concentration as a key stress management strategy in order to help individuals more effectively respond to stressors [19]. According to the findings, MBSR program has been effective in reducing psychological symptoms [13, 20]. However, the potential benefits of MBSR program were not addressed in reducing depression, anxiety and stress among unplanned pregnant women. Accordingly, the purpose of this study was to investigate the effectiveness of counseling of MBSR as an intervention to reduce unwanted pregnancy depression, anxiety and stress.

Methods

TYPE OF STUDY

The data were collected from a randomized clinical trial in which the effect of independent variable, MBSR, on dependent variable, psychological reactions (e.g. anxiety, depression and stress), was measured.

SAMPLES AND STATISTICAL POPULATION

Participants were eligible pregnant women with unplanned pregnancies under 32-weeks of gestational age. Studies show that women with unwanted pregnancies are less likely to seek prenatal care and sometimes may not return until late in pregnancy. Since the purpose of this study was only to investigate the effect of mindfulness on mental disorders in women with unwanted pregnancies; therefore, to access more samples, we examined pregnant women under 32 weeks of gestational age. Sampling was carried out in Sirjan-kerman health center from 2018 to 2019.

INCLUSION CRITERIA

Inclusion criteria involved having a spouse aged 15-49 years, pregnancy less than 32 weeks [21, 22] and not suffering neuro-psychiatric disorder, absence of drug abuse, Lack of psychiatric medication as well as lack of convulsions and mental disability, readiness and consent to participate in this study.

EXCLUSION CRITERIA

The exclusion criteria included missing more than 2 sessions in training course, failure to follow instructions and exercise related to each session, participant's unwillingness to continue, stressful events, acute and unexpected events at each stage of the plan and acute psychotic disease.

SAMPLE SIZE AND SAMPLING

Using software GPower V.3.1 and sample size formula to compare mean values at two groups and taking $\alpha = 0.05$ and $1-\beta = 0.9$, standard deviation of 6.22 depression in the study of Hosseini Shahidi et al. [23], and the difference of average at least 5 aspects of depression in two groups into account, the sample size included in each group was estimated to be 25 subjects. Taking the

loss of sample size by 15%, 30 subjects were considered. In this randomized cluster sampling, 6 health centers were selected from the existing 19 centers. Two health centers selected from each districts of the city; One center was considered as an intervention and one as a control. Thus, all pregnant mothers under 32 week of pregnancy were contacted by telephone and those who had unplanned pregnancies were invited to clinic to complete the questionnaire. Women who had a stress score higher than 14 or an anxiety score higher than 7 or a depression score higher than 9 were identified. So, 60 people, 10 eligible patients from each center were selected. Afterward, among those with psychological symptoms, 30 subjects were selected for intervention group and 30 subjects were selected for control group, randomly (Fig. 1).

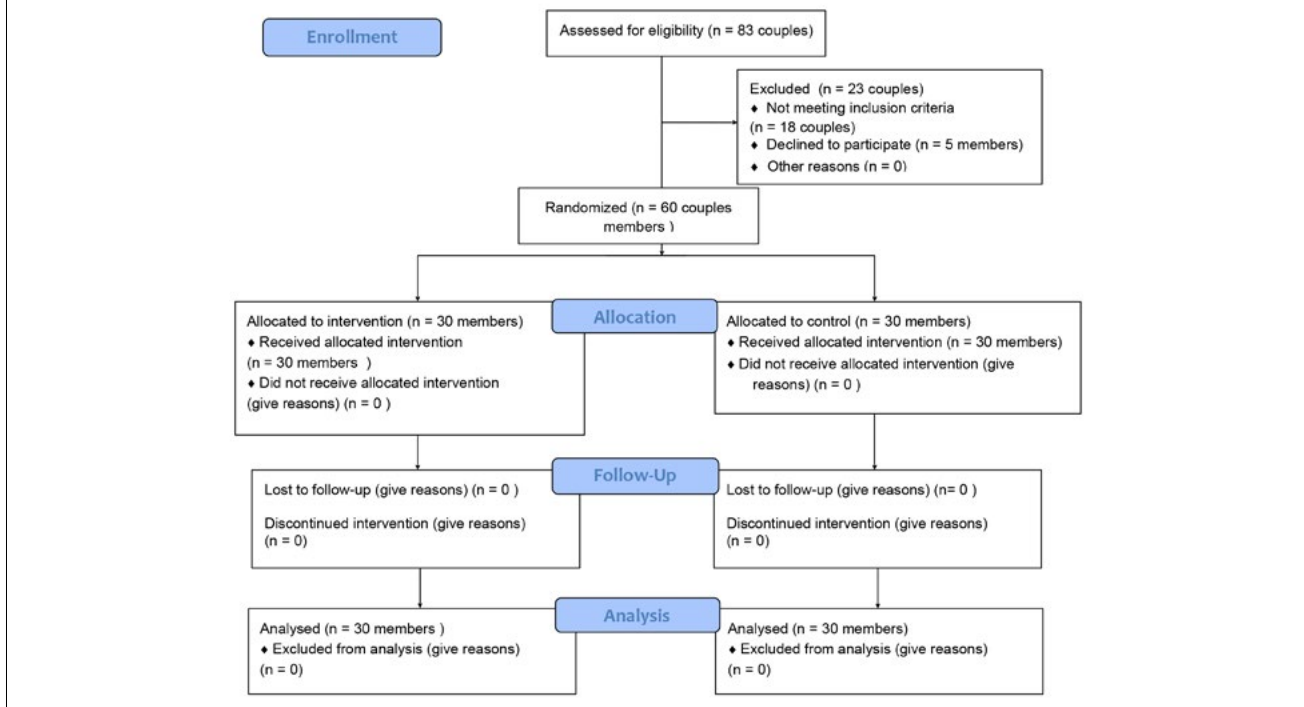
DATA COLLECTION AND METHODOLOGY

The protocol for this study was reviewed and approved by the human ethics committee of Kerman University of medical science (IR.KMU.REC.1397.487). 60 women with unplanned pregnancies who had at least one designated case of cut off for stress, anxiety or depression responded to the invitation to participate and informed and written consents were obtained from the participants.

Subjects were randomly divided into two groups of MBSR treatment and control. The main content of MBSR program was standard yoga, sitting, walking, breathing, body scan and eating meditation; that was performed by a mental health midwife who had educated in counselling in midwifery and was trained about several kinds of intervention for improving mental health. This program was conducted for 8 sessions and each session lasted for 2 hours (one session per week). Participants followed instructions for mindfulness meditation, exercise group discussion and homework assignments during 8 weeks. The control group received only routine pregnancy training and care. The summary of training session is presented in Table I. In the eight sessions and at the end of the program, the questionnaires were again reviewed for depression, anxiety and stress in each group. control group were at waiting list and also after the post-test, an educational pamphlet containing a summary of the contents of the counseling sessions was provided to them.

MEASURING TOOLS

Depression, anxiety and stress DASS-21 scale was used. This scale contains 21 items related to three subscales of depression DASS-21, anxiety DASS-21 and stress DASS-21. That is the summarized version of fundamental DASS-21 questionnaire that includes 7 items per subscales. Items were expressed on a 4-point Likert spectrum ranging from 0 to 3 meaning 0 = no and 3 = most of the time, and the sum of the scores obtained from each scale would be multiplied by 2. The range for each scale is from 0 to 42. Higher scores reflect higher levels of depression, anxiety and stress. The Cronbach's Alphas for depression, anxiety and stress were 0.82, 0.90 and 0.93, respectively [23].

Fig. 1. Consort flow diagram of participants.**Tab. 1.** Summary of mindfulness-based stress reduction (MBSR) intervention session.

Session	Schedule per session
Pre-session	Early acquaintance with the participants, establishing a proper relationship aiming at filling in the questionnaires correctly, building confidence and performing the pre-test
First session	Introducing the therapist and the participants to each other as well as explaining the rationale for the treatment, the way it works, the psychology of stress, its response to raisins, body scan exercises
Second session	Discussion on homework and body scan and meditation practice, and distributing second session booklets and meditation audio file
Third session	Discussion on sitting meditation with a focus on breathing and practicing Hatayoga and limiting its application due to pregnancy
Fourth session	Discussing walking meditation and discussing the experiences of the participants during the exercises and present yoga
Fifth session	Talking about homework and focusing on mind-boggling thoughts, discussing participants' experiences during rehearsals and recording unpleasant events
Sixth session	Talking about homework and meditation and body checking and discussing participants' experiences during workouts and recording enjoyable events and presenting homework on meditation and scanning body and mind in everyday life
Seventh session	Talking about homework and meditation sitting and discussing participants' experiences during the practice and presenting homework and distributing the seventh session booklet and meditation audio file
Eighth session	reviewing all sessions and summarizing them with participants and providing guidelines for continuing mindfulness exercises after the end of the course and post-test

In a study by Henry and Crawford (2005) and present study, these coefficients were reported as -0.851, -0.712 and 0.875, respectively. The cutoff scores from which the samples were included were considered 15 for stress, 8 for anxiety and 10 for depression.

UNPLANNED PREGNANCY

We consider pregnancy based on positive pregnancy test that was taken at health center. We examined the unwanted pregnancy based on a number of questions:

1. did you plan to have a baby before the pregnancy?;
2. did you feel happy when you found out you were pregnant?;
3. did you seek approaches for your abortion?;

4. did you and your spouse plan to get pregnant?;
5. when you became pregnant, did you plan to be pregnant or did you wanted to become pregnant in the future?

DEMOGRAPHIC INFORMATION BACKGROUND PROPERTIES

Demographic information of fertility characteristics was initially evaluated including age, age of marriage, age of first menstruation, age of first pregnancy, number of children, type of previous pregnancy, the type of unwanted pregnancy, the type and cause of current unwanted pregnancy and consistency with

Tab. II. Participants' characteristics.

Characteristics	Intervention group		Control group		P-value
	N	%	N	%	
Type of unwanted pregnancy					
Mistimed	23	76.7	21	70	0.559
Unwanted	7	23.3	9	30	
History of unplanned pregnancy					
Positive	3	10	3	10	0.99
Negative	27	90	27	90	
Cause of UP					
Low age difference between children	9	30	8	26.7	0.742
Financial problems	6	20	4	13.3	
Marital problems	3	10	1	3.3	
Lack of preparation	10	33.3	7	23.3	
High age and sufficiency of number of children	7	23.3	5	16.7	
Inconsistency with pregnancy					
Mother	13	43.3	14	46.7	0.99
Father	1	33	0	0	
Both	16	53.3	16	53.3	
Prenatal prevention method					
Normal	23	76.7	19	63.3	0.575
Lack of prevention	3	10	6	20	
Tablet	2	6.7	2	6.7	
IUD	1	3.3	1	3.3	
Ampoules	1	3.3	0	0	
Condom	0	0	6.7	2	
Education					
Under the diploma	3	10	3	10	0.99
Diploma	15	50	15	50	
Associate's degree	4	13.3	4	13.3	
Bachelor	8	26.7	8	26.7	
Employment state					
Housewife	28	93.3	28	93.3	0.99
Employed	2	6.7	2	6.7	
History of depression					
Positive	4	13	3	10	0.99
Negative	26	86.7	27	90	
Income level					
Less than 90\$	3	10	3	10	0.99
90\$ to 170/94\$	13	43.3	13	43.3	
170/95\$ to 256/41\$	10	33.3	10	33.3	
256/42\$ to 341/88\$	4	13.3	4	13.3	
More than 341/88\$ millions	1	3.3	1	3.3	
Type of previous delivery					
Natural childbirth	13	43.3	13	43.3	0.99
Cesarean	7	23.3	7	23.3	
No delivery	10	33.3	10	33.3	

a = Chi-square or fishers exact test.

partner, education, employment status and family income level.

DATA ANALYSIS

SPSS version 22 was used to analyze the data. Chi-square, T-test and Mann-Whitney U were used to compare baseline values of demographic and dependent variables between the two groups. Mann-Whitney U and Wilcoxon Test were used to compare stress, anxiety

and depression variables between the intervention and control group.

Results

SAMPLE SPECIFICATIONS

Tables II and III show that there were no significant differences between intervention and control groups

Tab. III. Participants' characteristics.

Characteristics	Intervention group	Control group	Test statistic	P-value
	Mean \pm SD	Mean \pm SD		
Age	28.93 \pm 5.62	29.30 \pm 6.32	-0.237 ^b	0.813
Age of first menstruation	13.36 \pm 1.58	13.13 \pm 1.008	0.680 ^b	0.5
Age of pregnancy	24 \pm 5.98	24.66 \pm 6.78	-0.404 ^b	0.688
Marriage age	21.66 \pm 3.38	21.1 \pm 4.42	-0.586	0.588
Age of first pregnancy	23.4 \pm 4.11	22.73 \pm 4.72	-0.401	0.688
Number of children	1.03 \pm 0.88	1.03 \pm 0.88	0.001	0.99
Number of parturition	1.03 \pm 0.88	1.03 \pm 0.88	0.001	0.99

^b: independent sample T test; c: Mann-Whitney U.**Tab. IV.** Comparison of stress, anxiety and depression between control groups (n = 30) and intervention group (n = 30).

Variable	Pre-test			Post-test		
	Intervention	Control	*P-value	Intervention	Control	*P-value
	Mean \pm SD	Mean \pm SD		Mean \pm SD	Mean \pm SD	
Stress	23.86 \pm 0.859	25.40 \pm 8.07	0.523	8.86 \pm 5.45	23.86 \pm 8.74	P < 0.0001
Anxiety	13.20 \pm 7.05	12.20 \pm 6.06	0.558	3.33 \pm 2.98	13.6 \pm 6.54	P < 0.0001
Depression	19.80 \pm 16.13	18.8 \pm 7.95	0.406	4.6 \pm 5.09	17.86 \pm 9.9	P < 0.0001

*Mann-Whitney U.

Tab. V. Comparison of stress, anxiety and depression before and after intervention by breakdown into intervention and control groups in women referred to health center.

Variable	Intervention		*P-value	Control		*P-value
	Pre-test	Post-test		Pre-test	Post-test	
Stress	23.86	8.86	P < 0.0001	25.40	23.86	0.436
Anxiety	13.20	3.33	P < 0.0001	12.20	13.60	0.212
Depression	19.80	4.60	P < 0.0001	18.8	17.86	0.434

*Wilcoxon.

with unplanned pregnancy in terms of demographic variables such as age, age of first menstruation, age of first pregnancy.

There was no significant difference between the two groups in terms of anxiety, depression and stress before intervention ($P > 0.05$). There were statistically significant differences between two groups after intervention based on Table IV ($P = 0$). The mean score of depression in the intervention group decreased significantly ($P = 0$). There was also slight decrease in the mean depression score in the control group. However, this decrease was not significant ($P = 0.343$). The mean score for stress in the intervention group decreased significantly after intervention ($P = 0$). In the control group, the mean score for stress decreased while this decrease was not significant ($P = 0.346$). The mean score for anxiety in the intervention group decreased significantly after intervention ($P = 0$) while the score in control group increased slightly ($P = 0.212$) (Tab. V).

Discussion

The purpose of this study was to evaluate the effectiveness of mindfulness based-stress reduction program on reducing the psychological symptoms of unplanned pregnancy. Results indicated a significant decrease in stress, anxiety and depression in the intervention group, which are in line with the results of other studies such as Guth et al. (2017) who examined the effects

of mindfulness on 54 pregnant women with psychotic symptoms and found a significant reduction in anxiety and depression symptoms. Mindfulness is an ideal and low-risk intervention that is associated with reducing stress, anxiety as well as improving mood and quality of life [24]. Also Setterborg et al. (2017) examined the effects of mindfulness based-stress reduction counseling on childbirth and parenting on pregnant women and found reduction in the symptoms of depression, anxiety and stress [25]. Jing et al. (2016) showed that mindfulness-based intervention significantly increases mindfulness, self-efficacy, coping strategy and significant reduction in emotional adjustment problems, passive and active coping strategy in pregnant women which is probably due to high degree of awareness at modern age without judgment in pivot mindfulness interventions and it seems to help cure emotional problems [26]. No significant difference was observed between control and intervention groups in the study of Krusche dphil et al. (2018) which is inconsistent with the findings of the present study. This is probably due to virtual teaching style of the consultation and the lack of regular attendance at the meetings such that in virtual education, due to absence advisor to address problems and questions of clients and the lack of social support from other participants, the level of contact with researcher and the low motivations in participants the level of learning is low [27]. In the study of Goodman et al. (2014), coping with anxiety through living mindfully which is kind of mindfulness-based cognitive therapy significantly reduces the level

of anxiety after intervention. Probably, it is because this program teaches common ways of responding to anxiety symptoms that include mindfulness techniques, cognitive approaches, training of anxiety and depression and cognitive distortions of anxiety and depression along with homework to encourage using mindfulness in daily life through regular practice [28]. The findings in study of Guardino et al. (2013) indicated the effectiveness of mindfulness to reduce stress and anxiety in pregnancy in the intervention group which was consistent with the present study. But the decrease in anxiety in the control group was not consistent with present study [22]; which is probably due to using book to increase information about pregnancy that works in stress management and some of them were attending a yoga class. The results of Nyklicek et al. (2018) and Hicks et al. (2018) showed that mindfulness skills during pregnancy are effective predictors of depressive symptoms during pregnancy and birth weight and are known as predictors of depressive symptoms in parents such that people with lower mindfulness showed higher levels of depression before delivery [29, 30]. Data analyzed in this study supported the possibility of offering a stress-reduction mindfulness program for women with unplanned pregnancy and can help reduce stress, anxiety, and depression in them. However, more similar studies are needed.

Conclusions

According to the results of the present study, early intervention in women with unplanned pregnancy can reduce stress, anxiety and depression and increase mothers' awareness, as pregnant mothers are vulnerable stratum of society and unwanted pregnancies increase mental health problems and awareness-making in the health system can be of particular importance.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

FKH and KA designed the work and drafted the manuscript. NKH and PD had prepared counselling package. PS and KA had full access to all of the data and took responsibility for the integrity of the data. YJ was responsible for accuracy of the data analysis. All authors read and approved the final manuscript.

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RESEARCH ARTICLE

Effect of lung function disorders and physical activity on smoking and non-smoking students

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Keywords

Physical activity • Lung function • Smokers • Non-smokers • Spirometry

Summary

Background. The number of young smokers is increasing, and hence their risk of respiratory problems. This risk is exacerbated by their low level of physical activity, which also reduces lung function. This study aimed to determine differences in lung function and levels of physical activity between smokers and non-smokers.

Method. This research was conducted from October 2019 to January 2020. The research design was cross-sectional, and a purposive sampling method was used. Pulmonary function was measured by means of spirometry, while physical activity was measured through a modified International Physical Activity Questionnaire (IPAQ).

Results. We enrolled 124 university students: 62 smokers and 62 non-smokers. A significant difference in lung function values (< 70 vs ≥ 70) was observed between smokers and non-smokers ($p = 0.00$). No difference ($p = 0.907$) in the level of physical activity was seen between smokers and non-smokers, with most subjects in both groups displaying moderate levels.

Conclusions. Students who smoked had more respiratory problems than those who did not. Although the level of physical activity did not correlate with respiratory problems, these problems were more common in the vigorous category.

Introduction

Lung dysfunction is one of the top five causes of death due to non-communicable diseases in Indonesia [1]. Lung function disorders are closely related to smoking. Indonesia has the third largest cigarette consumption in the world [2], and smoking is common among people of all ages, especially the young ones. Most teenagers have already consumed cigarettes, and many are habitual smokers [3]. Students who smoke admit that they are aware of the harmful effects of smoking on health, but they still ignore these effects, claiming to be “less certain” of the dangers of smoking.

Cigarettes contains nicotine, tar and carbon monoxide [4]. Nicotine and carbon monoxide in the bloodstream thicken the blood and narrow the arteries. Moreover, the tar contained in cigarettes can coat the lung tissues and reduce the elasticity of the air sacs, making breathing difficult [5]. Lung volume is measured to evaluate the normality of respiratory function [3]. A tool that is commonly used for this purpose is spirometer, which measures the forced expiratory volume in the first second (FEV1) and the forced vital capacity (FVC) [6]. Many students say that they do not have enough time to do physical activities, as they think that the time devoted to such activities would reduce the time available for learning. What they do not realize, however, is that physical exercise can have beneficial effects on their cognitive ability (attention, memory, concentration) and maintain mental health [7, 8]. In 2013, 26.1% of Indonesians were classified as having an insufficient level of physical activity.

By 2018, this percentage had risen to an estimated 33.5%. Similarly, in East Java, the prevalence of people who did not do physical activity was around 28.5%. Various studies have reported that people of all ages in almost all countries are too sedentary [9]. According to Basic Health Research, the prevalence data show that many people do not engage in physical activity, despite its importance for health. Physical activities have beneficial effects on the respiratory system [10], improving lung function [11] and increasing the vital capacity. Indeed, an individual who takes regular physical exercise can train the respiratory muscles, with the result that a greater volume of oxygen can enter the pulmonary capillaries, and lungs capacity increases [12-14]. Moreover, intense physical activity can reduce systemic and bronchial inflammation, improving both lung function and quality of life [15].

Previous studies have found that smokers are physically less active than non-smokers [16, 17]. The present study investigated the effect of impaired lung function and physical activities in smoking and non-smoking students. The questionnaire used to measure physical activities was adapted from the International Physical Activity Questionnaire (IPAQ) [18, 19]. In order to measure lung function, a handheld spirometer was used. A handheld device was chosen because it was light and easy to carry, and because the results would be immediately available. Previous research conducted in Jordan by Banur et al. [20] and Nawafleh et al. [21] found that smokers and non-smokers differed in terms of their lung function (FEV1/FVC).

Method

RESEARCH DESIGN

The research design was cross-sectional. Data were collected through questionnaires administered from November 2019 to January 2020 in Surabaya. The ethics committee of the University of Surabaya approved the study protocols (No. 120/KE/XII/2019).

RESEARCH VARIABLE

In this study, the independent variables were smokers and non-smokers, while the dependent variables were lung function and physical activities. Impaired lung function was defined as an FEV1/FVC value less than 0.7 [22]. Lung function was tested by means of the Contec SP10 Spirometer.

Physical activity is any activity or movement carried out by the body as a result of energy expenditure by the skeletal muscles [23]. The questionnaire referred to physical activity carried out during the course of a week. Respondents were divided into categories according to their physical activity: Mild Physical Activity (< 600 METs), Moderate Physical Activity (600-1,500 METs), and Vigorous Physical Activity (> 1,500 METs) [24]. In this study, the intensity of physical activity was measured in METs (metabolic equivalents of task). Physical activities were calculated by means of the METs level (physical activity intensity) multiplied by the length of time (minutes) spent on the activity in a week [18, 19].

POPULATION AND SAMPLE RESEARCH

The study population consisted of male students attending a private university in Rungkut sub-district, Surabaya. The inclusion criteria were: age > 18 years and absence of respiratory or cardiovascular diseases which might affect the measurement of lung function and physical activities. A purposive sampling method was used.

DATA COLLECTION

Subjects who stated that they were willing to participate in the study and filled in the informed consent form were immediately asked to complete a physical activity

questionnaire consisting of the modified IPAQ questions; their lung function was then measured by means of spirometry.

DATA ANALYSIS

Differences in lung function and physical activity between smokers and non-smokers were determined by means of the chi-square test. Subjects were described in terms of age and body mass index (BMI).

Results

Subjects were grouped according to sex, age and treatment history. Table I shows the number of respondents (124), subdivided into non-smokers (62) and smokers (62).

In the group of smokers, the degree of smoking was assessed by means of the Brinkman index, which is calculated by multiplying the number of cigarettes smoked per day by the duration of smoking in years [26]. The index has 3 categories: light smokers (0-199), moderate smokers (200-600), and heavy smokers (> 600) [26]. All our smokers fell into the light category and smoked filter cigarettes of various brands (62 of 62).

The results of lung function testing are shown in Table II. Most of the subjects (42 of 62 smokers and 60 of 62 non-smokers) did not experience respiratory problems, though the results of the chi-square test revealed a significant difference ($p = 0.00$) between the two groups.

The profile of the physical activities carried out by the subjects is shown in Table III. Physical activity was divided into 3 categories: mild (< 600 MET-minutes/week), moderate (600-1500 MET-minutes/week) and vigorous (> 1,500 MET-minutes/week). Most of the subjects (26 smokers and 27 non-smokers) reported moderate levels of physical activity. The chi-square test results showed no difference ($p = 0.907$) in the level of physical activity between smokers and non-smokers (Tab. IV).

Tab. V shows that almost one third of the smokers (20/62) had respiratory problems, and that more than half of these (11/20) engaged in moderate physical activity. Only 2 of the non-smokers had respiratory problems, both of whom were in the light activity category).

Tab. I. Frequency distribution of characteristics.

Respondents' characteristics		Smokers (n: 62)		Non-smokers (n: 62)	
		Number	Percentage (%)	Number	Percentage (%)
Age (years)	18-19	8	12.90	12	19.35
	20-21	17	27.42	21	33.87
	22-23	22	35.48	25	40.33
	24-25	15	24.20	4	6.45
BMI (kg/m ²) [25]	Underweight (< 18.5)	10	16.31	9	14.52
	Normal (18.5 ≤ 25)	47	75.81	45	72.58
	Overweight (25 ≤ 27)	3	4.84	2	3.23
	Overweight (≥ 27)	2	3.23	6	9.68

BMI: Body Mass Index.

Tab. II. Lung function values in smokers and non-smokers.

Lung function value		Smoker group (n: 62)		Non-smoking group (n: 62)		P value
		Frequency	Percentage (%)	Frequency	Percentage (%)	
FEV1/FVC value (%)	< 70 (with respiratory problems)	20	32.26	2	3.23	0.00
	≥ 70 (without respiratory problems)	42	67.74	60	96.77	

Tab. III. Profile of type of physical activity.

N.	Type of physical activity	Duration (minutes)	Smokers (n: 62)		Non-smokers (n: 62)	
			Number	Percentage (%)	Number	Percentage (%)
1	Walking 100 m	5	3	4.84	1	1.61
		10	5	8.06	3	4.84
		15	7	11.30	26	41.94
		20	3	4.84	2	3.23
		30	26	41.94	11	17.74
		40	1	1.61	0	0
		60	17	27.42	16	25.81
2	Walking > 100 m	Not done	0	0	3	4.84
		10	1	1.61	5	8.06
		15	6	9.68	11	17.74
		30	18	29.03	13	20.97
		40	1	1.61	0	0
		45	2	3.23	1	1.61
		60	23	37.10	23	31.10
3	Driving vehicles (cars, motorbikes)	120	2	3.23	0	0
		Not done	9	14.52	9	14.52
		10	1	1.61	0	0
		15	5	8.06	2	3.23
		20	1	1.61	5	8.06
		30	6	9.68	6	9.68
		35	3	4.84	0	0
4	Cycling	60	21	33.87	19	30.64
		120	10	16.13	13	20.97
		180	3	4.84	7	11.29
		240	6	9.68	4	6.45
		Not done	6	9.68	3	4.84
		10	2	3.23	1	1.61
		30	2	3.23	3	4.84
5	Cooking	60	4	6.45	1	1.61
		120	1	1.61	2	3.23
		180	2	3.23	1	1.61
		Not done	51	82.26	54	87.10
		10	4	6.45	10	16.13
6	Washing	15	3	4.84	7	11.29
		30	7	11.29	6	9.68
		60	3	4.84	4	6.45
		Not done	45	72.58	35	56.45
		5	1	1.61	3	4.84
		10	2	3.23	6	9.68
		15	6	9.68	3	4.84
		30	10	16.13	13	20.98
		60	10	16.13	8	12.90
		120	2	3.23	3	4.84
		Not done	31	50.00	26	41.93

Continues

Follows

Tab. III. Profile of type of physical activity.

N.	Type of physical activity	Duration (minutes)	Smokers (n: 62)		Non-smokers (n: 62)	
			Number	Percentage (%)	Number	Percentage (%)
7	Sweeping, cleaning room /house	5	6	9.68	6	9.68
		10	11	17.74	11	17.74
		15	4	6.45	6	9.68
		30	5	8.06	21	33.87
		60	10	16.13	4	6.45
		120	1	1.61	3	4.84
		Not done	25	40.32	11	17.74
8	Carrying water	1	0	0	11	17.74
		2	24	38.71	14	22.58
		4	0	0	11	17.74
		10	8	12.90	8	12.90
		Not done	30	48.39	18	29.03
9	Playing football	10	1	1.61	0	0
		30	1	1.61	4	6.45
		45	1	1.61	0	0
		60	17	27.42	5	8.06
		120	10	16.13	8	12.90
		Not done	32	51.61	45	72.58
10	Playing volleyball	60	2	3.23	4	6.45
		120	2	3.23	1	1.61
		Not done	58	93.53	57	91.94
11	Playing badminton	60	9	14.52	5	8.06
		120	1	1.61	5	8.06
		180	2	3.23	2	3.23
		Not done	50	80.64	50	80.64
12	Swimming	30	2	3.23	4	6.45
		60	1	1.61	0	0
		120	5	8.06	5	8.06
		Not done	54	87.10	53	85.48
13	Cleaning the garden, burning trash	10	1	1.61	5	8.06
		20	2	3.23	0	0
		30	2	3.23	2	3.23
		60	1	1.61	2	3.23
		120	2	3.23	1	1.61
		Not done	54	87.10	52	83.87
14	Playing musical instrument	15	1	1.61	1	1.61
		30	7	11.29	2	3.23
		60	4	6.45	3	4.84
		120	1	1.61	1	1.61
		180	1	1.61%	0	0
		Not done	48	77.42	53	85.48
15	Gymnastics/aerobics	10	0	0	1	1.61
		25	0	0	1	1.61
		30	0	0	5	8.06
		60	0	0	1	1.61
		90	0	0	1	1.61
		120	0	0	2	3.23
		150	0	0	1	1.61
		Not done	62	100	50	80.165

Discussion

Most subjects, whether smokers or non-smokers, did not experience respiratory problems (Tab. II). This was probably due to their young age, in that their exposure to

cigarette smoke had not yet impaired their lung function. Nevertheless, a significant difference ($p = 0.00$) was seen between the two groups in terms of lung function values. The results of the present study are similar to those of the research conducted in Jordan by Banur et al. [20] and

Tab. IV. Physical activity of smokers and non-smokers.

Physical activity classification		Smokers (n:62)		Non-smokers (n:62)		P value
		Number	Percentage (%)	Number	Percentage (%)	
Category	Light	14	22.58	12	19.35	0.907
	Moderate	26	41.94	27	43.55	
	Vigorous	22	35.48	23	37.10	
Total		62	100	62	100	

Tab. V. Cross-tabulation of lung function values and physical activity levels in smokers and non-smokers.

Physical activity classification		Smokers (n: 62)		Non-smokers (n: 62)		Total
		With respiratory problems	Without respiratory problems	With respiratory problems	Without respiratory problems	
Category	Light	9	5	10	2	26
	Moderate	15	11	27	0	53
	Vigorous	18	4	23	0	45
Total		42	20	60	2	124

Nawafleh et al. [21], who also observed differences in lung function (FEV1/FVC) between smokers and non-smokers. Cigarettes contain harmful chemicals, such as carbon monoxide, which can enter the bloodstream and bind hemoglobin. Hemoglobin should bind to oxygen. However, when the carbon monoxide content exceeds that of oxygen, it binds the hemoglobin. This can disrupt the pulmonary blood vessels, which become narrower and less elastic, causing the lungs to expand [27]. In this study, lung function was measured by means of hand-held spirometers, which are small, portable and inexpensive. Moreover, spirometry results can be screened simply and accurately [22].

Several factors can affect lung function:

- *age*: lung function tends to decline with aging [28]. Lung function continues to increase up to the age of 25 years, and then remains stable for approximately 5-10 years. Subsequently, lung function begins to decrease after the age of about 40 years [29, 30]. Indeed, with aging, the muscles of the diaphragm decrease, and the lung tissue that helps keep the ducts open can lose elasticity, reducing the caliber of the airways [31];
- *gender*: pulmonary development continues throughout childhood and adolescence [32]. Women's lungs are smaller than men's, and have fewer bronchioles [33]. For this reason, and because most smokers are male [34], we enrolled only male subjects in the present study;
- *smoking*: cigarette smoke contains around 4,000 chemical compounds, more than 100 of which are carcinogenic and mutagenic and harmful to health [35]. The damage caused depends on the length of exposure; the longer the exposure, the greater the effect will be [36]. Thus, over time, the lung function of a smoker will deteriorate in comparison with that of a non-smoker [37]. According to some studies, many people think

that light smoking has no harmful effects. In one such study, however, it was found that former smokers and those who smoked less than 5 cigarettes per day had already done moderate damage to their lungs, and that, in two-thirds of cases, chronic obstructive pulmonary disease (COPD) could well ensue [38]. Light smoking can impair lung function within 1 year, while heavy smokers can suffer the same effect within 9 months. The respondents involved in this study smoked filter cigarettes of different brands and with different levels of nicotine and tar. However, the cigarette brand did not affect the results of the study. Indonesian Government Regulation number 81 of 1999, regarding smoking and health, states that cigarettes are allowed to contain no more than 1.5 mg of nicotine and 20 mg of tar. The filters used in cigarettes can significantly reduce the tar and nicotine content of the smoke. According to previous research, the nicotine content in unfiltered cigarette smoke is greater than that of filtered cigarette smoke [38, 39];

- *physical activity*: regular physical activity increases respiratory efficiency, improving the functioning both of the lungs and of the other organs of the body. Swimming and gymnastics are particularly beneficial, the latter being an aerobic exercise that can easily be performed [40, 41].

This study involved respondents aged 18-25 years, which means that their lung function was still maturing [30]. If smoking begins at that age or less, it can have serious consequences and may be a risk factor for COPD [42]. In the present study, all subjects were less than 60 years old, and none were classified as geriatric (Tab. I). Thus, the age factor did not affect our results. BMI can also affect the functioning of the lung, and respiratory dysfunction due to obesity can affect FVC and FEV1 [43]. However, as most of our respondents had normal BMI values (Tab. I), the BMI factor did not affect this study.

The study involved 124 subjects, who were equally divided into 2 groups: smokers and non-smokers. We chose to enroll male students, since previous research has indicated that men are physically more active than women [44]. As shown in Tables IV and V, 26 smokers (41.94%) engaged in moderate physical activity; 22 (35.48%) in vigorous activity, and 14 (22.58%) in light activity. Similarly, 27 non-smokers (43.55%) engaged in moderate physical activity, 23 (37.10%) in vigorous activity, and 10 (19.35%) in light activity. Research conducted by Kwan et al. [45] has shown that physical activity tends to decline among young adults, particularly university students.

Physical activity has various beneficial effects on health, such as maintaining/losing body weight, strengthening bones and muscles, and reducing depression and stress. It can also prevent several diseases, including heart disease and stroke, and reduce the risk of high blood pressure, diabetes and several cancers, such as breast and colon cancers [46, 47].

The five physical activities most frequently carried out by the participants in our study were: walking more than 100 m; driving vehicles (cars, motorbikes); washing; sweeping and cleaning rooms/houses; carrying water. This study involved respondents aged 18-25 years. They can at least perform physical activities for 150 minutes at moderate intensity throughout the week, or perform physical activities for 75 minutes with heavy intensity throughout the week, or a combination of moderate activity and strenuous activity (Not clear. Perhaps you mean: The WHO recommends that such subjects carry out moderate-intensity physical activity for at least 150 minutes per week, or strenuous activity for 75 minutes, or a combination of moderate and strenuous activity) [23]. In the present study, the physical activity carried out by both smokers and non-smokers was of moderate intensity. Several factors can act upon a person's physical activity [48], including:

- *intrinsic factors*: these refer to the person's internal motivation, and are often connected with the good or bad feelings elicited by physical activity;
- *environmental factors*: the individual's surroundings, including the weather, can encourage or discourage physical activity;
- *physical considerations*: those who take regular physical exercise tend both to look and to feel good; they will therefore be motivated to continue their physical activity. Conversely, tiredness and lack of fitness will discourage physical activity;
- *routine factors*: the routine necessities of everyday life will obviously impact on the time and energy that an individual is able or willing to devote to physical activities.

Physical activity can be measured by means of accelerometers and pedometers and through self-report questionnaires (IPAQ-S, RPAQ, PAR). In this study, we used only self-report questionnaires, which have the advantage of being economical and easy to administer; admittedly, however, the data obtained will depend on what respondents remember [49].

The present study has some limitations. Firstly, the sample was relatively small. Secondly, smoking habits and the intensity and duration of the various physical activities were referred subjectively. However, the answers to types of physical activity such as carrying water were clear, i.e. lifting large 19 L water containers or medium-sized 10 L containers. Finally, in establishing the exclusion criteria, information on medical history was provided only by the respondents themselves and a complete medical examination was not carried out.

Conclusions

Most subjects (60/62 non-smokers and 42/62 smokers) had no respiratory problems, though the chi-square test results showed a significant difference ($p = 0.00$) between the two groups in terms of lung function values (< 70 vs ≥ 70). Most subjects (26/62 smokers and 27/62 non-smokers) had moderate levels of physical activity. The chi-square test results showed no difference ($p = 0.907$) between smokers and non-smokers in terms of their level of physical activity.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors discussed the results and contributed to the final manuscript.

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RESEARCH ARTICLE

"It's beyond the pale to smoke hookah": perceptions of Iranian adolescents on social unacceptability of hookah smoking

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Keywords

Hookah smoking • Adolescents • High school students • Social unacceptability • Qualitative

Summary

Introduction. Globally, the popularity of hookah smoking, as a social and entertaining behavior, is increasing among adolescents and youths. The present study aimed to explore the perceptions of high school students on Social Unacceptability (Arabic/Persian term = *Qabahat*) of Hookah Smoking (SUoHS) in an Iranian context.

Methods. In this qualitative study, 31 student adolescents in Tabriz, Iran, were invited to participate in semi-structured individual interviews and focus group discussions (FGDs). Data were analyzed using interpretative thematic analysis.

Results. The unacceptability of hookah smoking was viewed at the "disreputability of hookah smoking and hookah smokers".

The students also explained SUoHS in the "incivility of hookah smoking and smokers in the society", "disrespectfulness of hookah smokers and their families", and "the consequences of hookah smoking".

Conclusions. The SUoHS is rooted in the social values and norms within communities. To decrease hookah smoking levels among adolescents, school health nursing interventions should be tailored to bridge the gap between their recognition of SUoHS and subsequent behavior change through creating group dynamics highlighting the domains of social unacceptability of the behavior.

Introduction

Tobacco smoking is a preventable risk factor for disease morbidity and mortality [1, 2]. Among the modes of using tobacco, hookah smoking (HS) is a remerging phenomenon that may increase the risk of oral, esophageal, and pulmonary cancer, as well as reduced pulmonary system function [3]. The word "hookah" is generally used for a particular method of tobacco smoking, in which smoke passes through water before inhalation [4]. Globally, the popularity of HS, as social and entertaining behavior, is increasing [5-8] among adolescents and youths [9, 10], particularly in the Middle East and North African (MENA) countries [11], like Iran [12]. The increased tendency towards HS among adolescents may be associated with their misunderstanding of the harmlessness of the behavior, compared to other forms of tobacco smoking. Considering such increasing popularity, HS is the new mode of tobacco smoking with a lower level of 'qabahat' (social unacceptability), compared to other modes of tobacco use, in the 21st century [13, 14].

LITERATURE REVIEW

'Qabahat' (qa(e)bāhat) is an originally Arabic term rooted in the term 'qobh', which means socially undesirable and unaccepted, aberrant, and deviant [15]. In the Persian language, 'qabahat' also means not in accordance with

accepted rules, social norms, or standards [15]. Findings of a study among students in Najaf-Abad County, Iran, have shown that the perception of low Social Unacceptability of Hookah Smoking (SUoHS), compared to other modes of tobacco use, caused the adolescents to easily tend to the behavior [16]. In another study in the U.S., one of the most frequent reasons for the university students' tendency towards HS was their perceptions on the high levels of social acceptance and popularity for HS [17]. It is usually postulated that HS at home reduces its social unacceptability for children and adolescents and such reduced unacceptability may facilitate the initiation and continuation of the behavior. Jahanpour et al., in a qualitative study, reported that the high popularity and the common use of hookah may have decreased the SUoHS among adolescents and have rendered it a normal and acceptable practice [13]. Sabahy et al. also noted low the SUoHS as a facilitating factor for the inclination of youth toward HS [18].

Despite the above-mentioned speculations in the literature regarding the importance of SUoHS, to our knowledge, no study has yet clearly attempted to define this phenomenon and to make sense of it in terms of the meanings people bring to the concept. Due to the increasing rate of HS among Iranian adolescents and the association of social desirability with their tendency towards HS, we aimed to explore the concept of SUoHS from the perspective of Iranian high school students. We are interested in finding

out how high school students perceive SUoHS. This will inform future researchers on how to consider SUoHS while investigating the cognitive determinants of HS among adolescents. Finding a better understanding of the phenomenon and its possible domains may also provide future researchers with a comprehensive conceptual framework while designing HS cessation programs among adolescents and young populations.

RESEARCH QUESTION

The following research question guided our study: “How do Iranian high school students explain the social unacceptability of hookah smoking?”

Methods

PARTICIPANTS AND DESIGN

This was a qualitative study with a thematic analysis approach conducted to explore the social unacceptability of HS among high school students. The study setting was the high schools in Tabriz, East-Azerbaijan province, Iran. The participants were 31 students (16 boys and 15 girls) at the range of 15 to 17 years of age in Tabriz high schools. The participants were not asked about their history of hookah smoking. To obtain views across a range of social circumstances, the students were selected from different socioeconomic backgrounds, based on their records at the schools. Inclusion criteria for the study were living in Tabriz, studying at grades two and three of the high school (11th and 12th grades), and the willingness of both the students and their parents to participate in the study. Ethical approval to conduct the study was obtained from the Ethics Committee at Tabriz University of Medical Sciences.

Among five education districts of Tabriz, a district was selected as the setting of work, and the participants were selected from the high schools situated in the district of interest. The first researcher visited the schools and clarified the objectives of the study to the administrators of schools. Then, the students were randomly invited to participate in the study, and if agreed were suggested to have an appointment with the first researcher in a private room at their school. Before setting the appointment, one parent of the students was contacted on the phone and informed of the objectives of the study. In the case of their oral agreement with the participation of their child in the study, the appointment with the student was set. After primary coordination, interviews were conducted in the time and place preferred by the participants. So, the students who were willing to participate in the interviews were included after obtaining informed consent. Before the interviews, the research objectives were first explained to the participants and, written informed consent was obtained from both the students and one of their parents. The interviews were voice recorded with their permission.

DATA COLLECTION

We developed an interview schedule contained open-ended questions to explore the students' perceptions

Tab. 1. The main question and its probing questions that were asked from the participants.

- How do you see the social acceptance and popularity of hookah smoking? Please describe it.
- How do you describe a boy or a girl who is smoking hookah?
- How do you see the family of a person who use hookah?
- What bears in your mind, when you see that your friend is smoking hookah?
- What are the characteristics of a hookah user in your society? Based on your viewpoint, why does he/she smoke hookah? What the reasons may be?
- How would you describe a ring of friends in a coffee shop who are smoking hookah?
- Based on your opinion, how do you explain hookah smoking among women?
- In your idea, what are the outcomes/consequences of hookah smoking? Who gets these consequences? Are they favorable or adverse?
- What would happen if hookah smoking does not exist? How would life change?

of the SUoHS. Firstly, three Focus Group Discussions (FGDs) with 13 participants (4-5 students in each FGD) were conducted to find a general understanding of the students' views of the phenomenon. Then, eighteen students were individually interviewed to dig deeper down into their perceptions of the SUoHS. The main question initially asked from the participants was ‘how would you explain hookah smoking?’, and then some probing questions (Tab. 1) were asked according to the interview schedule and the participants' answers. In the two modes of data collection, the probing questions were different and varied from one interview to another. The selection of probing questions for an interview was based on the results discovered during the data analysis of the prior interview. The first researcher (KK), with considerable experience in conducting qualitative interviews with adolescents, conducted the FGD sessions, and facilitated the discussions by asking some probing questions and encouraging all participants to join in the discussions. Another researcher of the study (HN), who did not have any participation in the discussions, supervised the sessions, and wrote down the required notes and comments to promote the discussion process. On average, the FGDs and the individual interviews lasted 1.15 hours and 45 minutes, respectively. All interviews were audiotaped applying a digital voice recorder. With fifteen interviews, we achieved theoretical saturation of the data, and no new code, category, and a theme emerged in the last interview.

DATA ANALYSIS

We transcribed the interviews verbatim and reviewed the text for accuracy. We then carried out a thematic analysis using the qualitative data analysis software MAXQDA₁₀ (2011). Individual interviews and FGDs were initially integrated for data completeness and confirmation. We assumed that each interview method reveals different parts

of the SUoHS and thus provides us with complementary views on the phenomenon. We also assumed that such integration may help expand the breadth and the depth of our findings. So, we conducted the individual interviews and the FGDs to explore the personal experiences of the students on the SUoHS and to examine their beliefs and opinions on the phenomenon, respectively. Moreover, during FGDs, three students were unable and/or refused to participate in a focus group. So, as a pragmatic reason to combine the interviews, we invited them to take part in an individual interview.

As suggested by Braun and Clarke [19], the thematic analysis may be approached in two ways; an essentialist/realist way or a constructionist way. Firstly, a qualitative researcher reports the experiences, meanings, and realities of participants, and latterly, the researcher explores the ways that experiences may be affected by a range of discourses within a community. We presumed that the students' views of the SUoHS may be influenced by social determinants, like the history of contacts with the behavior, culture, and socioeconomic status of their families. We, therefore, applied a constructionist framework, with a focus on the latent/interpretative level of the underlying viewpoints, assumptions, and conceptualizations of the students. We read and re-read the transcripts, and drew the initial codes from the data. Then, in close discussion within the research team, we collated the codes into themes and developed a coding frame. All interviews were conducted and analyzed by the first author (KK), and she derived the themes from her preconceptions. When conducting and analyzing the interviews, she had the research question in mind. We, thus, took an epistemological strategy to uncover the adolescents' perceptions of the SUoHS, as a concept with a high degree of subjectivity. To account for inter-rater reliability, a second researcher (HN) randomly selected and coded one in six raw transcripts. We (all authors), thus, checked the agreement with the themes and ensured that both researchers deduced similar themes from the texts. We, eventually, made some minor changes to terminology, although no change was made to the emerging themes.

ETHICS APPROVAL

This research was approved by the Ethics Committee at Tabriz University of Medical Sciences (ethical approval code: IR.TBZMED.REC.1396.1067). The participants were told about the aim of the study and were assured of the confidentiality of data. All participants and one of their parents signed a consent form before data collection.

Results

The students were between 15-17 years of age and were studying either in the 10th or the 11th grades of high school. During thematic analysis, the predominant theme aroused was termed as "disreputability of hookah smoking and hookah smokers". The students explained the SUoHS as a maladaptive behavior. They also viewed

the unacceptability of behavior at the impudence, impertinence, and rudeness of the hookah smokers. The participants perceived HS as rude and disrespectful behavior. They considered the smokers as individuals that disrespect the people around them while smoking. The results were universal across the students, regardless of their age and gender.

Themes were grouped as follows: *incivility of hookah smoking and smokers*, *disrespectfulness of hookah smokers and their families*, and the *consequences of hookah smoking*.

INCIVILITY OF HOOKAH SMOKING AND SMOKERS

Based on the students' opinion, the SUoHS was seen in the rudeness and unsociability of the behavior and those who perform it. They believed that the people in the society have a highly negative opinion of hookah smokers. For this theme, three main categories were identified as follow:

- *Behaving against social values and norms*: as participants believed, hookah users behave against the social norms and values and disregard the culture of society. "*These people have come to value a thing [hookah smoking] that is, in fact, a disvalue. This behavior is against religious and social values*" (participant number 7; p. 7). They believed that hookah smokers were a plague and a burden on society. "*I say they're a burden on society because these are the people who do not serve it. They just cause trouble*" (p. 6). "*I say, you're a plague on society*" (p. 5).
- *Violating the others' rights*: the students believed that hookah smokers violate the rights of people in the community. The smokers bother people around them because of the bad smoke and the bad smell of hookah. "*Hookah use may disturb others as well. Maybe those around you cannot tolerate it*" (p. 6). They also reported that hookah smokers do not respect others and are troublemakers for their society. "*This behavior is not respectful; they do not respect others*" (p. 7). According to another participant, hookah users may, "*harass some people... may insult girls...*" (p. 29).
- *Being untrustworthy*: the participants believed that hookah users are untrustworthy and cannot be acknowledged or approved by others. "*Maybe these are people we cannot trust anymore*" (p. 6).

DISRESPECTFULNESS OF HOOKAH SMOKERS AND THEIR FAMILIES

The students considered the SUoHS in the lack of respect and courtesy towards the smokers and their families. This theme was grouped into three categories:

- *Negative attitude towards hookah smokers*: the students perceived HS as a rude behavior, because the smokers were seen as individuals with playfulness, weak willpower, irresponsibility, poor knowledge/experience, and promiscuity. They believed that smokers were bad role models within the community and maybe also attracted to addiction. According to them, hookah users pave the way for ruder behaviors by smoking hookah, as this behavior may mark

the beginning of using narcotics, and addiction. *"Hookah itself is very addictive and one becomes dependent on it by experimenting it even once with friends"* (p. 11). Participants believed that hookah users have lost their identity, do not pursue any clear goal in life, and waste their life. *"First, they have lost their identity. Second, they have lost themselves by doing this"* (p. 5). They also believed that hookah users have weak willpower and they lack the skill of saying no. *"Hookah users may have no willpower. That is, they lack the will not to pursue it [hookah smoking]"* (p. 29). *"These people are playful. They do not care about anything else"* (p. 13).

According to them, hookah users are ignorant and are, unmindfully, proud of their HS. *"One can say that these people are ignorant of what they are doing"* (p. 7). Participants also believed that hookah users are promiscuous, improvident, hooligans, rowdy, and dishonorable, and may do anything. *"Maybe one can refer to them as a hooligan person with improvident and undisciplined behavior"* (p. 28). *"I believe those who use hookah are promiscuous"* (p. 14). Participants considered hookah users as smoky, shameless, liars, criminals, and abusive individuals. In total, they perceived hookah users as a negative role model in society. They also believed that hookah users have a bad personality, and can mislead others. *"These people are considered as smokers in the society"* (p. 11). *"What you expect of a graceful and dignified person in terms of the language they use and the way they dress?"* (p. 6).

- *Deeply disrespectful attitude toward female hookah smokers:* many students believed that female hookah users have forgotten their true nature (as a beauty symbol), messed up their physical and spiritual beauty, and may even have illegitimate relations with others. *"I think she [a female hookah smoker] has forgotten her nature and the goal of her creation"* (p. 7). They presented a more negative attitude toward HS for females, compared to males. They considered these women shameless, unchaste, nasty, notorious, and rowdy. *"When we see some of them are smoking hookah, they seem to be nasty and notorious"* (p. 6). They also believed that these women are Khiabani girls [street girls: a local folk expression used to explain the women (particularly girls) who have run away from their family] who desert their families and home, turn to whorehouses, and go astray. *"These are often girls running from home and having problems with their parents. They've turned to streets and men"* (p. 22).
- *Derogatory attitude toward the family of hookah users:* the students would often report that in the families of hookah users there was not a good parent-child relationship. Due to their familial problems, the parents mistrust their children. *"[It is] a family who never trust their children"* (p. 25). *"their parents may have problems and do not have good relationships"* (p. 29). They also believed that such families do not raise their children well and cannot control them. *"They do not have the culture of parenting, have not raised their*

children well" (p. 14). Based on their ideas, these families were either too strict or too lenient. *"They may be families who have imposed too many limitations on their children from the beginning"* (p. 31). *"I think they are careless and do not care about their children at all"* (p. 25).

According to them, such families are unaware and ignorant families who consider HS as a healthy hobby and do not know its harms. *"They think it is a healthy hobby"* (p. 19). They also believed that HS is a normal behavior in the users' families. They viewed these families as promiscuous, shameless, degenerate, ignorant, uncultured, and lowborn families. *"They have not been born in a high-class family"* (p. 14). *"The family of hookah users is too uncultured family"* (p. 28).

CONSEQUENCES OF HOOKAH SMOKING

Based on the students' ideas, HS was considered to be a socially undesirable behavior because it damages the physical, mental and familial health of the smokers. They also believed that the behavior may damage their social health. The sub-categories are explored in more detail below:

- *Self-harm:* a majority of participants believed that HS was harmful and may cause cardiac and pulmonary diseases and cancer, and may damage one's physical beauty. *"Those who use hookah may be suffered from different diseases, like pulmonary diseases"* (p. 17). *"It makes you lose your physical beauty"* (p. 14). They commented that hookah users are dependent on the behavior, and explained the users as unhealthy individuals with poor mental health who may even attempt suicide. *"Hookah users are depressed guys who may attempt to kill themselves"* (p. 14).
- *Harm to society:* according to students, HS may damage the community health and development. They perceived HS as a behavior that facilitates the spread of different diseases and substance use within the community, and thus endangers community health. *"Hookah endangers our health and destroys the health of our family, community, and society"* (p. 3). Not commonly commented on, some students believed that individuals from different age groups congregate in hookah lounges where fighting, violence, and ethnic groupings are common. The promotion of behavior within society results in the development of hookah lounges, which consequently promote violent behaviors in the community. *"In these places, there are many delinquents, and fights and violence are common, the ethnic grouping is common"* (p. 18).
- *Harm to the family ties:* many students believed that smokers do not pay attention to their family, have misbehavior with their family members, and have weak parent-child ties. *"A characteristic of hookah smokers is that they do not pay any attention to their family"* (p. 28). As they noted, it may also cause detachment between the smoker and his/her family and what he/she was going on. *"It makes you move away from things you like"* (p. 31). *"[hookah smok-*

ers] *actually destroy God's blessing with their own hands*" (p. 7). "*they [hookah smokers] do not respect their parents or do not ask their permission*" (p. 23).

Discussion

To the best of our knowledge, this was the first qualitative study to explain the SUoHS from the viewpoints of adolescents. The students explained the SUoHS in disreputability and incivility of hookah smokers and their behavior within the society, and the disrespectfulness of smokers and their families. They also perceived the SUoHS in the consequences of behavior. These findings suggest that the concept of the SUoHS originates from the social context of society, and is rooted in the social values and norms related to smoking within communities. The social values affect the attitude and subjective norms of individuals toward the behavior. The present study helps to explain why smoking prevention and/or cessation programs may not lead to behavior change. According to the theory of planned behavior [20, 21] and the health belief model [22, 23], the first step to hookah smokers implementing HS cessation involves them perceiving themselves to be at risk of health problems as a result of smoking. They would be also affected by the significant others around them in terms of either continuing or quitting the behavior. They would then need to believe in their ability to stop smoking. Before these cognitive factors, there may be considerations on the significant role of social factors, like social valuing of the smokers and their behavior. The perception of adolescents on the way that society values their behavior may influence their attitude and subjective norms toward HS. All these factors together may constitute the perception of adolescents on the SUoHS, which may, in turn, influence their intention to practice the behavior. In other words, as a possible presumption, HS may not be prevented or quit if there would be no consideration of the role of the SUoHS.

Based on our data, the students perceived hookah users as untrustworthy individuals who do not respect the rights of others. They believed that HS is against social values and norms. These findings are consistent with those reported by Khalil et al. [24] in a qualitative study in the East Mediterranean region. Their results described HS by women as a behavior that opposes society and social norms. As they suggested, the social context of HS is crucial to understanding the behavior. In more conservative communities where norms and customs are well-defined and confirmed, there may be some social limitations for HS as compared to more liberal societies. Maziak et al. [25] in a study in Syria reported traditions and norms as the main reasons noted by women for not smoking.

Our data indicated that the SUoHS lies in the disrespectfulness of hookah users, particularly female hookah users, and their families. Our participants perceived hookah users as promiscuous, playful, and irresponsible individuals. Similarly, Gholami et al. [26] in a qualitative study in Iran identified that people had a

negative attitude towards hookah users, demonstrating the decreased popularity of the users in society. Our participants also believed that the social unacceptability of this behavior is much stronger for women, compared to men, and explained such women as shameless and promiscuous; a finding consistent with previous research [24], suggesting that being a female hookah user is viewed as cheap and shameful. The SUoHS was also explained in the perceptions of adolescents on the family of hookah users. Based on our data, when HS is common within a family, the social unacceptability of behavior is broken down. In such families, the child may feel free to perform other obscene behaviors, like cigarette smoking and alcohol misuse, within family environment, which may attenuate respectfulness towards parents over time. Roskin and Aveyard [27], in a qualitative study in Canada, identified that regular HS within a family was considered as a normal activity, which may be similar to watching television over time. Another Iranian study among adolescents showed that lack of family supervision increased the odds of HS [16]. Our data also indicated that the SUoHS may be partly due to the consequences of behavior. Students believed that HS was socially undesirable because it could damage the users and their society. In a systematic review [28] on the motives, beliefs, and attitudes towards HS, achieving peace and pleasure was among the main motives for HS. Mohammadkhani and Rezaei [16] also showed associations between HS and hopelessness among adolescents. They also revealed that family conflicts have significant correlations with the tendency towards HS. Similarly, the students in our study contended that HS was undesirable because it weakened users' relationships with their families. Accordingly, they could gradually get away from their families, and have poor and strained relationships with their parents.

Jahanpour et al. [13] in an Iranian qualitative study reported relationships between culture and the tendency of adolescents/youths towards HS. According to our participants, the SUoHS was partly seen in the damage that it may cause to the community health and development. They believed that HS is now getting to be considered as an acceptable norm in public places, as it is easily accessible. Such a high level of accessibility within the community may have decreased the SUoHS and has consequently increased the frequency of the behavior in society. In a qualitative study in Malaysia, availability and inexpensiveness were reported as the factors leading to a tendency towards HS [29].

LIMITATIONS

We were able to include students from a range of socioeconomic backgrounds, however, the findings may not represent the views of students who did not participate in the study and may therefore be biased towards students who are more interested in participating in scientific researches. We triangulated our data in the FGD sessions with the data collected during individual interviews to confirm and cross-validate the findings from different interview methods. However, considering

the methodology, social desirability bias may be possible. To limit this threat, we selected an interviewer with experience in conducting qualitative interviews and focus groups.

Conclusions

Adolescents in our study described the SUoHS from different dimensions. They perceived the social unacceptability of HS in the disreputability of hookah smokers and their behavior, disrespectfulness and incivility of the smokers and their families, and the consequences of behavior. The SUoHS originates from the social context of society and is rooted in the social values and norms within communities. These social values may affect the attitude and subjective norms of individuals toward the behavior.

To decrease hookah smoking levels among adolescents, school health nursing interventions should be tailored to bridge the gap between their recognition of SUoHS and subsequent behavior change through creating group dynamics highlighting the domains of social unacceptability of the behavior. The results of the present study can serve as a basis for future studies on the role of the SUoHS in adolescents' tendency towards the behavior. Future studies should consider our results to develop relevant indicators/instruments for measuring the SUoHS among adolescents, with the hope to provide sufficient evidence for HS prevention/cessation interventions.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Study design: HN, KK, AM, and HA. Study conduct: HN, KK, and AM. Data collection: KK and HN. Data analysis: HN, KK, and AM. Data interpretation: HN, KK, AM and HA. Drafting manuscript: HN and KK. Revising manuscript and content: HN, KK, and AM. Approving final version of manuscript: All authors. HN takes responsibility for the integrity of the data analysis.

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RESEARCH ARTICLE

Assessment of healthcare worker's hand hygiene and infection prevention practices of their personal belongings in a healthcare setting: a survey in pre COVID-19 era and literature review on standard disinfection practices

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Keywords

Healthcare workers • Mobile phones • Stethoscope • Hands • Aprons • Hygiene practices • COVID-19

Summary

Background. Healthcare workers' (HCW) hands and personnel belongings are vehicles of transmission of nosocomial infections. Knowledge, attitude, and practice of hand hygiene have been extensively studied suggesting adequate knowledge but poor compliance. Similar data on aprons, mobile phone and stethoscope disinfection practices are lacking. This becomes an extensively important topic of discussion in current COVID-19 pandemic where inadequacy in hygiene practices is devastating.

Aim. To study the knowledge, attitude, and infection prevention practices of HCWs aprons, electronic devices, stethoscopes, and hands.

Methods. A cross sectional questionnaire-based survey was conducted among HCWs of Medicine ward and ICU.

Results. Sixty-six HCWs responded to the survey. Awareness that hands, aprons, mobile phones, stethoscopes could cause cross

transmission and knowledge of correct practices was present in majority of the respondents. Hand hygiene was performed by 65.2% of the respondents before touching a patient and 54.5% after touching the patient surroundings while 13.6% performed only when it was visibly soiled. Mobile phones and stethoscopes were disinfected by 13.6 and 30.3% of the respondents after each patient encounter, respectively. Aprons were washed after using them at a stretch for a median duration of 5 days (1-30 days). Forgetfulness, lack of reinforcement, lack of time, inadequate awareness on standard disinfection practices and fear of damaging electronic devices from disinfectants use were reasons for poor compliance.

Conclusions. There is an urgent need to spread awareness and formulate standard guidelines on disinfection practices especially for mobile phones, stethoscopes, and aprons in addition to reinforcing hand hygiene practices.

Introduction

Developing countries face a high burden of nosocomial infections [1]. It affects the disease course of hospitalized patients by increasing length of hospital stay, morbidity, mortality and imposes an additional financial burden. Many of these infections are caused by drug resistant microorganisms which are difficult to treat [1, 2].

Microorganisms causing nosocomial infections could be acquired from the hospital environment. Healthcare workers (HCW) act as a potential source of transmission through their hand and contaminated personal belongings (clothes, stethoscopes and electronic devices) [3-7].

Hand hygiene is the single most effective intervention in reducing health care associated infections. Time and again this has been reinforced among HCWs yet the compliance of hand hygiene is low [8]. Despite adequate knowledge, callous attitude among HCWs has hampered the practice of hand hygiene.

Medical devices especially stethoscopes have been found to be contaminated by various pathogenic bacteria.

Studies have demonstrated the presence of Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant Enterococci (VRE) and *Clostridium difficile* on their surfaces. In the absence of adequate disinfection practices they can cause cross transmission [9, 10]. Infection prevention compliance and instrument disinfection practices among healthcare workers is poor [11]. Similar is the case with mobile phones and aprons [12, 13].

Studies have mainly focused on assessing hand hygiene practices [14, 15]. However, HCWs' level of knowledge, attitude and practices of disinfecting their personal belongings, which are neglected yet potentially infectious sources is unexplored. It becomes important in the current scenario of COVID-19 pandemic where studies have shown the presence of the viral particles on hands and various inanimate objects acting as potential sources of infection [16]. Knowledge regarding immediate pre-COVID-19 era hygiene practices could help identify pitfalls and act imminently during COVID-19 era where every effort at infection prevention could prove exponentially beneficial. This study was

conducted with the objective of assessing knowledge, attitude, and infection prevention practices of HCWs aprons, electronic devices, stethoscopes, and hands.

Methods

A questionnaire-based cross sectional study was conducted during November and December 2019 among health care workers working in wards and Intensive Care Unit (ICU) of Medicine Department at a tertiary care centre in New Delhi, India. Health care workers included doctors and nurses. This study was ethically approved by institute ethics committee.

A preformed questionnaire using the Google forms format was made. The questions were pertaining to hygiene practices among healthcare workers with respect to hand, aprons, stethoscope, and electronic devices. The questions under each section were framed to assess their knowledge, their attitude towards infection prevention, and their day-to-day practice. A set of questions were circulated as pilot among 10 participants and the following questions were finalized based on their feedback and applicability along with suggestion from experts. Final questionnaire (Tab. I) included five questions each for assessing hand hygiene, stethoscope, and apron disinfection, while there were six questions for electronic devices. The questionnaire was circulated among the HCW via the Google link and could be filled only once. The respondents could voluntarily take up the survey. Confidentiality was maintained by not using any respondent identifiers and making the responses to the questionnaire completely anonymous. A descriptive statistical analysis involving frequencies and percentages was performed to assess the hygiene practices.

Results

Sixty-six healthcare workers in Medicine wards and ICU responded to the questionnaire during the study period (Tabs. I, II). It included 38 junior residents, 21 senior residents, 3 nurses, 2 consultants and 2 interns. Fifty-nine (89.4%) of them worked in medicine ward and seven (10.6%) of the HCWs worked in ICU. Median experience of working in a healthcare setup was 4 years (range: 1-18 years).

Assessment of hand hygiene practices revealed that, all healthcare workers were aware of the significance of hand washing and that lapses could cause cross transmission. Ninety four percent reported that they were sure of all the steps of hand washing and the rest were unsure. All HCWs reported that they washed their hands however the scenarios in which they did it were different. Majority, 81.8% HCW did hand washing before any clean or aseptic procedures, 87.9% of them washed their hands after encountering body fluids and 77.3% after touching a patient. However, only 65.2% of them practiced hand hygiene before touching a patient and 54.5% after touching the patient surroundings. Hand

hygiene practices were followed by 13.6% HCWs only on being visibly soiled. Alcohol based hand rubs were used by 94% of them and 71.2% washed their hands with soap and water when they were visibly soiled. Eight healthcare workers reported that they did not practice adequate hand washing due to forgetfulness, lack of on spot reinforcement and lack of time.

All healthcare workers carried electronic devices to the hospital which universally included the mobile phones. Other devices used were tablets, laptops, and pulse oximeters. Usage of electronic devices amidst patient care was reported by 78.8% HCWs. Although all were aware that electronic devices can cause cross transmission, only 89.4% of them cleaned their devices, out of which only 13.6% disinfected it after each patient encounter and 75.8% did it only when it was visibly soiled while 10.6% HCW never disinfected their devices. Alcohol based disinfectant were commonly used by 85.9% HCW to disinfect their devices. Lack of knowledge of correct technique of disinfection and the fear of damaging their devices due to disinfectant formulae were the reasons provided by those who did not disinfect their device.

Stethoscopes are routinely used for patient care by around 91% HCWs and infection prevention practices involving this commonly used medical device were evaluated in our study. Around 98.5% HCW were aware that stethoscopes could be potential sources of cross transmission of infection. Although 93.9% of them disinfected their stethoscopes only 30.3% of them did it after each patient encounter, 6.1% of them never disinfected and the rest of them did it only when it was visibly soiled. Alcohol based disinfectant was used by all of them and mainly the diaphragm (46.9%) was disinfected. Lack of knowledge was reported as the reason for not disinfecting their stethoscopes.

Aprons are worn by over 91% HCW regularly during patient care. About 97% HCW were aware of risk of cross contamination, yet most of the study population involving around 94% of them carried aprons back home after duty. Unwashed aprons were used at a stretch for a median of 5 days (range: 0-30 days). Tap water with detergent was used for disinfection. All of them reported of washing their aprons however those who did not regularly wash gave the reason of lack of time. Everyone, irrespective of the practicing speciality, reported the need for hospital scrubs for patient care which could thereafter be left back in the hospital itself for disinfection.

Discussion

Our study was done to assess the knowledge, attitude, and practice of infection prevention measures amongst HCWs. All potential sources of infection including hands, electronic devices, clothing, and stethoscopes were analysed for hygiene practices. Wide spectrum of HCWs were sampled including consultants, residents, interns, and nurses working in both ward and ICUs.

Almost all HCWs in our study reported that they were aware of the fact that hands, electronic devices, aprons,

Tab. I. Responses to the survey.

Question	Response - number (%), n = 66		
I. Hand hygiene			
1. Are you aware that hands can cause cross contamination and infection in your patients?	Yes: 66 (100%)		No: 0
2. Will you be able to perform all the steps of hand washing?	Yes: 62 (94 %)	Maybe: 4 (6%)	No: 0
3. Under what scenarios do you wash your hands?	A. Before any clean or aseptic procedures: 54 (81.8%) B. After touching body fluids: 58 (87.9%) C. After touching the patient: 51 (77.3%) D. Before touching the patient: 43 (65.2%) E. After touching patient surroundings: 36 (54.5%) F. Only when hands are visibly soiled: 9 (13.6%)		
4. Disinfectant used	A. Alcohol based hand rub: 94% B. Soap and water when hands are visibly soiled: 71.2%		
5. Reasons for not performing adequate hand hygiene	8 (12.1%): forgetfulness and lack of on spot reinforcement, lack of time		
II. Electronic device disinfection practices			
1. Do you carry electronic devices to your workplace?	Yes: 66 (100%)		No: 0
2. What electronic devices do you carry?	A. Mobile phones: 66 (100%) B. Tablets: 20 (30.3%) C. Pulse oximeters: 20 (30.3%) D. Laptops: 12 (18.2%)		
3. Are you aware that electronic devices can cause cross contamination and infection in your patients?	Yes: 66 (100%)		No: 0
4. Do you use your device while caring for your patients?	Yes: 52 (78.8%)		No: 14 (21.2%)
5. Do you clean your devices and under what circumstances?	Yes: 59 (89.4 %) A. Only when visibly soiled: 50 (75.8%) B. After each patient encounter: 9 (13.6%)		No: 7 (10.6 %)
6. Disinfectant used	Alcohol based disinfectant: 85.9 %		
III. Stethoscope disinfection			
1. Do you use stethoscope during routine patient care?	Yes: 60 (91%)		No: 6 (9%)
2. Are you aware that stethoscopes can cause cross contamination and infection in your patients?	Yes: 65 (98.5%)		No: 1 (1.5%)
3. Do you clean your devices and under what circumstances?	Yes: 62 (93.9 %) A. Only when visibly soiled: 42 (63.6%) B. After each patient encounter: 20 (30.3%)		No: 4 (6.1%)
4. Which part of the stethoscope do you clean?	A. Diaphragm only: 31 (46.9%) B. Diaphragm and tubings: 18 (27.3%) C. Diaphragm, tubings and earpiece: 13 (19.7%) D. Soiled portion: 10 (15.2%)		
5. Disinfectant used	Alcohol based disinfectant: 100 %		
IV. Apron disinfection			
1. Do you use apron regularly during routine patient care?	Yes: 60 (91%)		No: 6 (9%)
2. Are you aware that aprons can cause cross contamination and infection in your patients?	Yes: 64 (97%)		No: 2 (3%)
3. How many days at a stretch do you wear your unwashed apron? Median (Range)	5 days (0-30 days)		
4. Disinfectant used	Tap water and detergent: 100%		
5. Which do you think is the best mode of getting your aprons washed?	Hospital should provide scrubs for patient care which can be left back in the hospital for disinfection: 100%		

and stethoscopes are potential fomites causing cross transmission and also agreed of having a fair knowledge on hygiene practices, however few lapses were observed in the responses pertaining to their practice of the same. Multiple studies have also reiterated the same with regards to poor compliance and practice of infection prevention hygiene practices among healthcare worker [12, 14, 15, 17-20]. WHO has recommended various steps and movements of hand hygiene [21]. However, the practice of five

movements around the patient zone was variable. Majority of them performed hand hygiene after patient contact, after exposure to body fluids and before aseptic procedures, however just above half of them did it before touching the patient and after touching the surroundings. Furthermore, 13.6% did it only when it was visibly soiled. A similar study reported 86% of respondents having knowledge about hands being a vehicle of transmission while only 53.8 and 32.5% knew about movements

Tab. II. Demographic profile.

Demographic characteristics		Number (%), n = 66
Designation	Consultant	2 (3%)
	Senior resident	21 (31.8%)
	Junior resident	38 (57.6%)
	Intern	2 (3%)
	Nursing staff	3 (4.5%)
Unit of surveillance	Ward	59 (89.4%)
	ICU	7 (10.6%)
Working experience-median (range)		4 (1-18) Years

and steps of hand hygiene [1]. A metanalysis revealed compliance of 52% (27-86%) for hand hygiene [22]. If similar compliance rates are followed in the current COVID-19 pandemic era, infection prevention would be impossible to achieve and hospitals would thus be hotspots of infection transmission rather than control and prevention.

Hand hygiene is the corner stone for prevention of hospital acquired infections. Poor compliance despite adequate knowledge is a major bottle neck for adequate infection control and prevention. Respondents in our study blamed lack of time as the reason for inadequate hand hygiene similar to other studies which has identified “being busy” as one of the factors influencing hand hygiene behaviour [23]. Availability of point of care hand hygiene products which includes alcohol based hand rubs closer to the patients and on-site reinforcement of importance hand hygiene will facilitate better integration of hygiene practices in the workflow [24].

Mobile phones are universally used by all healthcare workers and majority reported of it being used during patient care. However only 13.6% of them disinfected after each patient encounter and 10.6% of them never disinfected their devices. Similar results have been published by a study wherein only 37% admitted of cleaning it regularly [25]. The benefit of using mobile phones in clinical areas should be weighed against the potential risk of contamination and cross infection. It is best avoided during patient care or to be disinfected with 70% isopropyl alcohol after each patient encounter taking care that moisture does not enter any of the openings and perform proper hand hygiene [26]. The most common reason for not disinfecting was out of the fear of damaging the device and many did not know the proper method of disinfection. There are concerns that more than 50% alcohol damages the screen and the phone manufacturing companies do not recommend any chemical being used. However in the wake of COVID-19 pandemic they too have recommended 70% isopropyl alcohol wipes [27-29]. There is no clear evidence that mobile phone hygiene reduces disease transmission. Nevertheless, mobile phone use should be minimized, hand washing, disinfectant wipes, headphone use and washable covers should be encouraged [26]. Extrapolating available data to current scenario could signify that HCW would carry coronavirus back home inevitably thus promoting fomite transmission of COVID-19 to family and friends. Hence there is an urgent need to stress on infection prevention

measures and even better refrained use of electronic devices during patient care in present day situation.

Stethoscopes are the most common medical device used and a recognized fomite, yet disinfection practices are poor. Only one third of them disinfected stethoscopes after each patient encounter and 6.1% never disinfected stethoscopes in our study. Studies by Sahiledengle B and Ghumman GW et al. have also reported that only 39.7% and 29% respectively disinfected their stethoscopes regularly, the rates have been less than 50% usually [18-20]. Several studies have concluded that disinfection of stethoscopes with 70% isopropyl alcohol reduces 99% of bacteria [30]. However lack of awareness of standard infection prevention guidelines and favourable attitude towards infection prevention are independent predictors of stethoscope disinfection after every use [20]. Regular disinfection of stethoscope, followed by hand hygiene and avoidance of sharing them has been suggested to prevent spread of COVID-19 [31].

Aprons/Lab coats are frequently used by healthcare workers during patient care. They are potential yet neglected cause of cross transmission. In our study it was seen that almost everyone carried back their aprons home and was washed at a median of 5 days with a maximum of a month at a stretch being unwashed. This is potentially dangerous and can lead to infection of the family members as well. Many agreed to lack of time being the reason for not washing their aprons. We suggest that hospital provide fresh scrubs daily for healthcare workers which can be left back for disinfection in the hospital before going back home.

The study design being cross sectional questionnaire-based survey, although throws light on important infection prevention practices prevailing, there might be response bias as the data is solely based on how faithfully HCWs reported on their practices as the study did not involve direct observation of their practices. Yet the reported correct practice was low in accordance with the published literature. Extrapolation of data on a larger scale would mandate larger prospective studies wherein the practices are observed for stronger evidence. Results may not be generalizable to various specialities of healthcare considering the setup of medical wards and ICU only considered in our study. Nevertheless, this study could be food for thought to implement more strict compliance with infection prevention measures by healthcare workers. The suggested recommendations on infection prevention hygiene practices in this manuscript can increase awareness among HCWs and help fight the COVID-19 pandemic.

Conclusions

Healthcare workers and their belongings are undoubtedly potential sources of infection. Despite adequate knowledge, poor compliance to infection prevention practices has hampered the progress in reducing nosocomial infections. Akin to widespread dissemination of information on

hand hygiene, standard guidelines, and reinforcement of hygiene practices for potentially infectious yet neglected fomites like mobile phone, stethoscopes, and aprons among all cadre of healthcare workers is necessary. The immediate pre-COVID era data discussed acts as a baseline to evaluate infection prevention practices prevailing amongst HCW and hence could be helpful to formulate strategies and infection prevention guidelines to combat the infectious pandemic.

Ethics statement

The work has been approved by institute ethics committee and that subjects gave informed consent to the work.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

VCK, AK conceived the study. VCK, AK, NR and MS were involved in making the questionnaire and collecting the responses. VCK wrote the manuscript and was guided by AK. MAK was involved in statistical analysis and script editing. AK, NR and MS were involved in script editing. NW was involved in script editing and script critical review. All authors read and approved the final version of the manuscript.

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RESEARCH ARTICLE

Health education intervention to improve vaccination knowledge and attitudes in a cohort of obstetrics students

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Keywords

Vaccines • Midwives • Knowledge • Health education • Pregnant women

Summary

Introduction. To improve the vaccination coverage in pregnant women it is important to increase their knowledge of vaccines and related preventable diseases. Midwives can play an important role because they are often the first contact for woman during her pregnancy. This study aimed to explore the vaccination knowledge and attitudes in a cohort of Obstetrics students in Italy and improve their knowledge through an informative health education intervention.

Methods. The study consisted in the administration of a first questionnaire followed by a health education intervention concerning all aspects of vaccinations. Then, a second questionnaire to evaluate the efficacy of the educational program was administered.

Results. From the pre-intervention questionnaire resulted that almost the whole sample (97.1%) were favorable to vaccines in general. Moreover, 65.7% of the participants declared a sufficient

level of vaccination knowledge but 62.9% found herself unprepared to answer questions and provide information about vaccinations. Concerning the answers about vaccination in pregnancy, the correct answers went from 17.1 to 68.6% respectively before and after educational intervention. The training intervention obtained a total consensus (100%). The most part of the students (85.7%) declared that the received information changed some of their beliefs and the entire sample (100%) stated that it improved their preparation.

Conclusions. Our results revealed some critical issues in the preparation of midwives about vaccinations and confirm the necessity to carry out health intervention campaigns to these health professionals that, for the role they play, they must necessarily be well prepared.

Introduction

In the last decades, the scientific community has paid a great and increasing attention to maternal immunization and several studies have showed that vaccinations in pregnancy are a safe and highly effective strategy not only for woman but also for unborn and newborn thanks to the passive transplacental transfer of antibodies [1-4]. Previous studies have well demonstrated that infections contracted during pregnancy can result in an increased risk of serious complications in mothers, adverse outcomes in newborn, lengthening of the hospitalization period, and higher mortality rate [5, 6]. However, despite these large and proven scientific evidences, the coverage rates among pregnant women remain consistently very low [7, 8]. Thus, several countries recommended maternal immunization and established immunization programs. In Italy, according to the World Health Organization (WHO) Global Vaccine Action Plan [9], the Ministry of Health issued the Vaccine Prevention National Plan 2017-2019 stating that women should routinely receive tetanus, diphtheria, and acellular pertussis (Tdap) vaccine between the 27th and the 36th week of every pregnancy (regardless of prior Tdap history), and influenza vaccine at any stage of pregnancy [10, 11].

It is well known that the success of a vaccination program may also depend on the knowledge and

awareness of those who are at risk, because a lack of information and fear of vaccination may result in a lower vaccine acceptance and hesitancy [12, 13]. Therefore, it is important to increase knowledge of vaccines and related preventable diseases in pregnant women, and to evaluate their attitudes and concerns that may affect their decisions. Several studies have been carried out to assess vaccination knowledge and acceptability in this particular group [14-17]. However, little literature on this topic is currently available in Italy [18-20].

Health professionals can play the most important role to increase knowledge and awareness in pregnant women and recommending vaccination [21, 22]. The strong link between health professionals' vaccination beliefs and vaccine uptake has been documented by several studies [13, 23, 24].

Midwife is often the first and important contact for the woman during her pregnancy, during labor, childbirth and the early postnatal period. This health category is responsible for providing care and supporting women to make informed choices and decisions about their care. For these reasons, midwives can play a key role in the prevention of infectious diseases and in the increasing of vaccine knowledge and awareness by informing and educating their patients. However, although they have become new actors in the effort to increase immunization coverage, their vaccine awareness and perception and

their preparation in this field have only been little studied in Europe. Improving their knowledge could help to increase vaccine coverage among pregnant women.

This study aimed to explore the vaccination-related knowledge and attitudes in a cohort of Obstetrics students in Italy and improve their knowledge through an informative health education intervention.

Methods

STUDY DESIGN

The survey was carried out in December 2019 by physicians with a specific education in vaccinations and public health assisted by experts in infectious diseases on students attending the Obstetrics course of the University of Messina, Italy. We have joined the participants of all three years of the course and we asked students to participate to our investigation. The study consisted of three steps.

In the first one, a written informed consent form and a brief anonymous first (pre-intervention) questionnaire were administered. This questionnaire collected socio-demographical data (age, gender, educational level) and the knowledge of vaccinations. Particularly, we asked if they were in favor of vaccination in general and during pregnancy, whether or not they had received vaccine information during the course of studies and how they assessed this information, their level of knowledge through questions about mandatory and recommended vaccinations and vaccines recommended during pregnancy.

In the second step, after the administration of this first questionnaire, we conducted an educational intervention concerning all aspects of vaccinations (general characteristics, current legislation about mandatory and recommended vaccines, vaccination of particular groups of people including pregnant women) through the use of slides and the supply of informative material to the audience. After the intervention, a debate was conducted in order to clarify with the audience any possible doubt. The entire step lasted about four hours.

Finally, in the third step, at the end of the educational session, a second anonymous questionnaire (post intervention) to evaluate the efficacy of the educational program (containing the same questions of the first one plus some questions about the satisfaction degree of the intervention), was administered.

STATISTICAL ANALYSES

All the obtained data were collected and analyzed with Prism 4.0 software. Descriptive statistics were used to find the percentages and the 95% Confidence Interval (CI). Chi-square test was used for the comparison between the answers (pre- and post-education program). The role played by the independent variables in the effectiveness of the program was assessed using nonparametric Spearman test. Significance was assessed at the $p < 0.05$ level.

Results

The sample consisted of 35 students attending all the three years of course. Particularly, 9 (25.7%) attended the first year, 17 (48.6%) the second and 9 (25.7%) the third. The participants were all women with an average age of 21.0 ± 1.1 y/o and all of Italian nationality. From the pre-intervention questionnaire resulted that almost the whole sample (97.1%) were favorable to vaccines in general, which they defined with various adjectives among which useful, effective, safe and necessary were the most frequent. Almost the entire sample (82.7%) declared that received information about vaccines during the course of study and the 63.4% evaluated as sufficient the quality of the received information. However, 36.6% declared as insufficient the information received. Moreover, 65.7% of the participants declared a sufficient level of vaccination knowledge but 62.9% found herself unprepared to answer questions and provide information about vaccinations. Finally, 80% stated they learned information mainly from Internet (42.9%) and traditional mass media (37.1%).

To evaluate the level of vaccination knowledge we asked to indicate the current mandatory vaccinations in Italy. Figure 1 shows the differences between the pre- and the post-intervention questionnaires. In particular, the correct answers ranged from 8.6 to 65.7% ($P < 0.0001$) (concerning respectively the pre- and the post-intervention questionnaires).

Moreover, 94.3% of the sample stated that would advise a pregnant woman to carry out vaccinations. Figure 2 shows how significantly change the vaccinations they would recommend in pregnancy analyzing the answers given to the pre- and the post-intervention questionnaires. For this type of questions, the correct answers went from 17.1 to 68.6% respectively before and after educational intervention ($P < 0.0001$).

Furthermore, we asked to express the level of concern about vaccine-preventable diseases. The results are shown in Table I.

Table II shows the differences between the pre- and the post-intervention questionnaire about the answers given to the questions regarding general vaccination beliefs and attitude of the sample.

The training intervention obtained a total consensus (100%), reaching the desired goal. The most part of the students (85.7%) declared that the received information changed some of their beliefs and the entire sample (100%) stated that it improved their preparation.

To further analyze the obtained results, we calculated the score obtained by each of the sample components as the sum of the exact answers given in the two questionnaires, both on compulsory and strongly recommended vaccinations in pregnancy. Specifically, the score calculated as the total of the correct answers increased from 2 of the pre- to 19 ($P < 0.0001$, OR: 0.0510, 95% CI: 0.0105-0.2465) of the post-intervention questionnaire. Analyzing separately the data between the two questionnaires, the score increased from 3 to 23 ($P < 0.0001$, OR: 0.0489, 95% CI: 0.0123-0.1933) and from 6 to 24 for what concerning strongly

Fig. 1. Differences between the pre- and the post-intervention questionnaires about the knowledge of the current mandatory and strongly recommended vaccinations in Italy.

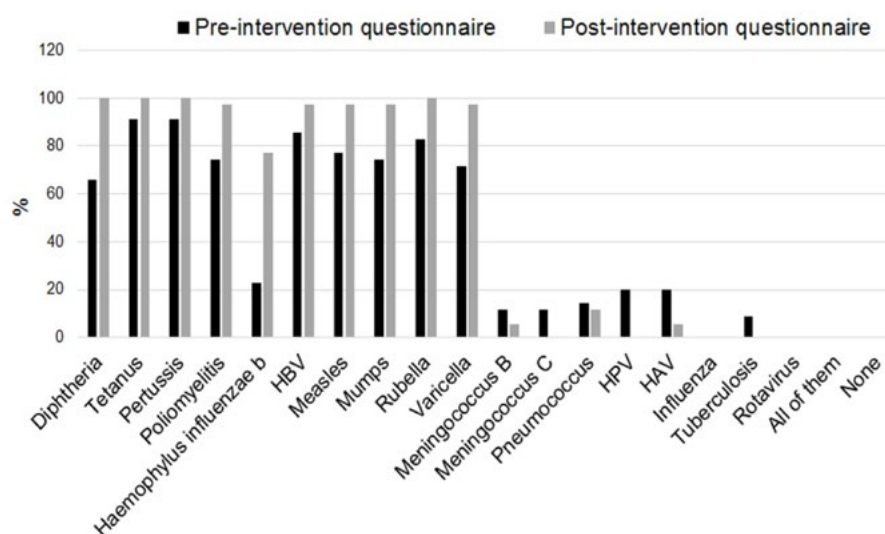
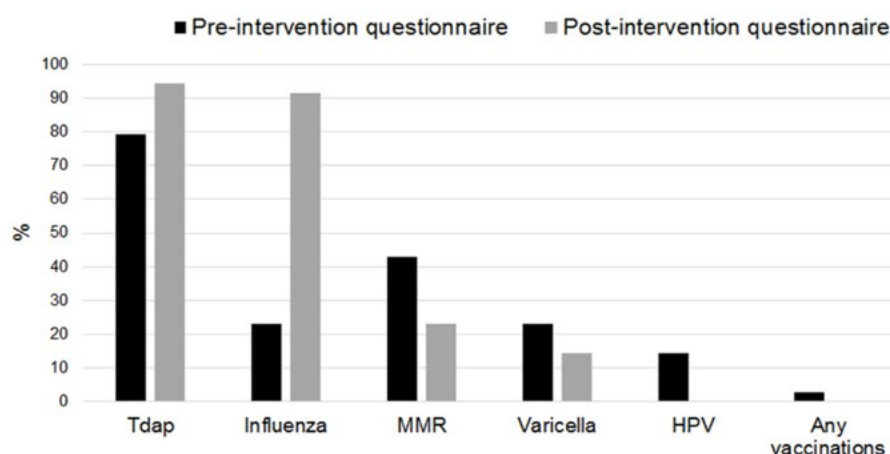


Fig. 2. Differences between the pre- and the post-intervention questionnaires on the strongly recommended vaccinations in pregnancy.



Tab. I. Percentages of expressed level of concern about vaccine-preventable diseases.

	Null	Low	Moderate	High	Very high	Empty
Diphtheria	0	17.2	31.4	20.0	11.4	20.0
Tetanus	0	5.7	22.9	31.4	25.7	14.3
Pertussis	0	8.6	20.0	37.2	11.4	22.9
Poliomyelitis	11.4	11.4	11.4	22.9	22.9	20.0
Hepatitis B	0	2.9	11.4	22.9	57.2	5.7
Measles	2.9	11.4	34.3	31.4	17.2	2.9
Mumps	2.9	11.4	42.9	22.9	5.7	14.3
Rubella	2.9	8.6	45.7	28.6	14.3	0.0
Varicella	8.6	20.0	48.6	11.4	8.6	2.9
Meningitis by Hib	11.4	5.7	5.7	25.7	48.6	2.9
Meningococcal meningitis	0	0.0	11.4	5.7	77.2	5.7
Pneumococcal disease	2.9	0.0	14.3	17.2	62.9	5.7
Rotavirus diarrhea	0	17.1	42.9	11.4	17.2	8.6

Tab. II. Differences between the pre- and the post-intervention questionnaires about the answers given to the questions about general vaccination beliefs and attitude of the sample.

	1 st questionnaire		2 nd questionnaire		P-value
	Agree	Disagree	Agree	Disagree	
Vaccines are important because they prevent diseases that can have serious effects	100	0	100	0	-
I think that administering multiple vaccines at the same time can be risky for children's health	28.6	71.4	2.9	97.1	P < 0.0001
Vaccines contain harmful substances	14.3	85.7	0	100	P < 0.0001
I am concerned about the side effects of vaccinations	40.0	60.0	20.0	80.0	0.0032
Getting vaccinated is important to protect the health of the community	100	0.0	100	0	-
Healthcare professionals often provide incomplete information on the side effects of vaccines	11.4	88.6	80.0	20.0	P < 0.0001
Vaccines are primarily an economic affair of the pharmaceutical industries	22.9	77.1	5.7	94.3	0,001
I don't care about the safety of the new vaccines available (meningococcus B, nonavalent HPV, Herpes Zoster)	31.4	68.6	0	100	P < 0.0001
Vaccinations must be individual and recommended based on health and medical tests; they cannot be the same for everyone	25.7	74.3	20.0	80.0	ns
The MMR (measles-mumps-rubella) vaccine can cause autism	17.1	82.9	0	100	P < 0.0001
I believe that children should contract measles, rubella, mumps and chickenpox naturally and not be vaccinated	11.4	88.6	0	100	0.0007
I don't believe the news about the alleged vaccine toxicity	68.6	31.4	88.6	11.4	P < 0.0001
The effectiveness of vaccinations has been scientifically proven	82.9	17.1	100	0	P < 0.0001
Smallpox has been eradicated from the planet thanks to vaccination	88.6	11.4	91.4	8.6	ns
In Italy, poliomyelitis and diphtheria have disappeared thanks to the improvement of hygiene conditions and not thanks to vaccinations	37.1	62.9	8.6	91.4	P < 0.0001
Serious side effects of vaccines are very rare	88.6	11.4	97.1	2.9	0.0489
There is a link between autoimmune diseases and vaccines	31.4	68.6	14.3	85.7	0.0063
Vaccinations increase the risk of developing allergies	17.1	82.9	2.9	97.1	0.0015
There is a link between vaccines and tumors	11.4	88.6	8.6	91.4	ns
Unvaccinated children are more resistant to infections	5.7	94.3	11.4	88.6	ns

recommended in pregnancy and strongly recommended and compulsory vaccinations in general respectively (P < 0.0001, OR: 0.0948, 95% CI: 0.0305-0.2943).

Both scores were positively related to the attended year of course (P < 0.05). Furthermore, the satisfaction degree expressed by the participants for educational intervention and the awareness of being able to give the right information to pregnant women were positively correlated to the score obtained from the post-intervention questionnaire (P < 0.01).

Discussion

In the perspective of increasing vaccination coverage for all population, it is important to know the opinions of health professionals involved in advising and/or offering vaccines to pregnant women, in order to bridge the gap between recommendation and implementation.

The acceptance rate of vaccinations during pregnancy is affected by several concerns especially regarding the maternal-fetal safety. Previous studies suggested that common barriers are fear of vaccine-transmitted infections with potential adverse pregnancy outcomes and lack of knowledge of national and provider recommendations [25, 26]. In order to counteract this

beliefs, it is crucial that midwives play an active role, as showed by previous studies in which pregnant women being 5 to 50 more likely to accept a vaccine if directly recommended by their provider [27-31].

Midwives are surely a reference figure for pregnant women as, during pregnancy, they can provide all the antenatal care for a pregnant woman playing a key role in promoting vaccinations. Therefore, it is crucial that this health category is well prepared and aware on vaccination topic. Recent studies showed that pregnant women and women with young children were willing to be vaccinated and they cited in particular midwives as their preferred source of information [22, 32]. Indeed, it has been showed that the uptake of Tdap and influenza vaccines by pregnant women, although the relative vaccination coverage are yet not optimal, has increased remarkably in last years, especially because of midwives recommending these two vaccines [33-35].

From our study resulted that there were no subjects among participants with anti-vaccination attitudes because the vast majority of the sample was favorable to vaccinations in general. However, from the pre-intervention questionnaire, we detected some critical issues concerning the general vaccination knowledge, corroborated by the detected poor knowledge of the current mandatory and strongly recommended

vaccinations in Italy and that a very high percentage of the sample declared to feel unprepared to provide information on this topic. Moreover, although almost the entire sample stated that it would advise a pregnant woman to carry out vaccinations, the answers about the strongly recommended vaccinations in pregnancy shows a rather poor knowledge. Particularly, a remarkable gap was detected between Tdap vaccination, which it would be advised by a large part of the sample, and influenza vaccination, of which only a small number of participants knew that it is strongly recommended in pregnancy. Even more serious, a rather high percentage of the sample declared that would advise vaccinations strongly discouraged in pregnancy such as MMR and Varicella vaccinations. Furthermore, from the request to express their level of concern about vaccine-preventable diseases, we found that the most part of the diseases arouse a moderate level of concern except for meningococcal meningitis and pneumococcal disease towards which the sample resulted more worried. The lack of concern regarded especially those diseases disappeared thanks to vaccinations (poliomyelitis and diphtheria) and poorly known diseases as *Haemophilus influenzae* b meningitis.

Moreover, from the pre-intervention questionnaire it is clear that a certain amount of the sample has many wrong preconceptions about vaccines such as the think that administering multiple vaccines at the same time can be risky for children's health, the fear that vaccines contain harmful substances, the belief that vaccines are primarily an economic affair of the pharmaceutical industries and that some vaccinations can cause diseases as autism, autoimmune diseases, allergies and tumors. Previous studies have shown that these concerns are the cornerstones of the anti-vaccine ideologies that unfortunately built their fortune on the lack of scientific knowledge [13]. For these reasons, we think that fighting these beliefs in healthcare workers could remarkably help in counteracting these dangerous movements and improve the vaccination rate of acceptance in general population. Our intervention was effective not only to decrease but, in some cases, even remove these concerns. The efficacy of our health intervention is also demonstrated by the remarkable differences between pre- and post-intervention questionnaires concerning the knowledge of the mandatory and strongly recommended vaccinations in general population, the strongly recommended vaccinations in pregnancy and the general vaccination beliefs and attitude. Particularly, the knowledge of all mandatory and strongly recommended vaccinations improved and, specifically concerning those strongly recommended in pregnancy, a remarkable result was reached for influenza vaccination. Moreover, the correlation between the score and the years of course shows that, although the vaccination knowledge has improved overtime, it appears necessary integrate the training provided by university with specific meetings and debates on vaccination topics.

Finally, from the declarations about the satisfaction rate, the most part of the sample stated that the intervention

changed some of their beliefs and the entire sample declared that it felt more prepared to answer questions and provide information about vaccinations.

Conclusions

Our study detected some critical issues in the preparation of the enrolled midwives and confirm the importance and necessity to carry out health education campaigns not only to general population [36] but also to health professionals that, for the role they play, they must necessarily be well prepared. Moreover, because previous studies have been shown that students have often a poor general health knowledge [37, 38], in order to increase awareness, we think that it is important to integrate the training provided during university courses with specific intervention, such as tutorial and meetings on vaccinations. Our results show that this methodology is advantageous to improve knowledge and preparation of the audience even with the evident limit presented by such a methodology. Indeed, it is well known that checking knowledge immediately after a training intervention could overestimate the results, assuming that not all information will remain for a long time.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

AD and GV conceived, designed and coordinated the research; AF and GV administered questionnaires and carried out the educational intervention; GV, AF, FM and PL contributed to the acquisition, interpretation of data, identified the endpoints analysed and prepared the figures and tables; AF and GV wrote the paper. All the Authors revised the manuscript and gave their contribution to improve the paper. All the authors read and approved the final manuscript.

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RESEARCH ARTICLE

Feasibility and reliability of the Self Administered Children's Lifestyle Assessment (SACLA), a new tool to measure children's lifestyle behaviors: the VIF Program

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Keywords

Lifestyle questionnaire • Children • Health • Reliability • Feasibility

Summary

Objectives. To develop a self-administered children health-related behaviors assessment, and to test its feasibility and reliability in a group of French children.

Methods. A sample of 216 children participated in the first stage of this study, dedicated to the feasibility assessment. An independent sample of 99 children participated in the assessment of reliability via questionnaire test and retest.

Results. Missing or inappropriate responses on different parts of the questionnaire ranged from 0 to 35%, more evident on the

drink intake and sleep areas. Some questions in fact have been modified or removed. No problems were reported on the dimensions of physical activity habits and sedentary behaviors. The mean percentage of agreement in test-retest reliability for the questionnaire dimensions was 78% (47-99%). Overall, kappa coefficients were good.

Conclusions. This questionnaire is an acceptable and reliable instrument for assessing lifestyle habits in French children.

Introduction

Overweight and obesity in children are considered the main childhood health problem in European countries. In 2010, based on International Obesity Task Force definitions and the World Health Organization's Childhood Obesity Surveillance Initiative, it was estimated that about 25% of European children (aged 6-9 years) were overweight and obese [1]. In a recent systematic review and meta-analysis, a high prevalence of childhood overweight and obesity was reported, although a trend toward stabilization in most European countries was shown [2]. In France, recent data suggested a quite stable prevalence of obesity, with a prevalence of overweight that is declining despite remaining high between 2013 and 2017 [3]. Overweight and obesity in children are associated with adverse health consequences from a physical, social, and psychological point of view [4]. Persistence of obesity into adulthood can also lead to increased morbidity of type 2 diabetes, cardiovascular diseases, cancer, and increased early mortality [5].

This epidemic phenomenon may be partly explained by unhealthy behaviors. Indeed, the roles of dietary and lifestyle factors in obesity, especially sugar-sweetened beverages, poor diet quality, physical inactivity, prolonged screen time, and short sleep duration are important risk factors for being

overweight and obese [4, 6-8]. Many implemented intervention or promotion programs that aim to encourage a healthy lifestyle in children and adolescents have been developed to reduce the prevalence of childhood and adolescent obesity [9]. However, one review concluded that most studies in nutrition education intervention research measured knowledge or behavioral capabilities in preschool and school-aged children, and that most studies assessed knowledge rather than behaviors [10]. In addition, for the assessment of nutrition behaviors in children, most of these measures were based on parental responses [11-14]. Several studies have shown the accuracy of parental responses to their children's nutrition behaviors to be weak to moderate [15-17]. It was thus concluded that relying on such parental responses might hamper researchers' abilities to detect relationships that have policy implications for the child nutrition community [15].

The burgeoning problem of unhealthy behaviors in children and the need for population surveillance have led to the development of a questionnaire on lifestyle habits that includes nutrition, physical activity, sleep patterns, and sedentary behaviors. Therefore, the aim of this study was to develop a Self-Administered Children Lifestyle Assessment (SACLA) questionnaire and to test their feasibility and reliability in a population of French children.

Methods

STUDY DESIGN AND PARTICIPANTS

This ancillary study used data from the *Vivons en Forme* (VIF; “live healthy”) Program. The VIF organization is a continuation of the obesity prevention scheme previously called EPODE (*Ensemble Prévenons l’Obésité des Enfants*), a community-based prevention program aimed at promoting healthier lifestyles among children and their families, and involving municipal services in charge of child education and care [18].

This present investigation is a test-retest study, which involved a portion of the children participating in the VIF Program. The study was conducted between January 2013 and June 2014. The development of the self-reported measure and feasibility assessment were conducted between January 2013 and August 2013; reliability assessment was performed between October 2013 and June 2014.

Six classes of 8-10 year-olds who involved the VIF Program in France participated in the study. An informative letter was given to parents explaining the objectives of the study and a guarantee that the data would remain strictly anonymous and confidential.

A total of 315 participants took part, and sample characteristics are shown in Table I. The reliability study was conducted over a 2-week period, requiring two participant contacts. During the first visit, the selected version of the questionnaire was completed, and demographic data were obtained. Up to 2 weeks later, participants completed the same questionnaire. Both questionnaires were completed by children in class at school under the supervision of a teacher. This study did not involve any intervention, and was conducted on a volunteer basis. Data were retrospectively

collected by the study organizational structure (<https://vivonsenforme.org>). In this context, written informed consent was not required according to French human research regulations. The answers provided by children were anonymous and confidential. This data collection was approved by the French National Commission of the Informatics Personal Data.

QUESTIONNAIRE

The SACLA questionnaire was written by a group of highly skilled professionals with experience of public health studies in nutrition. Before data collection for reliability assessment, an initial pretest questionnaire was completed by a sample of 216 children. This pretest was conducted to evaluate the clarity, comprehensiveness, and acceptability of each question, as well as questionnaire length, and the quality and response rate for each question. Questions were deleted or modified if they were completed by less than 80% of subjects. After each step, appropriate changes were made to produce the final questionnaire.

The final questionnaire consisted of 20 questions divided into four parts:

- *introductory part*: demographic and social information;
- *part one*: dietary habits;
- *part two*: lifestyle habits;
- *part three*: physical activity. The demographic information comprised gender, date of completion, and the class level.

Dietary habits (part one; 11 questions) were assessed by dietary history (closed-ended questions). It was completed by questions about drinking habits and a food frequency questionnaire about consumption of fruit, vegetables, dairy products, sweets, salted snack foods, and type of beverages. Questions about lifestyle habits (part two; 6 questions) were also divided into several sections: (i) sleep habits; (ii) duration and mode of commuting to school (passive or active transport); and (iii) sedentary behaviors. The answers to these questions were a simple choice according to several defined answers. Questions about physical activity habits (part three; 3 questions) were divided into three sections: (i) sport practice; (ii) physical activity during recess; and (iii) child self-perceived levers and brakes of physical activity. Closed-ended questions were also used for this part.

STATISTICAL ANALYSIS

Categorical variables are expressed as percentages. The test-retest reliability was evaluated using the intraclass correlation coefficient (ICC) for quantitative items, simple Cohen’s kappa coefficient for nominal variables, and weighted Cohen’s kappa coefficient for ordinal variables for categorical items [19]. The values of concordance coefficients (ICC and kappa values) are as follows: poor agreement of values < 0.45; average-to-good agreement of values = 0.45-0.75; and excellent agreement of values > 0.75 [20]. Statistical testing was performed at the two-tailed a level of 0.05. Data were analyzed with SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Tab. I. Sample demographic characteristics.

	Phase 1*		Phase 2*	
	N	%	N	%
City				
Total	216	100	99	100
Vitré (Ile et Vilaine)	117	54	-	-
Anzin (Nord)	43	20	-	-
Royan (Charente-Maritime)	56	26	-	-
Roncq (Nord)	-	-	50	50
Saint-Martin-de-Crau (Bouches du Rhône)	-	-	25	26
Vieux-Condé (Nord)	-	-	24	24
Gender				
Boys	95	44	50	51
Girls	121	52	49	49
School levels				
CE2	95	44	55	56
CM1	121	56	44	44
Type of school				
Private	37	17	-	-
Public	136	63	-	-
Priority education area	43	20	-	-

* Phase 1: feasibility study; phase 2: test-retest study.

Results

FEASIBILITY

Missing or inappropriate responses on different parts of the questionnaire ranged from 0 to 35%. Table II shows the rate response mean for each dimension of the questionnaire. The highest proportion of problems was reported on the drink intake dimension. Some questions on this item in fact have been modified or removed. Problems were also reported on sleep dimension (both week and weekend) and least frequently on physical activity habits.

Tab. II. Mean rate response according to each part of the questionnaire.

	Rate response (%)
Part 1: dietary habits	
Breakfast	100
Morning snacking	89.7
Tea time	100
Afternoon snacking	99.0
Snacking front of the TV	99.0
Foods intake	85.8 to 98.0
Drink intake	69.7 to 99.0
Part 2: lifestyle habits	
Sleep Week	72.7
Sleep Weekend	64.6
Mode of commuting to school	94.9
Screen	93.9
Part 3: physical activity habits	
Practice sport	99.0
Recess	98.0
Feeling	94.9

Tab. III. Test-retest reliability of the questionnaire (retest after 2 weeks).

	Number of items	Agreement (%)	Reliability index*
Part 1: dietary habits			
Take Breakfast	1	88.7	0.66 (0.48-0.84)
What	9	75.8 to 88.9	0.62 (0.46-0.76)
Take Morning snacking	1	79.6	0.66 (0.53-0.80)
What	4	85.7 to 98.6	0.70 (0.65-0.91)
Tea time	1	80.8	0.19 (0-0.43)
Afternoon snacking	1	82.6	0.62 (0.46-0.78)
Snacking front of the TV	1	80.6	0.61 (0.45-0.77)
Foods intake	9	42.7 to 64.3	0.40 (0.27 to 0.49)
Drink intake	6	37.2 to 75.5	0.39 (0.18 to 0.56)
Part 2: lifestyle habits			
Sleep week	1	NA	0.37 (0.17-0.52)**
Sleep weekend	1	NA	0.41 (0.23-0.56)**
Mode of commuting to school	1	97.9	0.96 (0.90-1)
Screen	5	91.4 to 92.5	0.83 (0.74- 0.84)
Part 3: physical activity habits			
Practice sport	1	99.0	0.97 (0.92-1)
Recess	1	90.7	0.71 (0.53-0.89)
Feeling	1	95.7	0.58 (0.21-0.95)

NA: not applicable; *Reliability index indicates the Kappa value [95%Confidence interval (CI)] or the median (range) of Kappa individual items values in case of multiple items per dimension unless otherwise as indicated; ** intraclass correlation coefficient (95% CI).

RELIABILITY

Test-retest reliability data for the questionnaire are presented in Table III. Test-retest agreement was observed in 37.2-99.0% of children respondents, with means of 72.1, 91.8, and 95.1% for dietary habits, sedentary behaviors, and physical activity habits, respectively. This agreement is generally confirmed by the kappa coefficients (Tab. III), which were 0.19-0.70 for dietary habits, 0.37-0.96 for lifestyle habits, and 0.58-0.97 for physical activity habits.

Discussion

Dietary intake and physical activity habits are major factors in the development of overweight and obesity. Reliable and valid instruments to measure the effectiveness of counseling on nutrition, physical activity habits, sedentary behaviors, and sleep in children are lacking. To our knowledge, this study is the first to develop a self-reported measure of lifestyle habits (including dietary, sleep, sedentary and physical activity behaviors) in French children, and to test its feasibility and reliability. The main result of our study is that the developed questionnaire can be considered acceptable and reliable for children aged 8-10 years.

Given the multifactorial nature of overweight and obesity, it was necessary to adopt a multidisciplinary approach to questionnaire development that focused on the diverse dimensions that predispose to childhood obesity [4]. Obesity is caused by the combination of a less active lifestyle, including sedentary behaviors, and a failure to reduce energy intake in line with reduced total energy expenditure arising from reduced physical activity [4, 6-8, 21]. In addition, patterns of reduced sleep duration have been reported simultaneously with patterns of increased obesity [22-24]. Many studies show that chronic partial sleep loss may increase the risk of obesity and weight gain [25-26]. Therefore, we

decided to develop a questionnaire with three dimensions: (i) dietary habits; (ii) lifestyle habits (including sedentary and sleep ones); (iii) physical activity. As noted, the majority of studies that assess behaviors in children are based on parental responses with corresponding weak-to-moderate accuracy [11-17]. Therefore, to improve the accuracy of assessment, we developed a questionnaire that was to be completed by the children themselves.

Concerning feasibility, our study clearly shows that the lifestyle questionnaire was easy to complete, with few missing values; it is thus highly feasible for use with children as a lifestyle measure. The very low proportions of missing data may be because a teacher or a trained person was at hand to help if necessary. The highest proportion of problems was reported on the dietary intake dimension. Some questions about drink intake have been modified or removed due to the high percentages of reported problems on these items. The item about the place where children used to have teatime was removed because answers from respondents diverged and the question was not closed-ended. Another difficulty, reported by teachers, concerned the question on snacking in front of the TV. Indeed, 14% of respondents quoted their evening meal and 8% their teatime. Therefore, we decided to develop the answers about snacking further and to formulate this question as closed-ended. The question “during meals at home, what do you drink most often (drink 1 and drink 2)?” has also been modified. The question about the second drink was answered by only 67% of respondents, and many children cited several drinks for their choice of second drink. However, the overall small proportion of missing or inappropriate responses confirmed the feasibility of the lifestyle habits questionnaire. In addition, to improve the comprehensiveness of the questionnaire, some unclear questions have been removed or modified following discussions with teachers and children after completion of the questionnaire.

Another outcome of our study shows fair-to-excellent levels of test-retest reliability of the questionnaire according to the established standards for reliability coefficients [20]. A similar questionnaire developed in the USA also showed moderate-to-strong test-retest reliability, with the retest after 8 weeks [27]. Our good overall reliability might be explained by a teacher being on hand to help children complete the second (retest) questionnaire. Reliability should therefore be tested further in a different context (e.g., without a teacher or trained person).

The current study has strengths and limitations. The main strength is the development of the first self-reported questionnaire of lifestyle habits (dietary, sleep, sedentary and physical activity behaviors) in French children to quickly assess children's nutrition behaviors. Another strength is the diverse population from several schools, although this was limited to a small convenience sample. Thus, the samples included are not necessarily representative of the population of French children as a whole. Regulatory and ethical constraints represent a further limitation of our study. It was not possible to record certain additional clinical data on children, such as body weight, height, and body mass index for this ancillary study; these parameters may have influenced the answers from participants [28, 29]. Moreover,

social desirability (the tendency to respond in such a way as to avoid criticism) and social approval (the tendency to seek praise) might also bias our results [30]. In addition, test and retest might also constantly be answered on the bases of a wrong self-perception. Our results should be taken with caution because an external evaluation is also missing.

Conclusions

Our results support the use of the Self-Administered Children Lifestyle Assessment (SACLA) questionnaire as an acceptable and reliable instrument for assessing lifestyle habits in 8-10 year-old French children. These initial results are promising and suggest that this instrument is suitable for use to compare population estimates of lifestyle behaviors.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Each author of this article contributed significantly to the study. MR and GB designed the research; GB and MR conducted the research; JV and VD analyzed the data; VD and AD performed the statistical analysis; JV wrote the paper; MR had primary responsibility for the final content; all authors read and approved the final manuscript.

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SYSTEMATIC REVIEW

Nursing students' experience of risk assessment, prevention and management: a systematic review

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Keywords

Clinical risk • Patient safety • Nursing students • Nursing curriculum

Summary

Introduction. As a fundamental dimension of quality, the patient safety and healthcare workers safety in the healthcare environment depend on the ability of each healthcare workers (whether administrators or technicians) to reduce the probability of error. This review focused on nursing students. The aim was to assess level and determinants of knowledge about risk assessment, risk prevention and risk management of nursing students.

Methods. A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Two reviewers searched the bibliographic databases Pubmed, Scopus and Cinahl to collect all the available articles in English and Italian issued between 2015 and August 2019. To obtain an exhaustive query of search, the following keywords were combined through Boolean

operators AND and OR: Clinical Risk Assessment, Nursing Education, Nursing Student*, Patient Safety. The authors assessed the quality of the evidence by using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method.

Results. Twelve papers are included. Although the literature on the nursing student's error is limited, their frequencies are worrying. Some authors have created a model of prevention of clinical error based on three level. However, the majority of nursing students don't feel confident with a patient safety. Many authors shown that patient safety education was delivery by lecture, laboratory or simulation sessions.

Conclusions. This review underlines the need to revise the nursing curriculum on patient safety and the need to think what educational methodology is the better for the student to create a safe care.

Introduction

The continuous search of *the best* for the healthcare workers, associated with the best for the citizens, has determined a strong acceleration towards the continuous improvement of the quality of care. Based on the first definition of quality in health care (by Avedis Donabedian), the U.S. Institute of Medicine identifies a quality service with the one that can increase the probability of the expected health outcome, in accordance with the best medical knowledge available.

As a fundamental dimension of quality, the patient safety and healthcare workers safety in the healthcare environment depend on the ability of professionals (whether administrators or technicians) to reduce the probability of error. If in practice the focus has long been on preventing or containing active errors, today we tend to emphasize the need to control risk factors.

Risk is a mathematical concept related to the possibility of suffering a harm in relation to more or less predictable circumstances. This concept, inherent in every human activity, can be translated into the health sector in terms of clinical, occupational, environmental and insurance risk [1, 2].

Clinical risk is closely linked to the healthcare facilities and the "care" provided by healthcare workers. Based on the general definition of risk, the Institute of Medicine (US) Committee on Quality of Health Care defines *clinical risk* as the probability that a patient is a victim of an adverse event, or suffers "any damage or discomfort attributable, even if involuntarily, to medical care provided during the period of hospitalization, which causes an extension of the period of hospitalization, a worsening of health conditions or death" [3].

All the regional, national and international organizations have as their priority objective the risk prevention in the healthcare settings through risk management programs [4], implementing a security model, capable of increasing the levels of control in the face of the impossibility of *zero risk*. In other words, it is legitimate to speak of a risk management system when strengthening analysis systems inspired by these principles [5]. The risk management process can be divided into four phases:

- risk identification, in which the most frequent risks and their specific components are identified;
- risk analysis, with reactive or proactive approach;

- risk treatment. in this phase, specific preventive measures are identified and applied in order to avoid a repetition of the event;
- monitoring.

In order to prevent and promote quality and safe care, local, regional, national and international health care organizations must identify and analyze all system failures. This literature review aims to examine the knowledge and behavior of the nursing student regarding risk identification, risk prevention and risk management.

Methods

STUDY DESIGN

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6] (Supplementary file). The protocol for this systematic review has not been registered or published.

SEARCH STRATEGY

According to the purpose of this review, the authors drafted a protocol based on the Population, Intervention, Outcome and Setting (PIOS) approach:

- P: nursing students;
- I: nursing knowledge or nursing behaviour;
- O: preventing medical error, preventing adverse drug error, patient safety, quality of care;
- S: hospital setting.

This research aims at answering the following questions:

- what behaviours are implemented by nursing students in order to reduce the risk of error?
- are students sensitized to the issue of clinical risk during their education?
- can lack of knowledge or poor knowledge induce to error?
- do a third-year student of a nursing school show more knowledge and appropriate behaviour of clinical risk prevention versus a first-year student?

Two reviewers searched the bibliographic databases Pubmed, Scopus and Cinahl to collect all the available articles in English and Italian issued between 2015 and August 2019. To obtain an exhaustive string search, the following keywords were combined through Boolean operators AND and OR: *Clinical Risk Assessment, Nursing Education, Nursing Student*, Patient Safety*.

INCLUSION AND EXCLUSION CRITERIA OF THE STUDY

The reviewers defined the characteristics that made up the eligibility criteria used to rule in or out the collected studies for this research study.

Inclusion criteria

- Studies focusing on nursing students and clinical risk: their knowledge and behaviour.
- Studies focusing on undergraduate program of clinical risk.

- Papers reporting the adverse drug event or medication error by nursing students.
- Intervention studies, including RCTs, Controlled Clinical Trials (CCTs) and all observational studies (e.g. cohort analytic studies, cross-sectional studies, case-control studies...), reviews.
- Peer-reviewed research articles published in English and Italian.

Exclusion criteria

- Studies focusing on nursing staff.
- Studies reporting the knowledge of nursing student on a specific pathology.
- Grey literature, such as dissertations, conference papers, proceedings etc.

STUDY SELECTION

In the very first phase, the results obtained from the research were imported into Endnote® database, then, duplicates were eliminated and only results in English and Italian were considered.

In the second phase, two authors independently reviewed each article loaded in the database. They first screened the records by reading their titles and abstracts, then, according to the eligibility criteria previously set, they excluded the irrelevant articles, while read the full text of the pertinent papers.

Thanks to this in-depth reading, they were able to exclude those studies that did not focus on clinical risk manager and nursing students.

QUALITY ASSESSMENT

The authors assessed the quality of the evidence by using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method [7].

Table I shows the quality assessment of each study included in the systematic literature review. For each study was reported: title of the article, objective of the study, design of the study, risk of bias, possible lack of reproducibility of the results (inconsistency), possible lack of generalizability (indirectness), imprecision (imprecision), further considerations.

Results

Initially, 336 references were identified, then, after the elimination duplicates, authors selected 12 relevant studies (Fig. 1). The main information concerning the relevant studies has been reported in a data extraction table (Tab. II).

The results obtained from the research of the scientific literature have been organized into three main interest categories, as explained below.

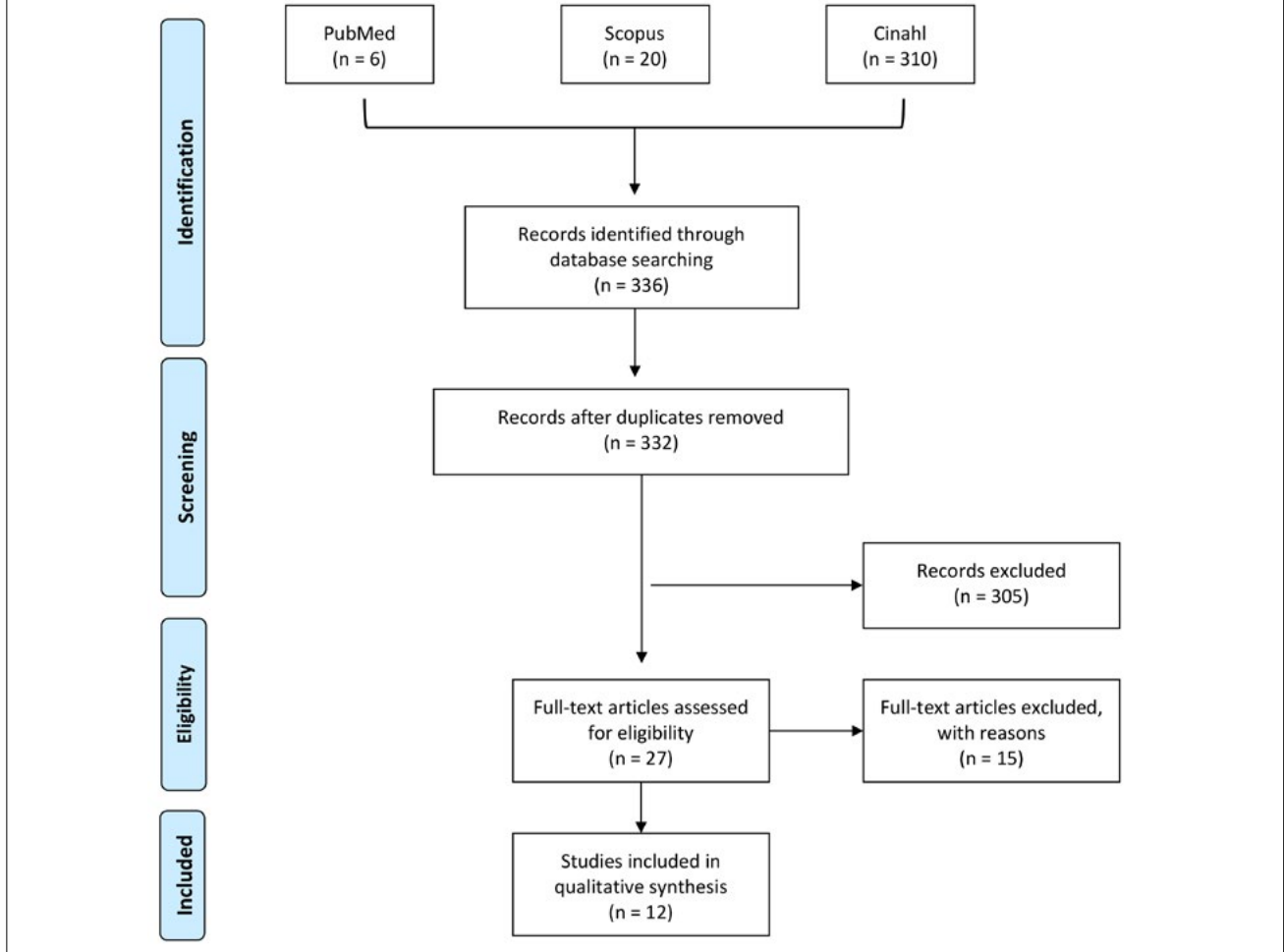
NURSING STUDENT AND CLINICAL ERROR

Although the literature on the nursing student's error is limited, their frequencies are worrying.

Tab. I. Qualitive assessment, grade.

Title of study	Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
A multi-university assessment of patient safety competence during clinical training among baccalaureate nursing students: a cross-sectional study	Assessing nursing students' perceived competencies during clinical education related to patient safety	Observational studies	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ LOW
Are clinical instructors preventing or provoking adverse events involving students: a contemporary issue	Understand the adverse event prevention techniques implemented by nursing students in order to assist clinical instructors and graduate programs in addressing this little-known issue	Observational studies	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ LOW
Self-reported confidence in patient safety knowledge among Australian undergraduate nursing students: a multi-site cross-sectional survey study	Describe the confidence of Australian first-, second-, and third-year nursing students with respect to patient safety knowledge gained in the classroom and clinical setting during the three academic years	Observational studies	Serious	Not serious	Not serious	Not serious	None	⊕○○○ VERY LOW
Knowledge and competence with patient safety as perceived by nursing students: the findings of a cross-sectional study	Describe nursing students' perceptions of their own knowledge and skills in patient safety and describe any differences between first, second, and third year students	Observational studies	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ LOW
Preregistration nursing students'perceived confidence in learning about patient safety in selected Kenyan universities	Assess theoretical and practical learning of skills related to patient safety as perceived by nursing students	Observational studies	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ LOW
Effects of a patient safety course using a flipped classroom approach among undergraduate nursing students: a quasi-experimental study	Examining the effects of a course on patient safety among nursing students in South Korea	Quasi-experimental study	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ HIGH
Patient safety education and baccalaureate Nursing students'patient safety competency: a cross-sectional study	Determine how and the extent to which patient safety education was provided and evaluate the competency of nursing students	Observational studies	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ LOW
Regulation and current status of patient safety content in preregistration nurse education in 27 countries: findings from the Rationing-Missed nursing care (RANCARE) cost ACTION Project	Establish how patient safety-related teaching is incorporated into undergraduate courses in 27 countries	Observational studies	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ LOW
Nursing students'interprofessional educational experiences in the clinical context: findings from an Italian cross-sectional study	Explore nursing students' interprofessional educational experiences and explore the factors supporting them	Observational studies	Serious	Not serious	Not serious	Not serious	None	⊕○○○ VERY LOW
The influence of situation awareness training on nurses' confidence about patient safety skills: a prospective cohort study	Understand senior nursing students' confidence in their patient safety skills; examine the impact of training on students' situational awareness	Observational studies	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ LOW
Nontechnical skills training and patient safety in undergraduate nursing education: a systematic review	Synthesize available evidence regarding nontechnical skills training to improve patient safety in undergraduate nursing education	Systematic review	Not serious	Not serious	Not serious	Not serious	None	⊕⊕○○ LOW
The attitudes of nursing students and clinical instructors towards reporting irregular incidents in the medical clinic	Examine why students and nurses do not report errors and whether they believe internal changes may increase reporting	Observational studies	Serious	Not serious	Not serious	Not serious	None	⊕○○○ VERY LOW

Fig. 1. PRISMA 2009 flow diagram (from: Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med 2009;6:e1000097, mod. For more information: www.prisma-statement.org).



In Turkey, about 39% of the students surveyed reported that they made an error during their nursing student internship, without harming the patient. In Italy, 29% of the students interviewed participated in or witnessed an adverse event, with a risk of harm to the patient in 85% of cases [8, 9]. Only a percentage between 25 and 40% of errors committed by students are appropriately reported; the rest remain silent due to a strongly punitive culture [8, 10]. A study conducted in 2019 estimates that the 11 and 27% of nurses would not report error or near misses because of the circumstances in which they occurred or because of lack of awareness, such as “reporting is not necessary because no harm has been caused”. A percentage between 22 and 33% of nurses, however, would not report them because of fear of consequences, such as “I cannot report anonymously” or “I am afraid of disciplinary action” [10]. The risk of error is increased by the students’ perception of “unsafe” clinical environment: high workloads, lack of nursing staff, frequent interruptions are described as the main causes of insecurity by the students [9]. The most reported events are represented by adverse events related to the administration of drugs, accidental falls, errors during blood samples.

Based on these observations and on the conceptual model of prevention developed by the WHO, Christensen [11] has developed a three-level model of error prevention:

- *primary prevention*: constant and in-depth training and education, creation of a culture of patient safety and quality of care; creation of a culture of safe learning is one that treats students fairly, observes mistakes, has accessible and acceptable leadership, involves students in decisions, promotes teamwork and trust, encourages questions;
- *secondary prevention*: replaces the “failure” of the first level. Where the error occurs, the tutors are responsible for guiding the student. A debriefing between the tutor and the student is useful, during which the latter can discuss his/her emotions, his/her reaction to the error; then, together, one can consider the changes that could be made to avoid the error;
- *tertiary prevention*: that includes first a rethinking of the didactic systems and an orientation of the didactic programs to the safety of the treatments and to the management of the error. Educational methodologies such as simulation are encouraged.

Tab. II. Data extraction table.

Author(s) and year of publication	Title	Materials and methods	Main findings	Conclusions
Alquwez, et al. (2019)	A multi-university assessment of patient safety competence during clinical training among baccalaureate nursing students: a cross-sectional study	Descriptive, cross-sectional, multi-university study	The percentage of agreement on the items of the health professional education in patient safety survey ranged from 61.5-76.5%. The dimension "understanding human and environmental factors" received the highest perceived competence, whereas the dimension "working in teams" received the lowest competence. Significant differences in students' patient safety competence from different universities were reported. Male students perceived their competence in "working in teams" higher than the female students. Students in their internship year had significantly higher levels of competence in all the six dimensions of the health professional education in patient safety survey than students in the third- and fourth-year levels	Saudi nursing students have positive perceptions towards their patient safety competencies. Significant differences were found in the patient safety competence of nursing students between universities, gender and year of study
Christensen (2018)	Are clinical instructors preventing or provoking adverse events involving students: a contemporary issue	Contemporary issues	This article proposes a framework to begin to understand nursing student error prevention, with the aim to assist clinical instructors, nursing faculty, and nursing leaders in addressing an unrecognized aspect of adverse events. If the three levels of disease prevention (primary, secondary, and tertiary) are adapted to understand nursing student error prevention, then the following framework emerges: a) primary prevention: creating a safe learning culture; b) secondary prevention: reducing the negative impact of errors on students; c) tertiary prevention: participating in systemic efforts to reduce the established problem	Clinical instructors have the capacity to create a safe learning culture, guide their students through the experience of making an error, and participate in processes that reduce them in the future
Usher, et al. (2017)	Self-reported confidence in patient safety knowledge among Australian undergraduate nursing students: a multi-site cross-sectional survey study	Multi-site, cross-sectional study used a web-based survey	Participants were most confident in their learning of clinical safety skills and least confident in learning about the sociocultural dimensions of working in teams with other health professionals, managing safety risks and understanding human and environmental factors. Only 59% of students felt confident they could approach someone engaging in unsafe practice, 75% of students agreed it was difficult to question the decisions or actions of those with more authority, and 78% were concerned they would face disciplinary action if they made a serious error	Patient safety voice develops and strengthens over nursing students' course of study and clinical placements, however it is concerning that a large proportion of students express difficulty in questioning the decisions or actions of those in authority positions and concerns about disciplinary action if errors are made. The integration of patient safety into nursing curricula and resulting teaching and learning strategies to facilitate student knowledge and competence is still in its infancy

Continues

Follows

Tab. II. Data extraction table.

Author(s) and year of publication	Title	Materials and methods	Main findings	Conclusions
Stevanin, et al. (2015)	Knowledge and competence with patient safety as perceived by nursing students: the findings of a cross-sectional study	Cross-sectional study	A total of 573 students (response rate 92.4%) participated. Around a quarter (28.8%) of students reported having experienced an adverse event or close call during their clinical experience. The settings where they learn were perceived as unsafe by 46.9% of students. PS knowledge and competence as perceived by students, was high (median = 4) in all factors and dimensions of the H-PEPSSIta tool. High PS knowledge and competence was reported by first-year students, moderate by second-year students and higher at the end of the third-year	Faculties and health-care institutions offering clinical placements have to share the responsibility of well-prepared future nurses, working together to improve PS through dialogue when issues are identified by students
Mbuthia, et al. (2019)	Preregistration nursing students' perceived confidence in learning about patient safety in selected Kenyan universities	Cross-sectional descriptive study	The students reported higher confidence about learning on the clinical aspects than on the sociocultural issues of patient safety with the lowest mean scores recorded in "Understanding human and environmental factors" and "Recognising, responding and disclosing adverse events". They reported significantly higher confidence scores in the classroom setting than the clinical setting with no significant difference in reported confidence across the years of study. They were less confident in speaking up about patient safety issues in the clinical areas with 52.2% feeling that reporting a patient safety problem will result in negative repercussions	The patient safety culture in the clinical placements sites needs to be conducive to enable, and not hinder, the acquisition of these competences
Kim, et al. (2019)	Effects of a patient safety course using a flipped classroom approach among undergraduate nursing students: a quasi-experimental study	Pre- and post-test quasi-experimental design with a non-equivalent control group	Pre- and post-test results demonstrated a significant increase in students' patient safety competency including attitude, skills, and knowledge. Mean scores of patient safety competency in the experimental group were significantly higher than in the control group	The flipped-classroom patient safety course was shown to be effective in improving patient safety competency in terms of attitude, skills, and knowledge among undergraduate nursing students
Lee, et al. (2016)	Patient safety education and baccalaureate nursing students' patient safety competency: a cross-sectional study	Cross-sectional study	The majority of students (81.6%) reported that they had received patient safety education during coursework. Patient safety education was delivered primarily by lecture rather than during laboratory or simulation sessions. The degree of coverage of QSEN competency and the students' self-reported competency in total and attitude scores showed statistical differences among nursing schools. Students' attitude score was significantly higher than skill and knowledge	This study confirm the need to revise the nursing curriculum and to use various teaching methods to deliver patient safety education more comprehensively and effectively. Furthermore, there is a need to develop an integrated approach to ensuring students' balanced competency

NURSING CURRICULUM AND PATIENT SAFETY

Patient safety and healthcare workers safety in the healthcare facilities is struggling to enter in educational programs despite its obvious importance [12]. This is confirmed by a survey conducted in Australia, according to which while on the one hand the general

concepts of clinical safety and effective communication were well rooted in nursing students, on the other hand they suffered from a knowledge gap on issues such as teamwork, risk management, knowledge of factors that increase clinical safety [13]. In addition, 78% of the respondents highlight the difficulty of reporting due to a punitive culture of error [14].

In summary, clinical safety competencies include safety during drug preparation and administration; infection prevention and control; surgical patient safety; and safety in invasive procedures. In addition, socio-cultural patient safety competencies must be implemented, including patient-centered care, teamwork, collaboration, evidence-based practice, improvement of quality, safety and information technology [15].

Nevertheless, the literature is unclear about duration, content, teacher qualification and teaching methods, as they vary for each study; it is therefore difficult to determine which is the best option to implement a safety course.

Through a further study conducted in South Korea in 2016 [16], nursing students from various universities were interviewed. More than 80% of the sample said they had experience in the field of patient safety. 85% of the students received knowledge about this topic through simple lessons, while 76% received it in clinical practice. The courses that dealt most with patient safety both in lessons and in practice were nursing, adult nursing, and management. Nevertheless, the topic was treated differently in different universities, showing statistically significant differences. Students were then asked to determine which subjects related to the skills needed to ensure patient safety had been covered in the curriculum. They stated that patient-centered care was the highest competence in the programs, with 97%; followed by evidence-based practice (90%), information technology (90%), teamwork and collaboration (84%), safety (84%), quality implementation (80%). These competences were mainly dealt with during the lessons, and little through simulations or workshops. 20% of the students stated that these competences were not treated during the of study.

The same conclusion was reached by the study conducted in Kenya in 2019 [15]: students learned more about patient safety in education than in clinical practice. This shows that there is a problem with the application of theoretical aspects in the practical context. In addition, the students were more confident with the clinical aspects of safety and less confident with the socio-cultural elements, which are key skills. Finally, the sample interviewed reported that patient safety aspects were not sufficiently covered in their study plan and do not feel confident about patient safety in clinical settings. A study carried out in 2019 aims to establish how teaching related to patient safety is incorporated into university courses in 27 countries [8]. This was done by examining how much and how each key topic identified by WHO is integrated into academic nursing education. Most of the respondents agreed that the topics were present at various levels in the training. Key topics such as safety in therapy management, infection control, or even introductory topics such as “what is patient safety” are integrated into programs of various subjects and are not treated as stand-alone topics in specific safety modules. For example, on the topic “infection prevention and control”, 98% of respondents indicated that it is present in academic programs, however only 16 universities treat it as an autonomous subject, while 51 reported that the topic is integrated throughout the university curriculum.

Similar results can be observed with the topic “safety in the management of drug therapy” [17].

NON-TECHNICAL SKILLS

An area that receives little attention is represented by non-technical skills (e.g. situation awareness), which relate to the way healthcare workers communicate and cooperate with each other. Emphasizing the importance of these skills is crucial, as estimates suggest that 70-80% of errors are the result of a lack of non-technical skills [18].

Through a literature review conducted in 2018 [19], it was possible to identify which non-technical skills were most frequently evaluated to improve patient safety:

- *communication*: the elements of communication skills are: sending and receiving information; clear and concise presentation of information, including therapeutic communication, listening, empathy, verbal and nonverbal communication; identification and elimination of barriers to effective communication;
- *awareness of the situation*: the elements required are: collection, recognition and understanding of information; anticipation of future events; awareness of patient safety;
- *decision-making process*: the elements of decision-making capacity are defined as: identification of various possible options, risk assessment and selection of options, re-evaluation/revision of results, definition of problems, process for reaching a decision;
- *leadership*: the main elements are: establishing and maintaining standards, supporting other team members, using strategies to cope with stress and pressure;
- *teamwork*: the main elements are: support to other workers, exchange of information and accurate reporting of news, coordination of team activities; assessment of roles and capabilities, conflict resolution. It has been documented that the collaboration of other professionals and the use of care models based on teamwork improve the quality and safety of care. Opportunities for interprofessional experience are not included in university programs, so student nurses reported only a few opportunities to have meaningful contacts with other health professionals during their education. As a result of this, students show little competence in teamwork. Among the factors that threaten the integration of interprofessional experiences in clinical training were: the organizational level, the management level, the practical level such as lack of time the cultural level such as a different perception of teamwork or a potential risk of superiority of one profession over the others. 40% of Italian students interviewed reported that “never” or “just a little” had the opportunity to learn from other professionals during their last clinical traineeship.

Discussion and conclusions

The picture provided by the literature is very clear: in the clinical practice, most students do not know what to

do to deal with the clinical risk, in order to ensure the safety and quality of care. The students are divided on the aspects concerning the presence of topics related to clinical risk in the university teaching modules. Even if they come from the same university and even from the same course, the opinions of the students appear to be in contrast. This could be because the subjects are not treated as autonomous subjects in the university career, but as many small teachings that integrate with each other over the academic years. So, it is up to the student to join these pieces and “create a module” on the clinical risk itself.

From here it is normal if the students of the same course do not show the same knowledge, the same attitudes and the same behaviours related to clinical risk and patient safety. The situation is made worse by the absence of practical simulations that provide for dealing with an error, a near miss, an adverse event. This obviously translates into the inability, in clinical practice, to identify an error, to report it in an appropriate way, and to implement behaviours aimed at its resolution.

From the studies analysed, it is doubtful whether the implementation of courses, seminars or, more generally, any educational intervention in addition to the basic university preparation is effective. Research shows an increase in knowledge and a greater awareness of clinical risk between pre and post educational interventions, and between control groups and experimental groups. But this occurs in the immediate post-operative period. Studies do not assess whether this knowledge is retained by the students in time. Therefore, it is not possible to conclude whether educational interventions are valid or not.

Indeed, some studies evaluate the Theory of planned behaviour related to patient safety among nursing students [20]. “For many students reporting an error would lead to a loss of trust in the nursing profession and this could prevent the report. Nevertheless, some of them affirmed to be positively judged when they did it. It was then observed that a better education on safety raised the level of self-confidence and the sense of responsibility of the students, making them more inclined to the drug therapy management” [20].

This review has limitations. One limit is the methodology with which the studies were conducted. Most of them are observational studies in which the survey of knowledge and skills was carried out through a written questionnaire given to the students, so it is not possible to assess the truthfulness of the answers given. Consequently, even the results derived from it do not allow to create with certainty, but with probability, the scenario described.

Although wandering is human, the analysis of global university contexts suggests increasing the knowledge about clinical risk and safety of care. Studies agree to implement these notions especially in nurses, because it is those health professionals who are closest to the patient, both in terms of physical proximity and in terms of time. Nurses also approach the patient holistically, so that care is expressed not only in the physical field, but also psychically and socially. Therefore, the complexity

of care is very high, and this requires extensive, solid knowledge, supported by scientific evidence, which will result in appropriate behaviour not only to prevent any risk, but also to deal with it once it has occurred [21].

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: MDM; Visualization: NG; Data curation: GBO, EDS, SD, GN; Funding acquisition: none; Methodology: MDM, NG, CN; Project administration: MDM; Visualization: GBO, MDM; Writing original draft: MDM, EDS ; Writing review & editing: NG, SD, CN.

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Supplementary file: PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	E1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	E1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	E1-E2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	E1-E2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	E2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	E2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Available upon request
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	E2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	E2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	E2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	E2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	E2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis).	E2
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	E2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	E2-E7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	E2-E7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	E2-E7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	E2-E7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	E2-E7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	E2-E7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	E2-E7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	E7-E8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	E7-E8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	E7-E8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	E8

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RESEARCH ARTICLE

Prevalence of consumption of psychoactive substances among construction workers

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Keywords

Construction workers • Addictive substances • Use • Misuse • Morocco

Summary

Introduction. The prevalence of psychoactive substance is constantly increasing in developing countries, and all occupational sectors are concerned. Construction sector is a particular target because of the heavy workload as well as family and social isolation. However, few studies have investigated toxic habits in this population in Morocco. The aim of this study was to determine the prevalence of addictive substances consumption, use, and misuse amongst construction workers and to appreciate the poly-consumption according to socio-demographic and occupational parameters.

Methods. This cross-sectional study was conducted amongst 1,128 construction workers. The interview with each person took place at occupational health service during his medical examination. The questions were formulated orally in French and/or in Arabic. The questionnaire covered socio-demographic and occupational parameters, toxic habits (tobacco, alcohol, cannabis and others psychotropic substances). The misuse was assessed by spe-

cific tests: dependence on smoking tobacco (Fagerstrom), Cannabis Abuse Screening Test (CAST) and Alcohol Use Disorders Identification Test (AUDIT).

Results. The prevalence of consumption was 47.9% for smoking tobacco, 12.7% for cannabis, and 20.1% for alcohol. Amongst consumers, the prevalence of dependence or misuse was 68% for smoking tobacco, 70.6% for cannabis and 63% for alcohol. 42.7% of construction workers had no toxic habit, 36.1% one toxic habit, 16.3% two toxic habits, 4.8% three toxic habits and 0.1% four toxic habits. The most frequent associations were tobacco-alcohol (8.1%) and tobacco-cannabis (3.7%).

Conclusions. Occupational health physicians have to play a key role in raising awareness and fighting against toxic habits. The prevention approach needs a cooperative spirit. It will be more accepted and applied if all construction workers and their representatives are involved in its elaboration.

Introduction

The prevalence of toxic habits is constantly increasing in developing countries and all occupational sectors are affected [1]. Construction workers are a particular target because they are exposed to strong psychosocial and organizational constraints related to difficult working conditions and financial difficulties, with a lack of employment prospects. This laborious activity, with job stressful demands, painful postures, atypical schedules and the distance of the family unit requires courage and strong involvement of the workers [2, 3]. Like immigrants, construction workers of rural origin have manual, tiring and dangerous activities (the so-called “3D Jobs”, *dirty, dangerous, difficult*), characterized by very intense rhythms, long hours of work and low income [4].

Moreover, the consumption habits of psychoactive substances are esteemed, or at least largely tolerated. Non-consumption can sometimes be a cause of exclusion aggravating then the social and family isolation of workers. This collective consumption being part of the sociability of the group, is a tool of discussion and debate about work’s difficulties [5, 6].

All psychoactive substances cause impaired alertness, a change in risk perception and/ or increased risk taking with consequences in terms of public health, prevention and work safety [7]. Work under the influence of illegal or legal psychotropic substances is an important cause of work-related accidents. Eighty two percent of workers in the construction sector reported injuries in the previous 12 months [8]. Several epidemiological studies have shown a positive association between their consumption and the risk of accidents at work in the building sector [9-11]. Security in construction is very worrying around the world. While much has been done to improve safety and health in developed countries, construction remains one of the most dangerous sectors because of its association with a high incidence of death and injury. According to global estimates by the International Labor Organization (ILO), more than 600,000 deaths have been reported each year in the construction sector [12]. The US Bureau of Labor Statistics reported that the highest number of fatal injuries among all sectors during the 2014 period occurred on construction sites, with at least 899 fatal workplace injuries [13].

However, few studies have focused on the evaluation of toxic habits in this population in Morocco. The aim of this study was to determine the prevalence of addictive substances consumption, use, and misuse amongst construction workers and to appreciate the poly-consumption according to socio-demographic and occupational parameters.

Methods

SUBJECTS

This observational and cross-sectional epidemiological study was conducted during in the 2017 and took place in a large building company of great works in Casablanca and Rabat. This survey involved all construction workers over 20 years old with at least two years of length of employment. The 1,128 employees were men and subdivided into three socio-occupational categories: 206 construction laborers (unskilled personnel), 802 bricklayers or masons (qualified personnel), and 120 foremen (supervisory personnel).

QUESTIONNAIRE

We used an individual questionnaire, which included sociodemographic (age, family status, and educational level) and occupational parameters (length of employment, working rhythm, and daily working time) and toxic habits: tobacco, cannabis, alcohol and others psychoactive substances. For the socio- occupational category, we have individualized construction laborers, bricklayers and foremen. The construction laborers (maneuvers) were defined as the people who work on site to do the physical work. The bricklayers (masonry workers) were defined as the workers using bricks, stone, concrete, and other materials. The construction foremen were supervising all aspects of the work. For tobacco smoking, we have individualized current smokers, former smokers and non-smokers. Subjects were categorized as current smokers if they smoked at the time of the survey or if they had stopped less than three months before the study and had smoked more than 100 cigarettes during their lives. Former smokers were those who stopped more than three months before the study and smoked more than 100 cigarettes during their lives. Non-smokers are those who have never smoked or smoked less than 100 cigarettes during their lives [14]. We quantified tobacco consumption in pack-years (number of packs smoked per day multiplied by number of years of smoking). To assess the dependence of cigarette smokers, we used the Fagerstrom test [15, 16]. The items were summed to give a total score of 0 to 10. The ordering of dependence was very low (0 to 2), low (3 to 4), moderate (5 to 6), high (7 to 8) and very high (9 to 10). For cannabis smoking, in the same way, we have categorized our population to current consumers, former consumers and non-consumers. We quantified the consumption in calumet-years. Among cannabis smokers, we used

the Cannabis Abuse Screening Test (CAST) [17, 18]. This test includes six items. To calculate a score, the responses are coded on a scale from 0 to 4. The total score obtained can range from 0 to 24 and indicates whether or not the questioned users are at risk. A score less than 3 indicated no addiction risk, a score of 3 or less than 7 indicates low addiction risk, and a score of 7 or above indicates high addiction risk.

Alcohol consumption was quantified in number of standard drinks per day. A standard drink contains a fixed amount of pure alcohol, *i.e.* 10 g. A standard drink is equivalent to 10 cl of table wine at 12°, 25 cl of beer at 5°, 3 cl of whiskey at 40°, and 7 cl of aperitif at 18°. Among drinkers, we have appreciated the risky consumption (abuse and/or dependence) by the Alcohol Use Disorder Identification Test (AUDIT) [19-21]. This test is a 10-point screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, alcohol-related behaviors and alcohol-related problems. A score of 8 or higher indicates the dangerous or harmful alcohol consumption. According to WHO, risky consumption can cause serious damage in the medium and long term. It corresponds in men to more than 3 standard glasses per day or to more than 21 standard glasses per week or to more than 4 standard glasses per drinking occasion.

We defined the use as a moderate or occasional consumption with a low risk to health, and the misuse is a consumption that may cause physical, social and / or psychological troubles. The misuse includes hazardous or spot abuse, harmful or repeated abuse, and addiction. We considered misusers as:

- dependent cigarette smokers with Fagerstrom test score higher than or equal to 5;
- addiction cannabis smokers with a CAST score higher than 7;
- risky alcohol consumers having a score higher than or equal to 8 (AUDIT test) or meeting WHO criteria (more than 4 glasses per drinking occasion or more than 21 glasses per week).

PROCEDURE OF THE STUDY

We previously contacted the human resource manager and the occupational physician to explain the purpose of the study and obtain their agreement and support. The interview with each worker took place at occupational health services and was carried out in the respect of the confidentiality after his information on the interest of our study. It lasted between 15 and 20 min for each person. The questions were formulated orally in French and/or in Arabic.

STATISTICAL ANALYSIS

The statistical analyses were performed using the SPSS version 11.5 software package. The differences between groups were compared using t tests for continuous variables and chi-square tests for categorical ones. The statistical level of significance was established at 5%. For a proportion, we calculated the lower and upper limits of the 95% confidence intervals (CI).

Results

RELATIONSHIP BETWEEN SOCIODEMOGRAPHIC PARAMETERS AND TOXIC HABITS (TAB. I)

The average age of total population was 34.6 ± 7.1 years. 41.2% were living alone and 52.8% in couple. 22% were illiterate, 46.7% had attended primary school, 25.9% secondary school, and 5.3% college or university. In general, the laborers were illiterate or had a primary educational level, the bricklayers had a primary or secondary educational level, and the foremen had a high educational level.

For tobacco smoking, the prevalence of current users was 47.9%, 95% CI (45, 50.8), former users 12.2% and never users 39.9%. For tobacco snuff, the prevalence of current users was 13.5%, 95% CI (11.5, 16.4), former users 7% and never users 79.5%. For hookah, the prevalence of current users was 8.7%, 95% CI (7, 10.4), former users 4.1% and never users 87.2%. For cannabis smoking, the prevalence of current users was 12.7%, 95% CI (10.7, 14.6), former users 12.5% and never users 74.8%. For alcohol consumption, the prevalence of current users was 20.1%, 95% CI (17.7, 22.4), former users 14.9% and never users 65%. For other psychotropic substances, the prevalence of current users was 2.8%, 95% CI (1.8, 3.7), former users 2.2% and never users 95%.

The average age of tobacco smokers was 34 ± 6.1 years, hookah smokers 28.2 ± 4.4 years, tobacco sniffers 37.6 ± 6.4 years, cannabis smokers 33.5 ± 6.2 years, alcohol consumers 33.8 ± 5.1 years and other psychotropic substances users 41.1 ± 8.9 years.

The prevalence of tobacco smoking (49.4 vs 43%; $p = 0.075$), cannabis smoking (13.9 vs 8.9%; $p = 0.041$) and alcohol consumption (22.6 vs 12.2%; $p < 0.0001$) was higher among construction workers under 40 years. The prevalence of hookah (11.3 vs 0.4%; $p < 0.0001$), tobacco snuff (24.1 vs 10.1%; $p < 0.0001$), and psychotropic

substances consumption (6.3 vs 1.6%; $p < 0.0001$) was higher in subjects over 40 years. The prevalence of toxic habits was higher among people living alone.

The prevalence of toxic habits (tobacco smoking, tobacco snuff, hookah, cannabis smoking and alcohol consumption) was lower among those with a superior educational level except for hookah and psychotropic substances.

The average age of onset of smoking tobacco was 13.9 ± 2.6 years, cannabis smoking 17.3 ± 3.3 years, alcohol consumption 18.7 ± 3.6 years, tobacco snuff 28.3 ± 6.5 years, hookah 17.8 ± 4.6 years, and other psychotropic substances 31.2 ± 2.6 years.

The average daily amount of tobacco smoking was 14 ± 5.9 cigarettes, of shisha 1.2 ± 0.6 , of tobacco snuff 17 ± 5.6 , of cannabis smoking 16 ± 5.8 calumets, and of alcohol 2.9 ± 0.6 drinks.

The harmfulness of tobacco smoking to health was known by 88% of construction workers, alcohol by 75%, cannabis by 55%, tobacco snuff by 25%, and hookah by only 15%. 94% of tobacco sniffers were former tobacco smokers. The hookah was considered safer for health by 82% of consumers who believed that dangerous substances smoked were filtered by water.

Attempts of weaning more than 2 days of abstinence were made by 63.1% of tobacco smokers, 76.8% of alcohol drinkers, 25.9% of cannabis smokers, 42% of hookah smokers and 32% of tobacco sniffers.

RELATIONSHIP BETWEEN SOCIO-OCCUPATIONAL PARAMETERS AND TOXIC HABITS (TAB. II)

The occupational categories were bricklayers (71.1%), construction laborer (18.3%) and foremen (10.6%). The average length of employment was 10.9 ± 5.3 years. The average length of employment was 10.2 ± 4.9 years for cigarette smokers, 6.9 ± 4.1 years for hookah smokers, 11.4 ± 5.2 years for tobacco sniffers, 7.6 ± 4.4 years for cannabis smokers, 10.6 ± 4.3 years for alcohol

Tab. I. Relationship between socio-demographic parameters and toxic habits.

	N 1,128	TS 540 (47.9)	S 152 (13.5)	H 98 (8.7)	C 143 (12.7)	A 227 (20.1)	OPS 31 (2.7)
Age (years)							
< 30	450 (39.9)	182 (40.4)	25 (5.6)	68 (15.1)	41 (9.8)	93 (20.6)	6 (1.3)
30-39	408 (36.7)	242 (59.3)	62 (15.2)	29 (7.1)	78 (17.3)	101 (24.3)	8 (1.9)
40-49	213 (18.9)	101 (47.4)	63 (29.6)	1 (0.4)	24 (11.2)	29 (13.6)	9 (4.2)
≥ 50	57 (5)	15 (26.3)	2 (3.5)	0 (0)	0 (0)	4 (7)	8 (14)
< 40	858 (76.1)	424 (49.4)	87 (10.1)	97 (11.3)	119 (13.9)	194 (22.6)	14 (1.6)
≥ 40	270 (76.1)	116 (43)	65 (24.1)	1 (0.4)	24 (8.9)	33 (12.2)	17 (6.3)
Family status							
Lives alone	465 (41.2)	238 (51.1)	73 (15.7)	77 (16.5)	77 (16.5)	120 (25.8)	18 (3.9)
Lives in a couple	663 (58.8)	302 (45.5)	79 (11.9)	21 (3.1)	66 (9.9)	107 (16.1)	13 (2)
Children and/or dependents							
Yes	637 (56.5)	249 (39.1)	74 (11.6)	17 (2.7)	69 (10.8)	70 (11)	22 (3.5)
No	491 (32.3)	291 (59.3)	78 (15.9)	57 (16.5)	74 (15.1)	157 (32)	9 (1.8)
Educational level							
Illiterate	249 (22)	130 (52.2)	68 (27.3)	4 (1.6)	14 (5.6)	46 (18.5)	4 (1.6)
Primary	527 (46.7)	267 (50.7)	65 (12.3)	45 (8.5)	72 (17.9)	99 (18.8)	14 (2.6)
Secondary	292 (25.9)	131 (44.8)	18 (6.2)	44 (15)	42 (14.4)	70 (23.9)	11 (3.8)
Superior	60 (5.3)	12 (20)	1 (1.7)	5 (8.3)	0 (0)	12 (20)	2 (3.3)

TS: tobacco smoking; S: snuff; H: hookah; C: cannabis; A: alcohol; OPS: other psychotropic substances.

Tab. II. Relationship between socio-occupational parameters and toxic habits.

	N 1,128	TS 540 (47.9)	S 152 (13.5)	H 98 (8.7)	C 143 (12.7)	A 227 (20.1)	OPS 31 (2.7)
Occupational categories							
Construction laborer	206 (18.3)	99 (48.1)	28 (13.6)	11 (5.3)	25 (12.1)	32 (15.5)	4 (1.9)
Bricklayers	802 (71.1)	396 (49.4)	107 (13.3)	34 (4.2)	101 (12.6)	158 (19.7)	17 (2.1)
Foremen	120 (10.6)	45 (37.5)	17 (14.2)	53 (44.2)	17 (14.2)	37 (30.8)	10 (8.3)
Length of employment (years)							
< 5	348 (30.8)	186 (53.4)	32 (9.2)	51 (14.7)	70 (20.1)	76 (21.8)	5 (1.4)
5-15	436 (38.7)	213 (48.9)	69 (15.8)	41 (9.4)	58 (13.3)	94 (21.6)	12 (2.7)
>15	344 (30.5)	141 (41)	51 (14.8)	6 (1.7)	15 (4.3)	57 (16.6)	14 (4.1)
Work schedule							
Typical	927 (82.2)	435 (46.9)	132 (14.2)	54 (5.8)	97 (10.4)	176 (19)	12 (1.3)
Atypical	201 (17.8)	105 (52.2)	20 (9.9)	44 (21.8)	46 (22.9)	51 (25.4)	19 (9.4)
Weekly working time							
≤ regulatory working time	267 (23.7)	119 (44.6)	22 (8.2)	30 (11.2)	44 (16.4)	62 (23.2)	9 (3.3)
> regulatory working time	861 (76.3)	421 (37.3)	130 (11.5)	68 (6)	99 (8.8)	165 (14.6)	22 (2.6)

TS: tobacco smoking; S: snuff; H: hookah; C: cannabis; A: alcohol; OPS: other psychotropic substances.

consumers, and 13.7 ± 5.9 years for other psychotropic substances consumers.

RELATIONSHIP BETWEEN SOCIODEMOGRAPHIC PARAMETERS AND MISUSE (TAB. III)

The average age of people who misuse was 34.7 ± 5.8 years for tobacco smokers, 35.3 ± 4.5 years for cannabis smokers and 32.8 ± 6.7 years for alcohol consumers.

The misuse was more frequent in people over 40 years old for tobacco smoking (73.3 vs 66.5%; $p = 0.201$), alcohol consumption (75.7 vs 60.8%; $p = 0.149$) and cannabis smoking (91.7 vs 66.4%; $p = 0.025$).

For tobacco smoking (85.7 vs 54%; $p < 0.0001$) and alcohol consumption (65.8 vs 59.8 %; $p = 0.426$), misuse was more frequent in people living alone, but for cannabis (74.2 vs 67.5%; $p = 0.489$) misuse was more frequent in people living in couple.

For the three habits, the misuse was more frequent in people with secondary education level for tobacco smoking (92.4 vs 60.1%; $p < 0.0001$), primary education

level for cannabis smoking (75.9 vs 64.2%; $p = 0.126$) and illiterates ones for alcohol consumption (84.8 vs 57.5%; $p = 0.001$).

RELATIONSHIP BETWEEN SOCIO-OCCUPATIONAL PARAMETERS AND MISUSE (TAB. IV)

The average length of employment of people with misuse was 10.8 ± 4.9 years for cigarette smokers, 7.5 ± 4.1 years for cannabis smokers and 11.9 ± 5.1 years for alcohol consumers.

For the cannabis smokers, misuse was significantly more common among bricklayers than other occupational categories (73.3 vs 43.5%; $p < 0.0001$). The misuse of tobacco smoking (73.3 vs 67.5%; $p = 0.627$) and alcohol consumption (75.7 vs 60.5%; $p = 0.117$) was slightly higher among the foremen.

The prevalence of misuse was slightly higher among those working more than 8 h for cannabis smokers (74.7 vs 61.4%; $p = 0.145$) and alcohol consumers (64.2 vs 59.7%; $p = 0.637$).

Tab. III. Relationship between socio-demographic parameters and misuse.

	TS 367/540 (68)	C 101/143 (70,6)	A 143/227 (63)
Age (years)			
< 30	109/182 (59.9)	23/41 (56.1)	67/93 (72)
30-39	173/242 (71.5)	56/78 (71.8)	51/101 (50.5)
40-49	72/101 (71.3)	22/24 (91.7)	23/29 (79.3)
≥ 50	13/15 (86.7)	0 (0)	2/4 (50)
< 40	282/424 (66.5)	79/119 (66.4)	118/194 (60.8)
≥ 40	85/116 (73.3)	22/24 (91.7)	25/33 (75.7)
Family status			
Lives alone	204/238 (85.7)	52/77 (67.5)	79/120 (65.8)
Lives in a couple	163/302 (54)	49/66 (74.2)	64/107 (59.8)
Children and/or dependents			
Yes	243/249 (97.6)	59/69 (85.5)	39/70 (55.7)
No	124/291 (42.6)	42/74 (56.8)	104/157 (66.2)
Educational level			
Illiterate	87/130 (66.9)	9/14 (64.3)	39/46 (84.8)
Primary	151/267 (56.5)	66/87 (75.9)	59/99 (59.6)
Secondary	121/131 (92.4)	26/42 (61.9)	38/70 (54.3)
Superior	8/12 (66.7)	0(0)	7/12 (58.3)

TS: tobacco smoking; C: cannabis; A: alcohol.

Tab. IV. Association between socio-demographic parameters and misuse.

	TS 367/540 (68)	C 101/143 (70.6)	A 143/227 (63)
Length of employment (years)			
< 5	101/186 (54.3)	46/70 (65.7)	31/76 (40.8)
5-15	159/213 (74.6)	48/58 (82.8)	63/94 (67)
> 15	107/141 (75.9)	7/15 (46.7)	49/57 (86)
Average	10.8 ± 4.9	7,5 ± 4.1	11.9 ± 5.1
Occupational categories			
Construction laborer	47/99 (47.5)	17/45 (37,7)	18/32 (56.3)
Bricklayers	287/396 (72.5)	74/101 (73.3)	97/158 (61.4)
Foremen	33/45 (73.3)	10/17 (58.8)	28/37 (75.7)
Daily working (h)			
8	81/119 (68.1)	27/44 (61.4)	37/62 (59.7)
> 8	286/421 (67.9)	74/99 (74.7)	106/165 (64.2)

TS: tobacco smoking; C: cannabis; A: alcohol.

Tab. V. Prevalence of toxic habits and their associations.

Frequency	Toxics	N = 1,128
0 toxic habit 482 (42.7)	-	482 (42.7)
1 toxic habit 407 (36.1)	T C A P	347 (30.8) 5 (0.4) 44 (3.9) 11 (0.9)
2 toxic habits 184 (16.3)	T + C T + A T + P A + P A + C	42 (3.7) 91 (8.1) 5 (0.4) 5 (0.4) 41 (3.6)
3 toxic habits 54 (4.8)	T + C + A T + C + P	45 (4) 9 (0.7)
4 toxic habits 1 (0.1)	T + C + A + P	1 (0.1)

T: tobacco smoking; C: cannabis; A: alcohol; P: other psychotropic substances.

PREVALENCE OF TOXIC HABITS AND THEIR ASSOCIATIONS (TAB. V)

Among total population, 42.7% had no toxic habit, 36.1% one toxic habit, 16.3% two toxic habits, 4.8% three toxic habits and 0.1% four toxic habits. The most frequent associations were tobacco-alcohol (8.1%) and tobacco-cannabis (3.7%).

Discussion

In 2014, the Moroccan National Observatory for Drugs and Addictions reported that the prevalence of tobacco smoking and alcohol consumption among Moroccan male population in general aged 20 and over was 34.5% and 14% respectively [1]. In our study, the prevalence of these harmful habits was higher: 47.9% for tobacco smoking, 8.7% for hookah, 13.5% for tobacco snuff, 12.7% for cannabis smoking, 20.1% for alcohol consumption, and 2.8% for other psychotropic substances consumption. The National Institute for Prevention and Education for Health in France (INPES) ranked the construction sector at the first places in consumption of toxic substances with global monthly prevalence of 32.7% [22].

The construction sector, maritime sector, catering, arts and entertainment were at the top of the pyramid of psychoactive substances consumption [2].

Construction workers would smoke more than the general population for a number of reasons and a combination of several factors including stress, strong psychosocial and organizational constraints related to difficult working conditions and financial difficulties, with a lack of employment prospects. This laborious activity, with heavy workload (painful postures, long hours working, atypical schedules, outdoor working in inclement weather), and the family and social isolation requires courage and strong involvement of the workers [4, 5, 23]. Occupational stress appears as a possible risk factor exposing to toxic habits. In construction sector, stress is born of a high psychological demand, low decision latitude and insufficient social support, aggravated by arduous and dangerous working conditions [24]. Construction workers are among the categories the most exposed to various occupational hazards (physical, chemical, biological, ergonomic and psychological) [23]. This professional sector is more likely to incur occupational injuries, even fatal, and to develop respiratory and dermatological diseases [25]. Moreover, the consumption habits of psychoactive substances are largely tolerated, and non-consumption can sometimes be a cause of exclusion aggravating the social and family isolation of workers. This collective consumption being part of the sociability of the group is a tool of discussion and debate about work's difficulties [5]. Among male construction workers, being resident in Spain for 7 years and sharing a home with friends are the most associated risk factors for increased alcohol consumption [23].

According to the INPES 2010 Health Barometer, 36.2% of regular smokers, 9.3% of alcohol users and 13.2% of cannabis users reported having increased their consumption as a result of problems related to their work in the last 12 months [22]. However, these results should not obscure the fact that professional activity overall remains a protective factor against addictive behavior, compared to an unemployment situation [26, 27].

In the Moroccan general population, a study conducted by the Ministry of health reported that the prevalence

of tobacco smokers was 32% among men: 35.2% among those aged under 45s and 23% among those over 45s [28]. In our study, the prevalence for these age groups was higher: 49.4 and 43% respectively.

International studies among construction workers conducted in many countries have shown a high prevalence of consumption of psychoactive substances. For Tobacco smoking, the frequency was 46.7% in Algeria [27], 51% in Australia [10], 45.3% in France [2], 43.3% in USA [11], and 49.1% in Hong Kong [9]. According to a study led in New Delhi (India) among the construction workers, 91% were tobacco users and among them 49% were using smokeless tobacco, 29% were cigarette smokers, and 22% were smokers and tobacco chewers [29].

In no Muslim countries, the consumption of alcohol is a sociocultural lifestyle and widely prevalent among population. In Morocco, the purchase, sale and consumption of alcohol are legally prohibited to Muslim people but in practice everyone can buy it. The prevalence of its consumption in Australian population was 82.4% [10]. In USA, 20% of construction workers reported drinking every day and 29.5% mentioned binge drinking five or more times in the past 30 days [11]. In France, 32.7% of construction workers reported binge drinking in the past month [2]. In our study, lower prevalence (20.1%) can be explained by underestimation related to religious, cultural and legal considerations. Islam prohibits alcohol consumption and related issues are taboo.

Cannabis is the illicit drug most used in the world [16, 17, 30]. Socio-geographical, economic and cultural factors play an important role in its consumption. Cannabis is grown mainly in northern Morocco and consumed in all the country because it is cheaper than manufactured tobacco. Although its production, distribution, sale and consumption are legally forbidden [1]. The prevalence of its consumption in our study (12.7%) was similar to the one found in France (13%) [31], and lower than the one reported in Australia (30.5%) [10]. The survey on the cannabis consumption in the building sector in 2010, has showed that 13% of building employees consume cannabis daily, almost twice as much as the rest of the workforce (6.9%) [22].

Water pipe is known under different names in parts of the world: hookah, narghile, shisha or goza. It is now the object of a renewed interest because its use has been spreading very fast among young people in Western countries and in Morocco. The number of cafes and establishments where the water pipe can be smoked is increasing and are attended mostly by young people. The arguments they use for justifying water pipe smoking are the "natural", health and safety aspect of the product, its fruity flavors (apple, strawberry etc.), the sharing of the dose enhancing a sense of community belonging, the novelty of the product, and a distinction from the smoking habits of adults. The conviction is that water acts as a filter and that this way of smoking tobacco is less dangerous than cigarette smoking. In our study, the hookah prevalence was 0.4% among those over 40 years vs 22.2% among the under 40s, that confirmed the recent craze for this habit imported from the Middle East and considered nowadays as a world epidemic [32, 33].

The use of other drugs (anxiolytic, antidepressant) by construction workers is difficult to assess, because they are used without medical advice [8, 9, 34, 35]. The literature suggests that drug abuse remains high in this population. Drug use includes not only the consumption of illicit drugs but also the misuse of prescription drugs such as sedatives, painkillers and stimulants [36, 37]. The construction community is more likely to experiment with cocaine and hallucinogenic mushrooms [21, 38]. The prevalence of this consumption in our study (2.8%) was much lower than that reported by the US (17%) and French (13.7%) surveys [2, 39, 40].

The prevalence of consumption of psychoactive substances is inversely proportional to socio-economic status [11]. The consumption of harmful habits among our construction workers living alone was higher than that of workers living in a couple, except for cannabis. Living alone will be a source of social stress [27]. In our study, the prevalence of toxic habits was higher among people with low levels of education except for psychoactive substances. The MARTA survey conducted among the Moroccan population showed that the prevalence of cigarette smokers was inversely associated with the level of education among men. Thus, the risk was higher among illiterate men than among those with a university level of education [12]. The lower-educated and lower-income construction workers had higher smoking rates [41].

Five surveys carried out in different occupational sectors in Morocco: fishermen [42], health care workers [43], dockers [44], truck drivers [45] and taxi drivers [46], have shown that the construction workers were:

- in second position for alcohol consumption: 20.1 vs 36.6, 9.6, 16.5, 11.8 and 10.5% respectively;
- in third position for:
 - cannabis smoking: 12.7 vs 36.2, 3.3, 9.1, 11.7 and 18.4% respectively,
 - tobacco smoking: 47.9 vs 58.5, 17.1, 30.5, 49.6 and 36.6% respectively;
- and in last position for consumption of other psychotropic substances: 2.8 vs 9.3, 11.6, 3.2 and 4% respectively.

A French survey aimed at estimating the excess of a tobacco-related pathology expected in occupational populations had shown that the study of mortality in the construction industry found an excess of deaths from bladder cancer of 28%, while the expected tobacco excess is 8% [47]. According to the GAZEL cohort, certain work constraints increase alcohol consumption: outdoor work (more than half of working time), work in a painful or tiring posture, exposure to vibrations, heavy loads, long, tiring or fast movements [24]. There seems to be a multifactorial relation in which biological, psychological, cultural and social factors intervene. Some authors have associated hazardous alcohol consumption with the type of work [48]. Construction and agriculture, both open to the inclement weather, traditionally offer hard work conditions, and ingestion of alcohol before beginning work is a common habit [23]. The harmfulness of tobacco smoking to health was

known by 88% of our construction workers. In an American study, 43.5% of construction workers thought that smoking should be allowed, and only 30.7% thought that smoking had a harmful effect on their safety [9]. In our study, snuff was considered less harmful to health than tobacco smoking, and usually as a weaning of tobacco smoking. The harmfulness of alcohol to health was known by 75% of our construction workers, while all Latino masons had limited knowledge of what constituted unhealthy drinking, and few could identify strategies to reduce their consumption [49]. However, an Italian study has shown a reduction in average alcohol consumption among building workers over the past ten years, but confirmed the correlation between the frequency-severity of accidents, absenteeism and average consumption alcohol [49].

In our study, the prevalence of misuse was 68% for tobacco smoking, 70.6% for cannabis smoking and 63% for alcohol consumption. These frequencies would be significantly higher than those of the general population reported by the Moroccan Observatory for Drugs and Addictions with 2% for alcohol abuse, 3.3% for toxic substances abuse and 2.8% of misuse of toxic substances [1].

The frequency of misuse of alcohol among our construction workers (63%) was significantly higher than those reported in the literature: 38% in Australia [10], 30% in India [29], 21.3% in Italy [50], 12.4% in the United States [11] and 6.8% in Hong-Kong [9]. This dependence was more widespread among our construction workers aged between 40 and 50 (79.3%), the illiterate (84.8%), and with seniority over 15 years in 86% of cases and with atypical hours in 76.5%. The most frequent associations were tobacco-alcohol (8.1%), tobacco-cannabis-alcohol (4%) and tobacco-cannabis (3.7%). Our results were similar to those of the 2014 health barometer of the INPES: association of tobacco-alcohol concerned 6.2%, and tobacco-cannabis-alcohol 1.8% [2, 20].

The consumption of psycho-actives substances is an alarming problem of public health and occupation safety, and has an impact on occupational and social life. Unfortunately, we do not have any Moroccan statistics on occupational injuries related to alcohol and drug use but we have some figures on road accidents. The latter are very costly because of human and material losses and the Moroccan roads are among the deadliest in the world. A vehicle kills approximatively 10 times more than in France or in the United Kingdom. Speeding, non-compliance with traffic laws and the use of psychoactive substances are the main causes of these accidents. The human factor is responsible of more than 80% of road accidents and alcohol is responsible of 3 to 11% of road accidents [46]. Alcohol is a recognized leading contributor to road accidents. Several legal texts about the fight against the consumption of addictive substances exist in Morocco. The physical and mental fitness of the construction workers is stipulated in Law 65-99 of the Labor Code, and in its application texts [51, 52]. Construction workers are subject to occupational health

Laws (Articles 304-341 of the Labor Code) and must undergo a medical examination for fitness for work by an occupational physician. The prevention of addictive behavior and its penalties are detailed in the Law related to the Penal Code and the Law related to the Commerce, Detention and Use of Poisonous Substances [53]. This latter Law combines the medical care of the consumers and the judicial repression of the dealers. Article 177 of the law related to the Traffic Code deals with screening and criminal sanctions for driving under the influence of alcohol, narcotics or some medications that are contraindicated while driving.

Our study presents two main limitations. Our survey was cross sectional, the healthy worker effect could create a selection bias. The weak points of self-reporting must be underlined especially for the consumption of psychoactive substances, mainly for alcohol. The prevalence of alcohol consumption was probably underestimated because the Muslim religion of our subjects prohibits its consumption, and the related issues remain taboo. There was no solution to avoid or limit individual variation in self-reporting. The target was a global quantification and approach. However, this study can be considered a faithful representation of the situation in Morocco.

Conclusions

Occupational health services are one of the pillars for conducting early interventions for prevention. In fact, work is the ideal place for the homogeneity of the population concerned, the free access to all employees and the possibility of follow-up activity. Construction workers are a population at high risk of psychotropic substances use. Collective and individual prevention measures and actions aimed at screening and increasing awareness are needed. The elaboration of the prevention approach needs a cooperative spirit. It will be more accepted and applied if all construction workers and their representatives are involved in its preparation. The occupational health physicians have to play a key role in the development and implementation of this preventive approach. The support and specialized care facilities must be available to ensure individual attention and early treatment when necessary. The implementation of information and sensitization about the danger of the consumption of psychotropic substances must be based on the result of prevalence surveys.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

OL: conception, execution; wrote the paper, interpretation of data. NM: conception, execution; wrote the paper. SL: conception, execution; wrote the paper. RH: conception, execution. FD: conception, execution; wrote the paper. CL: conception, execution; wrote the paper, interpretation of data.

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RESEARCH ARTICLE

Days away from work injury and associated factors among waste collectors in Mekelle city, Northern Ethiopia

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Keywords

Days away from work injury • Waste collectors • Mekelle

Summary

Introduction. In most cities of low-income countries, waste management is a labour intensive task, which exposes workers to numerous occupational hazards. This study was aimed to investigate the magnitude of days away from work-related injury and associated factors among organized waste collectors in Mekelle city, Northern Ethiopia.

Method. A pre-tested questionnaire and observation checklist based cross-sectional study design was employed from June 1 to 30, 2017. Data was analysed using SPSS for windows 20.0. Descriptive statistics and logistic regression methods were used to describe the study population and assess the association between dependent and independent variables, respectively.

Result. From the total of 279 waste collectors involved as a study participant, 10% of them reported at least one day away from

work injury during the last twelve months. Being married is 87% less likely to be injured as compared to be a single. The odds of injury were 4.5 times higher among personal protective equipment users as compared to their counterparts. Waste collectors, who had less than 1000 Birr per month income, were 3 times more likely to be injured than those with income greater than 1,001 Birr. **Conclusions.** Days away from work injury among waste collectors is a public health problem and has an impact on the economic and social well-being of workers. Therefore, strengthening the provision of personal protective devices and ensuring its utilization is highly recommended.

Acronyms and abbreviations

DAFWI: Days Away from Work Injury
ECSA: Ethiopian Central Statistical Agency
ILO: International Labor Organization
ICC: Intra-class Correlation Coefficient
GNP: Gross National Product
PPE: Personal Protective Equipment
SPSS: Statistical Package for Social Science
SME: Small Scale Enterprises
WHO: World Health Organization

Introduction

Occupational injury is a major problem in many economic sectors and affects large numbers of workers [1, 2]. About 30-50% of the worker's working place is unsafe and the majority proportion of the global workforce has no access to occupational health services which is a contributing factor for work related injury [3, 4]. International labor organization (ILO) estimated that globally, 320,580 fatal injuries taken place due to occupational exposure [5]. In addition to its public health impact, occupational injury has a socio-economic importance due to loss of workdays, long term disabilities, reduced work ability and capacity due to partial disabilities, premature

retirement from work and deaths [2, 5]. More than six million workers are absent four or more days from their workplace due to occupational injury [6]. In sub-Saharan Africa, about 42 million work-related accidents take place that cause at least three days' absence from work [7]. Study conducted in Zambia reported from 4,998 (8.1%) injured study participants, 60.5% of them reported having stayed away from work as a result [8]. The economic costs of work related illness, injuries and death is massive at individual, enterprise, national and global levels. Roughly more than 4% of global GNP every year losses is estimated due to compensation, lost working time, interruption of production, training and retraining, medical expenses, and so on [7, 9]. This is more economical burden for developing countries as 70% of the world working population live in [9].

Studies revealed that the cause and the magnitude of occupational injuries depend on factors such as: sex, age, work experience and working hours, job satisfaction, educational status, type of work and working condition [2]. Though occupational injury has profound health and economy impact, it remains neglected in developing countries, where only 5-10% of the workers have access to occupational health services because of social, economic, and political challenges [9]. Occupational health research in developing countries is unable to recognize the social and political context of work

relations and lack political commitment to translate scientific findings into effective policies [1]. In Ethiopia, workplace related illnesses and injury represent a major public health concern due to rapid expansion of industrialization. Ethiopia will have a major shift towards industrialization in the coming decades [6]. Occupational diseases and injuries globally are known to affect the GDP due to economic losses for compensations and medical expenses, although this contribution in the Ethiopian context is not yet known. Information on occupation-related diseases and injury or accident is not well organized or systematically recorded, evaluated, or monitored in the Ethiopian work setting. In developing countries including Ethiopia, waste management procedures are characterized by a dominance of manual labor tasks, which therefore exposes waste professionals to a number of occupational hazards of variable nature, occurring at every stage of the waste management process [6, 10-13]. Several studies noted that working as a waste collector is associated with a high risk of occupational injuries [13-18]. A study done in Addis Ababa shows an overall occupational injury prevalence rate among waste collectors in the last 12 months was 383 (43.7%). Utilization of personal protective devices and family size in the household were statistically associated with injury [6]. However, prevalence of occupational alone injuries does not clearly indicate its severity which can be indicated by the loss of workdays due to occupational injury. Moreover, there is no comprehensive study on occupational health hazards among small scale organized micro enterprise in Mekelle city where there are a number of workers engaged in the collection of solid waste. Thus, the study was aimed to investigate the magnitude of injury that involves lost workdays and associated factors.

Methods

Study Area and Design Cross-sectional study design was used to determine prevalence day away from work injuries and associated factors in Mekelle City. Mekelle is located in northern Ethiopia (783 km away from Addis Ababa). The city is located between latitude of 13°32' north and longitude of 39°28' with a total population of 215,546 and an annual growth rate of 5.4% is among the fastest growing cities in Ethiopia [19]. The daily solid waste generation rate is 0.22 kg/c/d. The municipality was able to collect only 33.4% of the total waste generated [20]. Currently, the solid waste collection system in the city is based on door to door collection of micro and small-scale enterprises. In general, there are eight micro and small enterprises engaged in solid waste management. The waste collectors were involved in house-to-house waste collection, street sweeping, and sorting at the dumping site. The majority of the waste is decomposable which directly transported and disposed to a fenced dumping site.

POPULATION

The source and study population for this study were all waste collectors engaged in solid waste collection of the city. Individual workers who have a minimum of 12 months' work experience were included.

SAMPLE SIZE DETERMINATION

There were 315 workers and of those, 279 were eligible for the study, i.e. they work for more than 12 months in the enterprises. All the eligible 279 waste collectors were volunteer and recruited to participate in the study.

DATA COLLECTION PROCEDURES AND QUALITY CONTROL

Structured questionnaire and observational checklist were used to collect data related to socio-demographic characteristics, occupational injury, previous occupational history and illness, smoking history, type and use of personal protective devices, training about occupational health and safety of the waste collectors.

The questionnaire was first prepared in English and translated into the local language (Tigrigna). The consistency of language translation was checked by translating back from Tigrigna into English. To evaluate and confirm the content of the data collection tool, pre-test was done on 5% of the questionnaire out of the study site before the main data collection and, some questions were modified before the actual data collection. On top of this, half day training was given for the data collectors and supervisors on the purpose of the study, content of questionnaires, and data collection process and techniques. The whole data collection process was supervised and monitored the principal investigator.

Face and content validity of the tool was determined based on the viewpoints of the experts to evaluate the validity and reliability of the questionnaire. Test-retest reliability of the tool was examined by pre-testing the tool on 5% of the sample size in a similar context. Therefore, the questionnaire was reviewed and analyzed for repeatability and internal consistency aspects. Cronbach's alpha coefficient was used to assess internal consistency and said to be internally consistent if a score of 0.8 and above. Repeatability was estimated using the intra-class correlation coefficient (ICC). Based on ICC reliability ranges of less than 0.4 (poor), 0.4-0.7 (fair to good), 0.6-0.8 (good), and 0.8-1 (excellent), the reliability of the questionnaire was considered excellent.

OPERATIONAL DEFINITION

Injury

Work related physical damage to body tissues as the result of exposure to occupational hazards.

Days-away-from-work injuries

The self-reported injuries that cause workers absent from work at least one day beyond the day of the event in the last twelve months prior the data collection.

Micro and small enterprise

Small scale unions that are organized by the government and involved in waste management activities.

STATISTICAL ANALYSIS

The collected data were entered to SPSS version 20.0 for analysis. Descriptive statistics like frequency distribution, mean, graphs were computed to explain the study population in relation to relevant variables. An association between dependent and independent variables was presented using odds ratios and 95% confidence intervals. Both Bivariate and multiple logistic regressions were used to test the association between the outcome and independent variables. Variables which had association at $P < 0.2$ during the bivariate analysis were a candidate to multiple logistic regressions.

Results

SOCIO-DEMOGRAPHIC CHARACTERISTICS

A total of 279 waste collectors were participated in this study. Female waste collectors account 69% of the respondents. The mean age of the respondents was 33.70 (± 12.245) years. Almost 63% of the respondents completed primary school. Almost, 93% of respondents were not permanently employed. The majority (68.8%) of the respondents were street sweepers. Regarding income, 63% of the respondents have a monthly income ranged from 500 to 1,000 Ethiopian Birr (Tab. I).

Tab. I. Socio-demographic characteristics of waste collectors in Mekelle city, June, 2017.

Variable	Category	Frequency	Percent
Sex	Female	194	69.5
	Male	85	30.5
Age	18-25	90	32.3
	26-35	79	28.3
	36-45	71	25.4
	> 45	39	14
Religion	Orthodox	265	95
	Muslim	10	3.6
	Catholic	2	0.7
	Protestant	2	0.7
Educational status	Primary school (1-8)	178	63.8
	Secondary school (9-12)	80	28.7
	Certificate and above	2	0.7
	Can read and write	19	6.8
Marital status	Single	101	36.2
	Married	92	33
	Divorced	65	23.3
	Widowed	21	7.5
Employment pattern	Permanent	21	7.5
	Temporary	258	92.5
Job category	Street sweeper	192	68.8
	Waste collectors	87	31.2
Income	< 500	74	26.5
	500-1,000	176	63.1
	1,001-1,500	29	10.4

Tab. II. Occupational behavior and work environment of waste collectors in Mekelle city, June, 2017.

Variable	Category	Frequency	Percent
Working experience	5 and less than 5 years	231	82.8
	Greater than 5 years	48	17.2
Working hours	8 and less than 8 hours	230	82.4
	Greater than 8 hours	49	17.6
Regular supervision of workplace	Yes	18	6.5
	No	261	93.5
Presence of hazard	Yes	231	82.8
	No	48	17.2
Had safety training	Yes	89	31.9
	No	190	68.1
PPE utilization	Yes	182	65.2
	No	97	34.8
Job satisfaction	Yes	171	61.3
	No	108	38.7
Type of PPE used	Glove	179	64.2
	Face mask	51	18.3
	Boot	93	33.7
	Other	92	33
Reason for not using PPE	I do not have	9	3.2
	No provision	72	25.8
	It doesn't need always	9	3.2

WORK ENVIRONMENT AND WORKER'S OCCUPATIONAL BEHAVIOUR

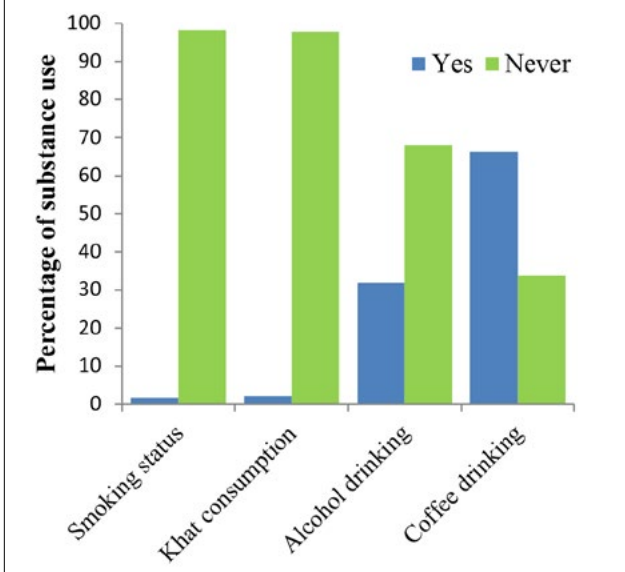
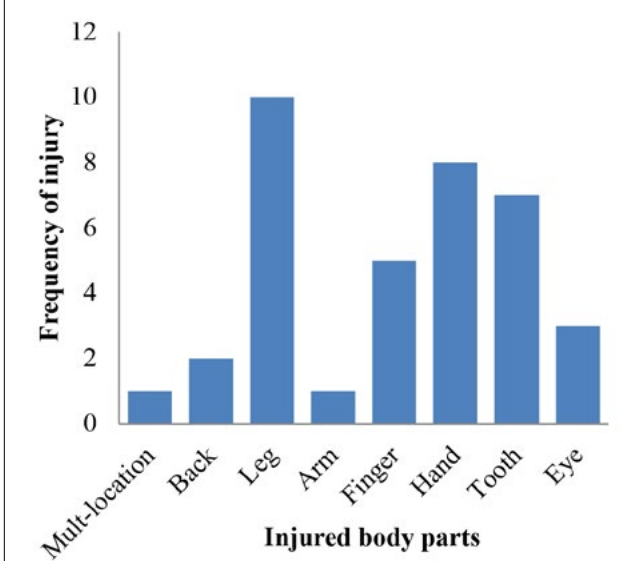
The majority (82%) of the respondents had five and less than five years' experience and worked eight and less than eight hours per day. Out of the 279 respondents, 93.5% of them reported their workplace was not regularly supervised. Presence of hazard was observed in 82.8% of the study participant's work place. About 31% of the respondents reported that no safety training was given during their employment time. Among the respondents, 65% of them were used at least one type of personal protective equipment (PPE). Glove (64.2%), face mask (18.3%) and boot (33.7%) were the commonly used type of personal equipment by the respondents. Lack of availability of PPE (25.8%) was the main reason reported for not using personal protective equipment (Tab. II).

Substance use

In the last twelve months, 89 (31.9%) and 185 (66.3%) of the respondents had a history of alcohol and coffee consumption respectively. However, around 98% of the respondents never had a history of smoking and "Khat" consumption (Fig. 1).

WORK RELATED INJURY

Of the 279 respondents, 29 (10.4%) respondents were reported at least one day away from work injury in the last twelve months. Leg and hand were the most reported injured body part of the waste collectors. Regarding the type of injuries, out of the respondents who had an occupational injury in the last twelve

Fig. 1. Substance use of waste collectors in Mekelle City, 2017.**Fig. 2.** Injured body part of waste collectors in Mekelle City, 2017.

months, eighteen respondents reported abrasion type of injury, two respondents reported fracture type of injury, one respondent reported cut type of injury and one respondent reported puncture type of injury. Waste collection (11 respondents) and Loading and unloading (10 respondents) were the major activities performed during injury time of solid waste collectors (Fig. 2).

Table III shows the distribution of occupational injuries in season and days. More injuries were occurring during winter (70%). Tuesday and Monday were the days that more injuries are occurring as it is reported by 9 and 8 respondents, respectively. Fifteen and ten respondents reported the injury were happening in the morning and at noon, respectively (Tab. III).

Tab. III. Season, day and time of Injury among waste collectors in Mekelle city, June 2017.

Variable	Category	Frequency
Day of injury	Monday	8
	Tuesday	9
	Wednesday	1
	Thursday	2
	Friday	1
	Saturday	1
	Sunday	1
	Don't remember	4
	Total	27
Time of injury	Morning	15
	Noon	10
	Afternoon	1
	Evening	1
	Total	27

FACTORS ASSOCIATED WITH OCCUPATIONAL INJURY

From all variables entered in the final multivariable model fitted for occupational injuries, sex, marital status, PPE utilization and income were remained significant after adjusting for other independent factors. Female were 96% less likely to be injured as compared to male (AOR = 0.04, 95% CI: 0.008-0.204). Being married is 87% less likely to be injured as compared to being a single (AOR = 0.130 95% CI: 0.027-0.621). The odds of DAFW injury were 4.5 times higher among those who do not use PPE as compared to their counterparts (AOR = 4.514 95% CI: 1.684-12.095). Waste collectors, who had less than 1000 Birr income, were 3 times more likely to be injured than waste collectors who had greater than 1001 Birr per month income (AOR = 3.008 95% CI: 1.081-8.371 (Tab. IV).

Discussion

This study revealed that the magnitude of days away from work injury was found to be 10.4%, which is relatively low compared to other previous studies [6, 15, 21, 22]. Besides the exclusion of injuries without lost workdays, the discrepancy could be due to difference in waste collection and segregation practices plus the utilization of PPE by waste collectors. Moreover, the majority of the participants of this study are street sweepers which are relatively less exposed to occupational injury.

Almost all the waste pickers involved in this study had experienced an injury that made them at least one day away from their work. This is probably due to the nature of the work and manually picking important materials from unsegregated wastes without personal protective equipment, which is common practice in most of low income countries [13, 23, 24].

In this study, abrasion was commonly reported type of injuries. Likewise, abrasion was reported as common type of injury in Addis Ababa waste collectors [6]. This is probably due to the effect of collecting, picking and transporting of unsegregated wastes that contain sharp

Tab. IV. Factors associated with occupational injuries among municipal solid waste collectors in Mekelle City, June, 2017.

Variable	Category	Occupational injury		COR (95% CI)	AOR (95% CI)
		Yes	No		
Sex	Male	24	61	1	1
	Female	5	189	14.872 (5.439-40.662)	0.04 (0.008-0.204)**
Age	18-30 years	24	112	7.500 (1.719-32.720)	0.774 (0.052-11.563)
	31-40 years	3	68	1.544 (0.250-9.531)	2.070 (0.205-20.945)
	Above 41 years	2	78	1	1
Marital status	Single	23	78	1	1
	Married	3	89	0.114 (0.033-0.395)	0.130 (0.027-0.621)**
	Divorced	2	63	0.108 (0.024-0.474)	0.666 (0.082-5.405)
	Widowed	1	20	0.170 (0.022-1.332)	1.201 (0.092-15.611)
Job category	Street sweepers	6	186	1	1
	Waste collectors	23	64	11.141 (4.342-28.586)	1.289 (0.145-11.469)
Job satisfaction	Satisfied	12	159	1	1
	Not satisfied	17	91	2.475 (1.132-5.414)	1.288 (0.451-3.682)
PPE Utilization	Yes	13	173	1	1
	No	16	77	2.765 (1.268-6.030)	4.514 (1.684-12.095)**
Income	Less than 1,000	19	110	2.418 (1.081-5.411)	3.008 (1.081-8.371)**
	1,001 and above	10	140	1	1
Working Hours	≤ 8 hours	20	210	1	1
	> 8 hours	9	40	2.362 (1.003-5.562)*	1.279 (0.456-3.590)
Alcohol drinking	Yes	12	77	1.586 (0.722-3.481)	1.724 (0.607-4.892)
	No	17	174	1	1
Coffee drinking	Yes	12	173	0.314 (0.143-0.690)*	2.790 (0.870-8.946)
	No	17	77	1	1

* Significant at $P < 0.05$ for COR; ** Significant at $P < 0.05$ for AOR; PPE: Personal protective Equipment; COR: Crude Odds Ratio; AOR: Adjusted Odds Ratio; CI: Confidence Interval; 1: reference.

objects such as tin, broken glass, bones, metal and other building materials [13, 25-27].

With respect to the injured body part, legs and hands are commonly injured body parts. Our result is comparable with other studies [6, 21]. Manually; loading, uploading and picking of wastes without wearing appropriate glove and shoes can increase the probability of a cut, bruises and ruptures [28].

This study found injury is less likely to occur in female as compared to male. This is attributed to the job category of respondents as more women were involved in street sweeping. With respect to the marital status, being married is less likely to be injured as compared to be a single. The reason is that married individuals have extra family responsibility and then they can take care of themselves. The occurrence of occupational injuries is significantly associated with monthly salary of the workers. This finding is in agreement with a study conducted in Ethiopia [6, 22]. This finding is not surprise, as individuals with higher salary have a better chance to buy and properly use personal protective equipment. This study revealed that occupational injury is significantly related to utilization of personal protective equipment. This was in agreement with the finding of other studies [6, 14, 22]. Proper utilization of PPE such as heavy-duty glove and boots will prevent a work related injury.

Female waste collectors were higher than male waste collectors (street sweeping) in our study. This finding is supported by other studies in other part of Ethiopia [6, 15]. The reason for this might be improving the livelihood

of women is the priority issue in developing countries and subsequently, this work sector is an emerging and categorized as one of small scale enterprises in which females can involve easily and actively due the nature of the work and the societal role expectations assigned to the different sexes [29, 30].

Self-reported data unsupported by clinical investigation were collected, which is considered as a limitation of this study. Hence, a further study on occupational injury supported by clinical investigation is necessary. Yet, despite this limitation, this study puts its significance on the magnitude of days away from work injury which indirectly indicate the severity of the injury and economical implication of the waste collectors.

Conclusions

In conclusion, this study confirms that day away from work injury among waste collectors is a public health problem and might have an economic and social well-being impact on the workers. Thus, priority has to be given to take an immediate measure. PPE utilization and monthly salary are the main determinant factors for days away from work injuries in small scale organized waste collectors.

Therefore, strengthening the existing occupational health and safety services in general, and the provision of PPE and ensuring its utilization in particular, is highly recommended.

Ethical statement

Ethical clearance was obtained from Mekelle University Ethical approval committee. Letter of permission was secured from Mekelle city municipality office and a written consent was obtained from each respondent by informing the purpose and significance of the survey.

Availability of data and material

The dataset contains confidential injury related data which should not be shared publicly, according to the journal ethical policy. Therefore, the data sets used and/or analysed during the current study are available from the corresponding author and can be shared on reasonable request.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

MB conceived and designed the study, performed analysis and interpretation of data. MB and BM participated in data collection and drafted the first manuscript; YA and AA did the data entry and critical review of the subsequent draft of the manuscript. All authors read and approved the final version of the manuscript for publication submitted to Journal of Preventive Medicine and Hygiene.

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RESEARCH ARTICLE

Reconstruction of asbestos exposure in workers suffering from pleural neoplasms and employed in sectors not generally associated with high exposure levels: the importance of an accurate standardized assessment of occupational medicine

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Keywords

Asbestos • Pleural mesothelioma • Standardized occupational medicine assessment

Summary

Introduction. Malignant pleural mesothelioma onset in workers exposed to asbestos is well known with reference to multiple working sectors. In some cases, occurring among workers of sectors characterized by a presumed lower relevance of asbestos exposure, the absence of a well-defined correlation can prevent their emergence and compensation. To improve definition of these cases, this article underlines the importance of a standardized approach to occupational anamnesis.

Methods. Thorough standardized occupational health assessment method application in a case of pleural malignant neoplasm occurred in a hauler, a job generally not associated with high levels of exposure to asbestos fibres.

Results. Assessment of malignant pleural mesothelioma diagnosis and dual mode relevant occupational exposure to asbestos during both truck driving and loading and unloading operations of asbestos-containing goods.

Conclusions. Systematic occupational medicine assessment with accurate standardized approach is essential for reconstruction of asbestos exposure, in order to highlight every aspect useful to establish causal link between cases of pleural mesothelioma and possible occupational and non-occupational exposure to the mineral, even in cases where the first-level occupational history does not appear to be suggestive.

Introduction

Malignant pleural mesothelioma occurrence among workers exposed to asbestos is a known fact with reference to multiple work sectors. However, in approximately 20% of cases of ascertained pathology it is not possible to identify an exposure to the mineral [1]. This element can determine a considerable obstacle to reporting the occupational origin of the disease and to its compensation. It is considered useful to introduce a systematic specialist occupational medicine assessment already at the time of clinical diagnosis, with the aim of reconstructing in a standardized way the possible occupational and non-occupational exposure to asbestos of patients with pleural mesothelioma.

Methods

This work describes the application of a standardized method of asbestos exposure's reconstruction to the case of a worker with pleural mesothelioma who requested occupational medicine assessment due to unsatisfactory initial etiological classification.

Worker's clinical history was reconstructed analysing health records relating to the diagnosis of neoplastic pathology, carried out by radiological tests, cytological examination on liquid taken during bronchoscopy and evacuative thoracentesis and histological examination conducted on tissues taken during thoracoscopy, performed to complete the necessary chemical pleurodesis procedure, and during autopsy. Occupational history was conducted by direct administration of a standardized questionnaire to the patient [2]. The questionnaire consists of several sections investigating several areas of interest: general information on the patient; smoking habit; physiological and pathological history; general information on the work activities; family history; environmental life context; evaluation of the reliability of the answers; professional in-depth history, with specific items for different work sectors; description of any activity carried out during military service; history of extra-occupational context.

Results

A 73-year-old male subject, resident in a municipality in the province of Venice, was visited in June 2018. Clinical

history was negative for previous neoplastic pathologies, and showed: atrial fibrillation in pharmacological treatment, Hashimoto's thyroiditis in spontaneous euthyroidism, leukopenia, thrombocytopenia, and prostatic hypertrophy. No previous thoracic trauma, pleurisy or radiotherapy have been reported.

The clinical onset dates back to April 2018 with appearance of wheezing dyspnoea, left thoracalgia and a persistent cough. During hospitalization, a chest X-ray showed: "Extended pleural effusion almost completely occupies the left pulmonary field with relative saving of the upper lobe. The right pulmonary field is normal and transparent. Right hilar shadow and right heart profile within limits. No pleural flaps on that side". Thorax CT scan with contrast medium showed: "Abundant pleural fluid effusion is evident in the left hemithorax, most evident at the base where it reaches an AP thickness of 70 mm. Recognizable atelectasis of most of the lower lobe with relative saving only of the lateral basal segment. Some pleural thickenings are present, in part calcific marginal on the right. Coarse plaques of pleural thickening largely calcified, the largest of 12 mm, are evident in the left diaphragmatic area. Some pleural plaques partly calcified in the left posterior costophrenic sinus and along the marginal ridge in the middle third of the left". Cytological examination of liquid taken during bronchoscopy showed: "Amorphous and blood material comprising macrophages, neutrophils, activated mesothelium and elements with nucleocytoplasmic atypia of suspected neoplastic nature". Cytological examination of liquid taken during thoracentesis showed: "Aggregates of cells with fusiform morphology in myxoid matrix. The cytological picture orientates for malignant mesenchymal neoplasia". The patient was then subjected to thoracoscopy and chemical pleurodesis surgery on the left. The histological examination carried out on biopsy samples collected during the intervention highlighted: "Fragments of parietal pleura with localization of epithelioid mesothelioma with pattern of trabecular growth; present hyaline plaques and inflammatory infiltrates; striated muscle tissue where undamaged; immunohistochemical analysis: calretinin+; WT1+; cytokeratin 5/6+, CEA-, BerEp4-, Ttf1-". Abdomen CT scan with contrast medium showed no signs of neofomations affecting the abdominal organs, nor the abdominal wall and its appendages. The only abnormal finding was a 25 mm diameter cyst on the left renal pole. The patient underwent cancer chemotherapy and died in August 2018 of cancer cachexia. The histological examination performed on the lungs taken during autopsy revealed "Fragment of pleura with extensive sclerolalinosi in contiguity with peritoneal fragment with diffuse mesotheliomatous epithelioid infiltration (calretinin+, MNF116+, AE1/AE3+, Podoplanin+/-, TTF1-). Left lung fragments with sclerolaline pleural plaques and epithelioid mesotheliomatous infiltration. Left and right lung parenchyma with emphysema, congestion, modest interstitial fibrosis, asbestos corpuscle count with Perls method gave negative results. Diagnosis: pleural mesothelioma epithelioid with peritoneal extension".

Reconstruction of exposure to asbestos fibres was carried out by directly administering the standardized questionnaire indicated by the ReNaM as a useful tool to substantiate the possible occupational and non-occupational exposures to the mineral [3]. The patient has also provided testimonial statements signed by co-workers concerning the way in which the assigned job duties were performed. From the occupational anamnesis the patient appears to have worked:

- from 1960 to 1965 and from 1967 to 1973 as a farmer at the family farm;
- in 1966 he served as a conscript with the armed forces;
- from 1966 to 1972 and from 1972 to 1998 as a hauler for two trucking companies in Venice.

Between 1966 and 1988 he drove FIAT brand trucks, models 682, 619 and 190/35; between 1972 and 1998 FIAT brand trucks, models 619, 190/35, 190 Turbostar and Mercedes-Benz brand, model Actros. During the activity of hauler, the worker systematically carried out loading, unloading and transport of different types of materials made of or containing asbestos: dust, flakes, slabs, pipes, fireproof clothing, gaskets, flanges, panels, corrugated sheets and flat plates. Asbestos or asbestos-containing materials were frequently contained in jute bags until the late 1970s of the last century. In fact, he transported these goods between Marghera's port and several companies in Northern Italy where asbestos was processed to produce different types of objects. The operations of loading and unloading of materials, both at Marghera's port and at the companies, were manually carried out directly by the worker, even inside warehouses and other enclosed places, always in absence of collective or individual protection devices. He also made some repairs by accessing the truck's engine compartment in case of some breakdowns along the way, as well as minor routine engine maintenance. He did not report maintenance operations on the braking system, although reporting several replacements of punctured tires. No suggestive elements emerged due to exposure to asbestos during farmer activity or during military service. Regarding any extra-occupational exposure to asbestos fibres, no relevant data emerged in relation to residence or extra-work activities. The patient had begun the activity of hauler at the age of about 21 years. At time of the diagnosis of malignant pleural mesothelioma he had turned 73 years old. The latency was 52 years. Based on the elements obtained from pathological anamnesis, occupational anamnesis and the assessment of exposure to asbestos fibres, it has been possible to identify the existence of a plausible causal link between occupational exposure to the mineral and the pleural neoplasm.

Standardized occupational anamnesis has in fact allowed to highlight a dual mode of occupational exposure to asbestos: one relating to the activity of portage and handling of goods and another one relating to the activity of hauler, generally considered as characterized by a non-significant exposure to asbestos. The standardized approach has therefore allowed to highlight not only the existence of a significant occupational exposure to

asbestos in the activity of the patient under examination but also to highlight how this was attributable to different aspects of the activity itself.

Therefore the first certificate of occupational disease was compiled, reports were prepared for the competent Authorities (according to the provisions of art. 365 of the Criminal Code) and to the National Institute for Insurance against Accidents at Work (INAIL) for epidemiological and statistical purposes (according to the provisions of Article 139 of Presidential Decree 1124/1965 and Legislative Decree 38/2000). The pathology has been recognized as caused by occupational exposure to asbestos.

Discussion

The clinical case of malignant pleural mesothelioma occurred in a 73-year-old subject at the time of diagnosis. The patient requested on his own initiative an occupational medicine assessment, believing that the etiological classification carried out in the hospital ward at the time of clinical diagnosis was not exhaustive. The age at which the subject started working involving exposure to asbestos was 21 years and latency was 52 years. These parameters are included in the respective intervals reported in the VI ReNaM Report in relation to the operating sectors of land transport and portage activities. In Italy, the National Mesothelioma Registry (ReNaM) periodically publishes a report in which the epidemiological information relating to mesothelioma cases arising in asbestos-exposed workers in different work sectors [1]. ReNaM's periodic reports, an epidemiological surveillance tool, can be a useful support for occupational health professionals involved in the correct attribution of asbestos exposure. Only few cases of pleural mesothelioma among transport workers have been reported [3, 4]. In addition, data published in ReNaM's latest report, in the section with the tables of the tasks involved in asbestos exposure by category of economic activity, in the maritime and air transport category indicates 134 cases of pleural mesothelioma recorded in the national register among drivers of heavy vehicles and trucks from 1993 to 2015 [1].

Diagnostic elements inferred from the outcome of health checks satisfied the requirements for diagnosis of malignant pleural mesothelioma as reported in the Sixth ReNaM Report [1]. Similarly, elements deriving from the standardized questionnaire allowed to include the case into the category of certain occupational exposure. With reference to the trucks normally used by the worker, FIAT 682 model is one of those in which the presence of asbestos has been documented. The mineral was found to be present in the vehicle in several parts and with different characteristics. In fact, it was found in form of a cord wrapped around the exhaust manifold. Asbestos fibers were found inside the driver's cab of this truck, in relation to the position of the chassis itself [5]. Authors of that work described a case of asbestosis in a

person who had been a hauler all his life, without ever having transported asbestos material or having carried out maintenance of the vehicles, and for which other expositive sources were not detectable extra-professional asbestos.

Another published clinical case is about a hauler who developed malignant pleural mesothelioma related to a short duration but high-level chrysotile working exposure during operations of loading and unloading of the vehicle over a period of a few months at an asbestos quarry. The authors of that work pointed out the plausibility of an exposure to the mineral even in an employment – that of the truck driver – usually not associated with high exposures [4].

It was also reported a case of malignant pleural mesothelioma that occurred in a hauler that for 30 years had driven trucks known in literature for contamination of the cockpit with asbestos fibre, without ever having transported asbestos materials or mediated maintenance of vehicles in the absence of extra-working mineral exposures [3]. That clinical case therefore highlighted the plausibility of the attribution of a case of pleural mesothelioma to exposure to asbestos deriving from the sole activity of driving trucks made with components able to release mineral fibre inside the driver's cab, in the absence of other exposure modes.

The work history described in this case report highlights a possible exposure of the worker to asbestos fibres in relation to the mechanical maintenance operations of the truck and the handling of objects made of or containing asbestos. The former involved accessing the engine compartment, disassembling, cleaning, repairing or replacing and reassembling different types of mechanical components. The handling operations of the transported goods were carried out in purely manual mode by the worker. He loaded the asbestos products or raw materials contained in jute bags onto the truck and unloaded them once they reached their destination. During these phases, especially with reference to the asbestos contained in bags, the dispersion of the material could be frequent with consequent possibility of inhalation by the worker, facilitated by the unavailability of individual devices to protect the respiratory tract. The bags could break easily, releasing large quantities of fibres also because they did not benefit from any special treatment but were treated like any other commodity.

The case of malignant pleural mesothelioma described in the present work presents a double mode of occupational exposure to asbestos fibre: a first one deriving from the direct manipulation of asbestos materials during the loading and unloading phases, and a second one deriving from the breathing of the mineral inside the cab also in relation to the maintenance operations carried out inside the engine compartment.

The description of this case underlines the importance of an in-depth and accurate standardized approach in the reconstruction of exposure, both occupational and non-occupational, to asbestos in order to highlight every aspect useful for the reconstruction of the causal link

between pleural mesothelioma cases and the possible opportunities of exposure to the mineral. With these aims, it is therefore important to subject cases of neoplastic diseases attributable to asbestos to occupational medicine assessment already at the time of clinical diagnosis, even when a first-level occupational anamnesis appears not to be relevant with reference to asbestos.

Conclusions

The described clinical case shows that standardized approach makes it possible to accurately determine possible scenarios of asbestos exposure even in cases for which a first-level occupational history is not suggestive. An occupational medicine assessment is advisable for all cases of neoplasms attributable to asbestos exposure, already at time of clinical diagnosis, in order to properly undertake the procedure for reporting and compensation for occupational disease.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Author performed interview with patient, questionnaire administration, literature research and paper writing.

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RESEARCH ARTICLE

Environmental sanitation and hygiene of elderly workers in Nakhon Si Thammarat Province, Thailand

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Keywords

Elderly workers • Housing sanitation • Food sanitation • Water sanitation • Indoor air quality

Summary

Introduction. Thailand will become a completely aged society in 2021 and a super-aged society in 2030, resulting in a high proportion of older people. Living environments, especially at home, play an essential health determinant for the elders.

Methods. This cross-sectional analytical study evaluated 319 households in Nakhon Si Thammarat Province according to the standard of housing sanitation for elders and assessed biological contamination in food, water, and indoor air in the homes.

Results. The housing assessment results revealed some issues that are necessary to be improved, i.e., the wet and dry areas in bathrooms were not separated (89.4%), there was no anti-slip sheet in the bathrooms (97.2%), and handrails were not suitably installed (96.2%). The proportion of coliform bacteria contamination in

the samples of cooked rice, side dish, dish, spoon, elderly hand, and drinking water was 93.3, 83.9, 82.5, 88.1, 78.0 and 97.5%, respectively. The average total bacteria count in bedrooms and kitchens was 111 CFU/m³ and 149 CFU/m³, respectively. The average total fungi count was 83 CFU/m³ in bedrooms and 93 CFU/m³ in kitchens. Most indoor air quality parameters complied with the standards.

Conclusions. Significant health risks for the elderly workers while living at home were injuries due to slipping fall in the house, especially in the bathroom, as well as foodborne and waterborne diseases. The health risks should be communicated to the elders. Prevention of the risks should be performed by the cooperation of relevant government agencies and the older adults in the study area.

Introduction

By 2050, the world's population aged 60 years and older was expected to be about 2 billion, and 80% of them will live in developing countries [1]. As a high proportion of older persons, governments should implement policies to address their needs and interests, including housing, employment, health care, and social protection [2]. Thailand will become a complete aged society in 2021 and a super-aged society in 2031 [3]. By 2040, there was estimated to be 17 million Thais 65 years and older, accounting for more than a quarter of the population. Together with China, Thailand already has the highest share of the older people of any developing country in East Asia and the Pacific [4]. The national survey found that 50.5% of Thai elders aged 60-69 years old are still working. The main reasons for them had physically able to work (47.7%) and had insufficient income to maintain their living and family (43.4%) [3].

Falls was a significant public health problem in older adults worldwide. Approximately 28-32% of more than 65 years of people fall each year, and up to 32-42% of those aged more than 70 years [5]. The study in Saudis found 49.9% of elders had experienced one or more falls for 12 months [6]. In the United States, 28.7% of older adults reported falling at least once in the preceding 12 months [7]. In China, 19.28% of older adults experienced fall incidents [8]. Injuries caused by falls in older persons

are frequent events and lead to post-fall syndromes, which result in death or long-term care needs [5]. Fall-induced traumatic brain injuries of elderly adults Finns increased 377% in women and 424% in men from 1970 to 2017 [9]. The study of fall-related injuries of Swedish registry data in year 1999-2013 found that the home was the most common location for fall injuries, as about 40% of all fall injuries [10]. 87.2% of the incidence of hip fractures caused by falling in the elderly in Nan province, Thailand, during 2015-2017 happened inside the house [11]. Many injurious falls occur around indoor stairs, and therefore the proper design of stairs and appropriate handrails (shape, diameter, and height) should be investigated [12].

Sanitation, hygiene, drinking water, and indoor air quality are essential issues for public health concern, especially in developing countries. In 2017, 45% of the global population (3.4 billion people) accessed a safely managed sanitation service; however, 2.0 billion people still do not have the necessary sanitation facilities. 71% of the population used safely drinking water services, but 0.78 billion people even do not have the essential functions [13, 14]. A study in Tigray, Ethiopia indicated that availability and proper utilization of latrine, hand washing, and water facilities were low [15]. Poor sanitation reduced human well-being and was estimated to cause 432,000 diarrheal deaths annually [13]. Older adults are vulnerable groups to microbial contaminants

and can be more at risk from waterborne and foodborne disease when living under unsanitary conditions [16]. Indoor environmental quality is a critical health determinant for elders because they spend more than 90% of their time in the indoor environment [17, 18]. Inadequate ventilation contributed to exposure to indoor air pollutants related to respiratory symptoms in older people [17-19].

In Thailand, one-third of the elderly (34.3%) had incomes below the poverty line (under 2,667 baht per month). Eighty percent of the elderly receiving allowances from the government (600-1,000 baht per month), but it was not enough for living [20, 21]. The cost of health care in Thailand was rapidly increased, especially in aging society situation. There was estimated that in case of without any control measures of the behavior lifestyle of the elderly, the cost will be increased from about 0.48-0.63 trillion baht to 2.2 trillion baht in 2032 [20]. Therefore, health promotion and prevention in the elderly are challenges for Thailand.

This research focuses on the elderly workers with age between 45-70 years old, who are still working and earning income, including formal workers (work in the government and private workplaces) and informal workers (self-employed workers). The research assessed housing sanitation, food and water sanitation, and indoor air quality in the house of the elderly worker in Nakhon Si Thammarat province, which has the highest number of older people in Southern Thailand [3].

Methods

The research project was approved by the Human Research Ethics Committee of Walailak University with the approval number WUEC-19-057-01 on 26 April 2019. This cross-sectional analytical study was set in Nakhon Si Thammarat province in 2 districts, Mueang and Tha Sala district. Mueang district was selected because of the highest of elderly worker proportion, and Tha Sala district was chosen because it has been set as the Long-term care sub-district of elders by the Health Promotion Center Region 11 Nakhon Si Thammarat since 2014. The population in this was the elderly workers with age between 45-70 years. They have worked in the study area for at least two years. The sample was calculated using the equation of Wayne WD (1995) [22] with a finite population.

$$n = \frac{NZ^2_{\alpha/2}p(1-p)}{[e^2(N-1)] + [Z^2_{\alpha/2}p(1-p)]}$$

Where n was the calculated sample size, N was the population of the elderly workers in total 112,117 people (82,877 people in Muang District and 29,240 people in Tha Sala District). p was the proportion of the sampling population, which was the proportion of the elderly workers to the total population in Nakhon Si Thammarat Province (0.28). Z was the reliability coefficient of 95% (level 0.05) with $Z (0.975) = 1.96$. e was the standard

error, which was set at 0.05. The calculated sample size in this study with reserving 5% for surveying and participating was 324 people. Simple random sampling was applied in the study. The samples were selected from the list of elderly workers in the database of Tambon Health Promoting Hospital.

Housing sanitation was assessed using the questionnaire, which was developed in the previous study by Nattaporn Sang (2019) [23], and it was already checked the content validity by the experts with the Item-Objective Congruence (IOC) index of 0.67-1.00. The first section was general information of the elderly workers, and the second section was the checklist form of housing sanitation. General information consisted of sex, age, religions, education level, income, and career. Housing sanitation assessment included general features of external and internal area, living room, kitchen room, bedroom, bathroom, household facilities, and environmental sanitation, a total of 38 items. The questionnaires were completed by face to face at the house of the elderly workers. The informed consent to participate in the study was informed to them before starting the inquiry process.

For food sanitation, coliform bacteria were detected in the samples of food (cook rice and the side dish), food contact equipment (plate and spoon), and food handler (elderly hand). The field test kit (SI-2 or DOH13) of the Research and Laboratory Development Center, Department of Health, Thailand, was used for the detection [24]. The principle of the SI-2 test kit is the ability of coliform bacteria to ferment lactose with acid and gas formation within 17 hours. The pH of the culture medium then will be decreased, which caused the color of the indicator to change from purple to yellow. This color-changing indicated coliform bacteria in the sample exceed the quality criteria of bacteria [25]. The testing was performed with an aseptic technique according to the manual of instruction. All the equipment, such as the cap and the neck of the culture medium bottle, cutter, and work-in plate and inspector's hand, were cleaned with 70% alcohol before carrying out the test. The test kit was stored in a dry and cool place. It can be stored at room temperature for about one month and stored in the refrigerator for about six months. For water sanitation, coliform bacteria contamination in the drinking water sample was tested by the field test kit for coliform in drinking water (DOH11), which was developed by the Research and Laboratory Development Center [24]. The culture medium was used to detect coliform bacteria after keeping in room temperature (25-40°C) for 24 hours. The medium color (clear red) will be changed to orange-red, brown-red, and yellow. Also, turbidity and the bubble gas will be appeared after shaking. These results indicated contamination of coliform bacteria in which the water is not safe for human consumption. The DOH11 is consistent with more than 85% with the multiple-tube fermentation technique [25]. Food and water samples being eating were collected for the test. For indoor air quality, total bacteria and total fungi were measured in the bedroom and the kitchen room. Gravity

Settling Plate (GSP) sampling was used to collect the bioaerosol. Blood Agar and Sabouraud Dextrose Agar were used as culture media for bacteria and fungi, respectively. Total bacteria and total fungi in indoor air were calculated by settling velocity of aerosol [26]. For quality control, the contamination of culture media every batch was tested before use for sampling, and seventy-one field blanks (approximately 10% of the samples) were performed. No contamination of bacteria or fungi was found in all sets of the prepared culture media and field blanks.

For data analysis, the results of the questionnaire and environmental sanitation were explained using descriptive statistics (*i.e.*, frequency, percentage, minimum, maximum, mean, and standard deviation). Factors affected the environmental sanitation were tested using a chi-square correlation. In case of limitation of the sample size, which reflected on more than 20% of the expected values in cells are less than 5, Fisher's exact test was instead conducted.

Results

CHARACTERISTICS OF THE ELDERLY WORKERS

A total of 319 elderly workers were included in this study (98.5% response rate). Most of them were female (72.1%), Buddhists (81.2%), and their education level was primary education (67.1%). Most of them were farmers/ fishery (26.3%), and their monthly income was 10,001-15,000 THB (315-472 USD) (35.7%). Detailed characteristics of the elderly workers were shown in Table I.

HOUSING SANITATION

The results of the housing sanitation assessment were shown in Table II. Most of the houses were in the criteria for all items in the general features, living room, and kitchen room. The house had a stable structure; the surrounding area of the house cleaned, and there was no cobweb inside the house. The living room was suitably arranged. The kitchens were cleaned and proper arrangement, sufficient ventilation and light and appropriate food keeping.

Most of the checked items in the bedroom were in the criteria. The bedroom had cleaned and proper arrangement, suitable insect prevention, and sufficient ventilation and light. The bed was an appropriate height to prevent falls. The mattress and pillows were suitable hardness to avoid the pain of the back and neck. However, 48.9% of the bedroom had a telephone or accessible emergency signal in case of an emergency. Most of the checked items in the bathroom were in the criteria. Every house had a toilet for excreta treatment. Toilet, water closet, water container, and the floor were cleaned and in good condition. There was proper ventilation, sufficient light, and the water was cleaned and enough for use. However, only 10.6% of the bathroom separated between wet and dry zone, and only 2.8% had anti-slip sheets in the bathroom.

All items of the door, chair, and the closets were in the criteria for household facilities. The door was in good condition and easily use. The chair had a suitable height, and the cabinets easily used. Most of the houses had the power plug with appropriate height for use, but 66.1% of them had electrical equipment in good condition and ready for use. Also, only 3.8% of the houses set the handrails and keep them in good shape for use. Only

Tab. I. Characteristics of the elderly samples.

Characteristics		Frequency (n = 319)	Percent
Gender	Male	89	27.9
	Female	230	72.1
Education level	Below primary education	4	1.2
	Primary education	214	67.1
	Secondary education/lower vocational	53	16.6
	Tertiary vocational	19	6.0
	Undergraduate	24	7.5
	Graduate studies	5	1.6
Monthly income	≤ 5,000 THB	100	31.4
	5,001-10,000 THB	114	35.7
	10,001-15,000 THB	48	15.0
	15,001-20,000 THB	19	6.0
	> 20,000 THB	38	11.9
Career	Farmer/fishery	84	26.3
	Merchant	66	20.7
	Government/company employee	60	18.9
	Self-employed	77	24.1
	Homemaker	32	10.0
Religions	Buddhism	259	81.2
	Islam	58	18.2
	Christianity	2	0.6

Tab. II. Conditions of housing sanitation.

Housing items (n = 319)	No. of passing (percent)
General features of external and internal area	
Strong structure of the house	310 (97.2)
The area around the house is clean and shady	307 (96.2)
In case of raising animals, functional separate and cleaned area	289 (90.6)
No debris scattered inside/outside the house	288 (90.3)
No cobweb inside the house	252 (79.0)
Living room	
Do not place things in the path	280 (87.8)
Suitable of the window height and furniture arrangement for seeing the outside view	283 (88.7)
The room uses bright colors and can be easily maintained	264 (82.8)
Kitchen room	
The room is proportional arranged and cleaned	281 (88.1)
Proper ventilation and sufficient natural light	277 (86.8)
Cabinet/ table is at least 60 cm above the floor	312 (97.8)
Cooked food has concealed containers or store in the pantry/refrigerator	296 (92.8)
Bedroom	
The room is clean and right arrangement	294 (92.2)
The room has the nets to prevent mosquito/ insects	262 (82.1)
Proper ventilation and sufficient natural light	271 (85.0)
Having a telephone or accessible emergency signals	156 (48.9)
The bed has a suitable height to prevent fall	259 (81.2)
The mattress and pillows are not too hard or too soft to prevent back pain/ neck pain	301 (94.4)
Bathroom	
Toilet and water closet are clean and in good condition	311 (97.5)
The water in the bathroom is clean and sufficient	313 (98.1)
Water containers and bowls are in good condition	314 (98.4)
Proper ventilation and sufficient natural light	284 (89.0)
The room is separated between wet and dry zone for anti-slip	34 (10.6)
The floor is cleaned, no residue which can cause slippery	290 (90.9)
Having anti-slip sheets placed on the floor	9 (2.8)
Household facilities	
The door handle and lock are in good condition	306 (95.9)
The door should be at least 90 cm width and easily pushed	308 (96.6)
The power plug is in 45-90 cm above the floor which can be accessible and avoid bending	309 (96.9)
Electrical equipment is ready to use	211 (66.1)
Handrails were installed with right conditions (firm, not slippery and easily cleaned)	12 (3.8)
The ramp is flat, 90-150 cm in width, not over 6 m in length and the slope is not over 1:12	135 (42.3)
The floor has distinct colors	149 (46.7)
The chair has a backrest, and the height is suitable that feet can be placed on the floor	268 (84.0)
Closets are sliding or drawers that cloths can be easily picked up	280 (87.8)
Environmental sanitation	
Solid waste is well separated and collected for further transported and disposed	215 (67.4)
The waste container has a lid, clean and sufficient for the amount of waste	76 (23.8)
Household wastewater is treated before discharging to the environment	82 (25.7)
No waterlogging in containers that may be a breeding site of mosquitoes	214 (67.1)

42.3% of the house installed the ramp with a suitable width, length, and slope, and only 46.7% of the house had distinct floor colors. A few houses were in the criteria for environmental sanitation. Only 23.8% and 25.7% of them had suitable waste containers and treated wastewater before discharge, respectively. Also, 67.4% of them had a proper separation and collection of solid waste, and the breeding site of mosquitoes was found at 33.9% of the houses.

FOOD AND WATER SANITATION

Detection of coliform bacteria in the sample of food, food contact surface, and elderly hand was shown in Table III. There was a high detection rate of coliform bacteria in all types of samples. The detection rate was 93.3, 83.9, 82.5, 88.1, 78.0% in the cooked rice, side dish, dish, spoon, and elderly hand, respectively. The type of drinking water and their detection rate of coliform bacteria were shown in Table IV. Most of the

Tab. III. Detection of coliform bacteria in food, food contact surface, and hand.

Type of samples	Number of test	Positive result*	Detection rate
Food-cooked rice	180	168	93.3
Food-side dish	56	47	83.9
Food contact surface-dish	297	245	82.5
Food contact surface-spoon	294	259	88.1
Hand	309	241	78.0
Total	1,136	960	84.5

* Positive result indicated contamination of coliform bacteria exceed the quality criteria.

Tab. IV. Type of drinking water and detection rate of coliform bacteria.

Type of drinking water	Total		Detection rate* (%)
	No. of household	%	
20 L bottled water	171	55.0	99.4
0.5-1.0 L bottled water	49	15.8	85.7
Water vending machine	24	7.7	100.0
Rainwater	23	7.4	100.0
Deep well water	19	6.1	100.0
Tap water	15	4.8	100.0
Shallow well water	10	3.2	100.0
Total	311	100.0	97.5

* Coliform bacteria detection indicated that water is not safe for human consumption.

households used bottled water for drinking water by which 55% was big bottled water (20 L), and 15.8% was the small bottled water (0.5-1.0 L). Rainwater, deep and shallow well water, and tap water were also used for drinking water for some households in the study area. The detection rate of coliform bacteria was 97.5% of all samples. Coliform in vending machine water, rainwater, deep and shallow well water, and tap water was 100% detected.

INDOOR AIR QUALITY

The measurement of total bacteria and fungi in indoor air was shown in Table V. The average amount of total bacteria in the kitchen (149 CFU/m³) was higher than that in the bedroom (111 CFU/m³). For total fungi, the average level was 83 CFU/m³ and 93 CFU/m³ in the bedroom and the kitchen, respectively. Most of the measurements were in the standard of Singapore [27], and Thailand (a draft of indoor air quality standard) [28], which specifies the concentration is not excess 500 CFU/m³ for both the total bacteria and total fungi in the indoor air. Only 4.4 and 6.8% of the measurements of total bacteria in the bedroom and the kitchen exceeded the standard. Also, 1.4 and 2.1% of the total fungi measures in the bedroom and the kitchen exceeded the standard.

FACTORS AFFECTED ENVIRONMENTAL SANITATION

Chi-square correlation between the environmental sanitation and affected factors (*i.e.*, characteristics of the elderly workers and housing sanitation) was shown in Tab. SI to Tab. SIII in the Supplementary information. The housing sanitation related to the cleanliness of the houses was selected for the correlation test. Factors affected the contamination of coliform bacteria in hand (p -value < 0.05) were gender, cobweb inside the house, the cleanliness of the kitchen room, bathroom ventilation, and wastewater treatment. No correlation was found between coliform contamination in other samples (*i.e.*, cooked rice, side dish, dish, spoon, and drinking water) and the factors of elderly characteristics and housing sanitation.

The career of the elderly workers affected airborne bacteria and fungi in both the bedroom and kitchen room. Bacteria and fungi in the bedroom were also affected by education and religion. Some housing sanitation factors, importantly, bathroom ventilation, solid waste collection and separation, and keeping of cooked food, affected airborne bacteria and fungi in the bedroom and kitchen room. Other correlated factors of housing sanitation affected some indoor air quality. These factors included debris scattered inside/outside the house, cobweb

Tab. V. Indoor air quality results.

Parameters	No. of household	Min-max	(Avg \pm STD)
Total bacteria in bedroom (CFU/m ³)	293	0-2.063	111 \pm 221
Total bacteria in kitchen (CFU/m ³)	290	0-1.844	149 \pm 262
Total fungi in bedroom (CFU/m ³)	290	0-835	83 \pm 109
Total fungi in kitchen (CFU/m ³)	287	0-806	93 \pm 128

The standard of indoor air quality is 500 CFU/m³ for total bacteria and total fungi.

inside the house, cleanliness of bedroom, cleanliness of bathroom's floor, cleanliness and sufficiency of waste container, wastewater treatment, and cleanliness of toilet and water in the bathroom.

Discussion

The main problems of housing sanitation in this study area were risk factors related to falls of the elderly workers, especially in the bathroom. Most of the houses had no separation of wet and dry zones (89.4%) and no anti-slip sheet in the toilet (97.2%), and the handrails were not correctly installed (96.2%). This study's result corresponded to other study areas in Nakhon Si Thammarat Province, Thailand, which showed similar problems found in the houses [23], *i.e.*, no separation between wet and dry zone (78.2%) and incorrectly installed of the handrails (92.5%). Thailand national survey of 83,880 households in 2018 found 6.8% of elderly falls within six months before the questionnaire day, and major causes of falls were slips (39%), stumble (36.6), and dizzy (9.3%) [3]. Another previous survey of elder's health problem in the Mueang district in Nakhon Si Thammarat indicated eye disorders (20.3%) and bone and joint disease (16.8%) [29]. These health problems stated the risk of fall accidents of older people that was a critical problem in the area. The study of the consequence of fallings in the elderly in Nan, Thailand, found increasing in hip fractures. The median of refracture time was 143 weeks, and 32.7% of patients take more than five years. 3.7% of patients died in the hospital, and the one-year mortality rate was 17.2% [9]. More research associated with falls, *i.e.*, characteristics, risk factors, burden, and consequence, is required, and preventing measures is challenges for the study area. Preventing falls in the elderly in the study area should have proceeded with the homeowner and local officers. Food sanitation was another issue in the study area. Although, the assessment results of housing sanitation showed most of the kitchen room was proportional arranged and cleaned (88.1%). Also, cooked food was kept correctly (92.8%), and there was a suitable height of cabinet or table for preparing food and maintaining the kitchen's equipment and cooking (97.8%). However, coliform bacteria contamination in the samples of food, food contact surface, and hand were high, with a rate of 78.0-93.3%. These results indicated a high risk of pathogen contamination, which might cause foodborne and waterborne diseases. High contamination of coliform bacteria might cause by many reasons, such as the insufficient hygiene of elderly workers such as hand washing, dishwashing, and heating food before eating [30-32]. During the survey we found that the elderly did not wash their hand before eating food, utensils were not be cleaned right after the meal and food waste was left on them, the holder of washed utensils was not be covered, and vectors (cockroaches, flies) were found in some

houses. Also, most of the houses (76.2%) had the problem of solid waste containers, which was no cover and insufficient for the generated amount. Besides, 74.3% of them were not treated the household wastewater (*i.e.*, dishwashing, laundry, bathing) before discharge into the land nearby the houses. Improper solid waste collecting and waterlogging of wastewater might be breeding sources of insects and vectors such as cockroaches, flies, and rats. This insect and vectors can cause bacteria cross-contamination in food and food contact surfaces [33].

Coliform bacteria contamination in drinking water was also high, with a rate of 97.5%. Only for some bottled water samples (0.6% of big bottled water and 14.3% of small bottled water) found negative results. Other sources of drinking water were 100% contaminated by coliform bacteria. High contamination of coliform bacteria in drinking water was detected in Thailand in previous studies. Their detection was 85% at Phayao province [34], 69.2% at Maha Sarakham province [35], and 53.3% at Nakhon Si Thammarat province [36] for drinking water samples from the vending machine and water purifier. These studies reported the contamination caused by improperly maintenance and cleanliness, and the filters of water vending machines have not been changed in time. Detection of coliform bacteria in tap water samples was 100% at Chaing Rai province [37] and 76.9% at Khon Khean province [38]. Causes of the contamination in these studies were leakage of the pipeline and sediment remaining in the pipeline, and no chlorine residue. Boiling water before drinking was suggested for tap water.

Detection of coliform bacteria in groundwater samples was 91.5% at Khon Kaen province [39], which caused by unsealed storage containers or bottles, the drinking cups were used without cleaning, and those cups were using the same cup for all members without washing hands. Coliform bacteria were detected for 75.6% of groundwater samples at Ubon Ratchatani province, and the results showed that septic tanks, wastewater, and waste disposal site located within a 30-meter distance near the groundwater wells [40]. Coliform bacteria were found in all rainwater samples (100%) at Nakhon Si Thammarat province [41]. The contamination caused by use first flush diverters, lack of cleaning, and no cover of the rainwater storage tank. Previous studies in Thailand reported that 90.7-100% of bottled water samples were in the standard for coliform bacteria in drinking water in a sealed container set by the Ministry of Public Health of Thailand [42-44]. However, high detection of coliform bacteria in bottled water was found in this study. During the survey, we observed that drinking water cups were not cleaned, and there was some dirt on the containers of drinking water, and most of the elderly workers were not wash their hands before drinking water. There were some studies of coliform contamination in drinking water in other countries and found high detection. A survey of fecal contamination of drinking water in Rwanda found 75.1% of samples

with detectable thermotolerant coliforms [45]. A study of microbial quality of community drinking water supplies in west Amhara, Ethiopia for 2004-2014 found that 44.7% of water samples had total coliform [46]. A case study in Kermanshah, Iran, detected fecal coliform in urban, rural, and private drinking water sources in ten years (2006-2016) with 48.4, 82.3, and 63.0%, respectively [47].

In this study, some housing sanitation issues (*i.e.*, cobweb inside the house, the cleanliness of the kitchen room, and the ventilation of the bathroom) were found to be affected factors of the coliform contamination of the elderly hand. Moreover, some factors such as washing hands before drinking and eating, cleaning and storage of utensils for food and drinking water, food waste disposal, and vector control were observed to be related to the contamination. Therefore, these inadequate sanitation and hygiene-related issues should be communicated and suggested to the elderly for the reduction of the contamination.

Indoor air quality in terms of total bacteria and fungi mostly complied with the standard, and most of the kitchen rooms and bedrooms were regularly cleaned. Some factors of house cleanliness affected airborne bacteria and fungi such as ventilation and cleanliness of the bathroom, cleanliness of bedroom, cobweb inside the house, solid waste management, and wastewater treatment. Regularly arrangement and clean the room with disinfection was an essential factor in reducing the amount of the bacteria and fungi in the indoor air [48]. The higher amount of fungi and bacteria found in the kitchen, compared to the bedroom, might be caused by the moisture from cooking and washing activities [49].

Conclusions

Assessment of housing sanitation for the elderly worker indicated health risk due to the falling accident, especially in the bathroom, because there were no anti-slip sheets and no separation of the dry and wet zone. Besides, we found some issues in the house that can cause a falling accident to the elders. Those issues included the handrails were not correctly installed, the ramp was an inappropriate shape, and the floor had not distinct colors. Solid waste and wastewater problems were other sanitation issues in the study area. Indoor air quality in the house was the problem for some homes. However, we found coliform contamination in most of the samples, including food, food contact surface, elderly hand, and drinking water. Therefore, foodborne and waterborne disease was the health risk to the elderly workers.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

The design and supervision of the research project were involved by all authors. JK has analyzed the data and interpreted the results and wrote the manuscript. All authors revised and approved the final manuscript.

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Supplementary information

Tab. SI. Correlation between environmental sanitation (coliform contamination in food surface contact and hand) and factors of characteristics of the elderly workers and housing sanitation.

Characteristics	Coliform in dish			Coliform in spoon			Coliform in hand		
	Negative (52)	Positive (245)	p-value	Negative (35)	Positive (259)	p-value	Negative (68)	Positive (241)	p-value
Gender									
Male	15 (5.1%)	64 (21.5%)	0.686	8 (2.7%)	70 (23.8%)	0.600	27 (8.7%)	59 (19.1%)	<u>0.013</u>
Female	37 (12.5%)	181 (60.9%)		27 (9.2%)	189 (63.4%)		41 (13.3%)	182 (58.9%)	
Education									
Primary school and below	35 (11.8%)	171 (57.6%)	0.724	25 (8.5%)	177 (60.2%)	0.711	41 (13.3%)	171 (53.3%)	0.094
Secondary school and higher	17 (5.7%)	74 (24.9%)		10 (3.4%)	82 (27.9%)		27 (8.7%)	70 (22.7%)	
Monthly income									
≤ 5,000 THB	12 (4.0%)	81 (27.3%)	0.369	14 (4.8%)	79 (26.9%)	0.363	25 (8.1%)	74 (23.9%)	0.639
5,001-10,000 THB	21 (7.1%)	85 (28.6%)		9 (3.1%)	96 (32.7%)		22 (7.1%)	86 (27.8%)	
≥ 10,000 THB	19 (6.4%)	79 (26.6%)		12 (4.1%)	84 (28.6%)		21 (6.8%)	81 (26.2%)	
Career									
Farmer/Fishery	14 (4.7%)	62 (20.9%)	0.153	13 (4.4%)	63 (21.4%)	0.148	18 (5.8%)	63 (20.4%)	0.159
Merchant	11 (3.7%)	55 (18.5%)		4 (1.4%)	60 (21.8%)		10 (3.2%)	55 (17.8%)	
Employee	8 (2.7%)	46 (15.5%)		4 (1.4%)	49 (16.7%)		16 (5.2%)	41 (13.3%)	
Self-employed	9 (3.0%)	62 (20.9%)		8 (2.7%)	63 (21.4%)		13 (4.2%)	61 (19.7%)	
Homemaker	10 (3.4%)	20 (6.7%)		6 (2.0%)	24 (8.2%)		11 (3.6%)	21 (6.8%)	
Religions									
Buddhism	41 (13.8%)	199 (67.0%)	0.692	31 (10.5%)	205 (69.7%)	0.189	58 (18.8%)	193 (62.5%)	0.331
Islam/Christianity	11 (3.7%)	46 (15.5%)		4 (1.4%)	54 (18.4%)		10 (3.2%)	48 (15.5%)	
Housing item No.2									
Not pass	1 (0.3%)	9 (3.0%)	1.000*	1 (0.3%)	8 (2.7%)	1.000*	1 (0.3%)	10 (3.2%)	0.466*
Pass	51 (17.2%)	236 (79.5%)		34 (11.6%)	251 (85.4%)		67 (21.7%)	231 (74.8%)	
Housing item No.3									
Not pass	4 (1.3%)	22 (7.4%)	1.000*	4 (1.4%)	21 (7.1%)	0.517*	7 (2.3%)	18 (5.8%)	0.451
Pass	48 (16.2%)	223 (75.1%)		31 (10.5%)	238 (81.0%)		61 (19.7%)	223 (72.2%)	
Housing item No.4									
Not pass	2 (0.7%)	24 (8.1%)	0.277*	3 (1.0%)	24 (8.2%)	1.000*	3 (1.0%)	26 (8.4%)	0.111
Pass	50 (16.8%)	221 (74.4%)		32 (10.9%)	235 (79.9%)		65 (21.0%)	215 (69.6%)	
Housing item No.5									
Not pass	7 (2.4%)	55 (18.5%)	0.148	7 (2.4%)	54 (18.4%)	0.907	6 (1.9%)	58 (18.8%)	<u>0.006</u>
Pass	45 (15.2%)	190 (64.0%)		28 (9.5%)	205 (69.7%)		62 (20.1%)	183 (59.2%)	
Housing item No.9									
Not pass	4 (1.3%)	27 (9.1%)	0.476	3 (1.0%)	28 (9.5%)	1.000*	3 (1.0%)	32 (10.4%)	<u>0.042</u>
Pass	48 (16.2%)	218 (73.4%)		32 (10.9%)	231 (78.6%)		65 (21.0%)	209 (67.6%)	
Housing item No.10									
Not pass	6 (2.0%)	32 (10.8%)	0.765	3 (1.0%)	34 (11.6%)	0.592*	7 (2.3%)	31 (10.0%)	0.569
Pass	46 (15.5%)	213 (71.7%)		32 (10.9%)	225 (76.5%)		61 (19.7%)	210 (68.0%)	
Housing item No.11									
Not pass	0 (0.0%)	4 (1.3%)	1.000*	0 (0.0%)	4 (1.4%)	1.000*	0 (0.0%)	7 (2.3%)	0.354
Pass	52 (17.5%)	241 (81.1%)		35 (11.9%)	255 (86.7%)		68 (22.0%)	234 (75.7%)	
Housing item No.12									
Not pass	3 (1.0%)	17 (5.7%)	1.000*	3 (1.0%)	17 (5.8%)	0.717*	3 (1.0%)	19 (6.1%)	0.429*
Pass	49 (16.5%)	228 (76.8%)		32 (10.9%)	242 (82.3%)		65 (21.0%)	222 (71.8%)	
Housing item No.13									
Not pass	3 (1.0%)	19 (6.4%)	0.776*	1 (0.3%)	21 (7.1%)	0.491*	5 (1.6%)	19 (6.1%)	0.885
Pass	49 (16.5%)	226 (76.1%)		34 (11.6%)	238 (81.0%)		63 (20.4%)	222 (71.8%)	
Housing item No.15									
Not pass	8 (2.7%)	33 (11.1%)	0.716	4 (1.4%)	36 (12.2%)	0.689*	7 (2.3%)	37 (12.0%)	0.292
Pass	44 (14.8%)	212 (71.4%)		31 (10.5%)	223 (75.9%)		61 (19.7%)	204 (66.0%)	
Housing item No.19									
Not pass	1 (0.3%)	6 (2.0%)	1.000*	0 (0.0%)	7 (2.4%)	1.000*	2 (0.6%)	6 (1.9%)	0.690*
Pass	51 (17.2%)	239 (80.5%)		35 (11.9%)	252 (85.7%)		66 (21.4%)	235 (76.1%)	
Housing item No.20									
Not pass	1 (0.3%)	3 (1.0%)	0.539*	0 (0.0%)	4 (1.4%)	1.000*	1 (0.3%)	4 (1.3%)	1.000*
Pass	51 (17.2%)	242 (81.5%)		35 (11.9%)	255 (86.7%)		67 (21.7%)	237 (76.7%)	
Housing item No.22									
Not pass	2 (0.7%)	27 (9.1%)	0.113	1 (0.3%)	27 (9.2%)	0.222*	2 (0.6%)	30 (9.7%)	<u>0.023</u>
Pass	50 (16.8%)	218 (73.4%)		34 (11.6%)	232 (78.9%)		66 (21.4%)	211 (68.3%)	
Housing item No.24									
Not pass	4 (1.3%)	22 (7.4%)	1.000*	1 (0.3%)	24 (8.2%)	0.332*	2 (0.6%)	25 (8.1%)	0.055
Pass	48 (16.2%)	223 (75.1%)		34 (11.6%)	235 (79.9%)		66 (21.4%)	216 (69.9%)	
Housing item No.35									
Not pass	17 (5.7%)	80 (26.9%)	0.996	10 (3.4%)	85 (28.9%)	0.614	19 (6.1%)	81 (26.2%)	0.378
Pass	35 (11.8%)	165 (55.6%)		25 (8.5%)	174 (59.2%)		49 (15.9%)	160 (51.8%)	
Housing item No.36									
Not pass	43 (14.5%)	184 (62.0%)	0.241	26 (8.8%)	197 (67.0%)	0.818	50 (16.2%)	183 (59.2%)	0.684
Pass	9 (3.0%)	61 (20.5%)		9 (3.1%)	62 (21.1%)		18 (5.8%)	58 (18.8%)	
Housing item No.37									
Not pass	40 (13.5%)	182 (61.3%)	0.691	28 (9.5%)	190 (64.6%)	0.400	41 (13.3%)	188 (60.8%)	<u>0.003</u>
Pass	12 (4.0%)	63 (21.2%)		7 (2.4%)	69 (23.5%)		27 (8.7%)	53 (17.2%)	

* Fisher's exact test coefficient, number of housing item corresponded to Table II Conditions of Housing Sanitation.

Tab. SII. Correlation between environmental sanitation (coliform contamination in food and drinking water) and factors of characteristics of the elderly workers and housing sanitation.

Characteristics	Coliform in cooked rice			Coliform in side dish			Coliform in drinking water		
	Negative (12)	Positive (168)	p-value	Negative (9)	Positive (47)	p-value	Negative (8)	Positive (303)	p-value
Gender									
Male	1 (0.6%)	49 (27.2%)	0.183*	3 (5.4%)	14 (25.0%)	1.000*	4 (1.3%)	82 (26.4%)	0.223*
Female	11 (6.1%)	119 (66.1%)		6 (10.7%)	33 (58.9%)		4 (1.3%)	221 (71.1%)	
Education									
Primary school and below	7 (3.9%)	125 (69.4%)	0.308*	5 (8.9%)	30 (53.6%)	0.715*	3 (1.0%)	210 (67.5%)	0.114*
Secondary school and higher	5 (2.8%)	43 (23.9%)		4 (7.1%)	17 (30.4%)		5 (1.6%)	93 (29.9%)	
Monthly income									
≤ 5,000 THB	5 (2.8%)	57 (31.7%)	-	1 (1.8%)	13 (23.2%)	-	0 (0.0%)	98 (31.5%)	-
5,001-10,000 THB	5 (2.8%)	61 (33.9%)		4 (7.1%)	18 (32.1%)		3 (1.0%)	108 (34.7%)	
≥ 10,000 THB	2 (1.1%)	50 (27.8%)		4 (7.1%)	16 (28.6%)		5 (1.6%)	97 (31.2%)	
Career									
Farmer/Fishery	4 (2.2%)	46 (25.6%)	-	1 (1.8%)	20 (35.7%)	-	0 (0.0%)	84 (27.0%)	-
Merchant	3 (1.7%)	39 (21.7%)		3 (5.4%)	6 (10.7%)		1 (0.3%)	65 (20.9%)	
Employee	1 (0.6%)	24 (13.3%)		2 (3.6%)	8 (14.3%)		2 (0.6%)	54 (17.4%)	
Self-employed	3 (1.7%)	41 (22.8%)		2 (3.6%)	9 (16.1%)		4 (1.3%)	69 (22.2%)	
Homemaker	1 (0.6%)	18 (10.0%)		1 (1.8%)	4 (7.1%)		1 (0.3%)	31 (10.0%)	
Religions									
Buddhism	9 (5.0%)	138 (76.7%)	0.463*	9 (16.1%)	41 (73.2%)	0.575*	5 (1.6%)	247 (79.4%)	0.179*
Islam/Christianity	3 (1.7%)	30 (16.7%)		0 (0.0%)	6 (10.7%)		3 (1.0%)	56 (18.0%)	
Housing item No.2									
Not pass	0 (0.0%)	9 (5.0%)	1.000*	0 (0.0%)	1 (1.8%)	1.000*	0 (0.0%)	10 (3.2%)	1.000*
Pass	12 (6.7%)	159 (88.3%)		9 (16.1%)	46 (82.1%)		8 (2.6%)	293 (94.2%)	
Housing item No.3									
Not pass	1 (0.6%)	19 (10.6%)	1.000*	0 (0.0%)	2 (3.6%)	1.000*	1 (0.3%)	26 (8.4%)	0.521*
Pass	11 (6.1%)	149 (82.8%)		9 (16.1%)	45 (80.4%)		7 (2.3%)	277 (89.1%)	
Housing item No.4									
Not pass	2 (1.1%)	16 (8.9%)	0.342*	0 (0.0%)	3 (5.4%)	1.000*	0 (0.0%)	28 (9.0%)	1.000*
Pass	10 (5.6%)	152 (84.4%)		9 (16.1%)	44 (78.6%)		8 (2.6%)	275 (88.4%)	
Housing item No.5									
Not pass	2 (1.1%)	42 (23.3%)	0.733*	3 (5.4%)	10 (17.9%)	0.419*	1 (0.3%)	64 (20.6%)	1.000*
Pass	10 (5.6%)	126 (70.0%)		6 (10.7%)	37 (66.1%)		7 (2.3%)	239 (76.8%)	
Housing item No.9									
Not pass	3 (1.7%)	22 (12.2%)	0.222*	1 (1.8%)	7 (12.5%)	1.000*	2 (0.6%)	32 (10.3%)	0.214*
Pass	9 (5.0%)	146 (81.1%)		8 (14.3%)	40 (71.4%)		6 (1.9%)	271 (87.1%)	
Housing item No.10									
Not pass	3 (1.7%)	18 (10.0%)	0.151*	0 (0.0%)	2 (3.6%)	1.000*	2 (0.6%)	37 (11.9%)	0.264*
Pass	9 (5.0%)	150 (83.3%)		9 (16.1%)	45 (80.4%)		6 (1.9%)	266 (85.5%)	
Housing item No.11									
Not pass	1 (0.6%)	4 (2.2%)	0.295*	0 (0.0%)	1 (1.8%)	1.000*	0 (0.0%)	6 (1.9%)	1.000*
Pass	11 (6.1%)	164 (91.1%)		9 (16.1%)	46 (82.1%)		8 (2.6%)	297 (95.5%)	
Housing item No.12									
Not pass	1 (0.6%)	11 (6.1%)	0.575*	0 (0.0%)	3 (5.4%)	1.000*	1 (0.3%)	20 (6.8%)	0.432*
Pass	11 (6.1%)	157 (87.2%)		9 (16.1%)	44 (78.6%)		7 (2.3%)	283 (91.0%)	
Housing item No.13									
Not pass	3 (1.7%)	13 (7.2%)	0.077*	0 (0.0%)	3 (5.4%)	1.000*	1 (0.3%)	22 (7.1%)	0.463*
Pass	9 (5.0%)	155 (86.1%)		9 (16.1%)	44 (78.6%)		7 (2.3%)	281 (90.4%)	
Housing item No.15									
Not pass	4 (2.2%)	26 (14.4%)	0.118	1 (1.8%)	7 (12.5%)	1.000*	1 (0.3%)	43 (13.8%)	1.000*
Pass	8 (4.4%)	142 (78.9%)		8 (14.3%)	40 (71.4%)		7 (2.3%)	260 (83.6%)	
Housing item No.19									
Not pass	0 (0.0%)	6 (3.3%)	1.000*	0 (0.0%)	1 (1.8%)	1.000*	0 (0.0%)	7 (2.3%)	1.000*
Pass	12 (6.7%)	162 (90.0%)		9 (16.1%)	46 (82.1%)		8 (2.6%)	296 (95.2%)	
Housing item No.20									
Not pass	0 (0.0%)	4 (2.2%)	1.000*	0 (0.0%)	0 (0.0%)	**	0 (0.0%)	6 (1.9%)	1.000*
Pass	12 (6.7%)	164 (91.1%)		9 (16.1%)	47 (83.9%)		8 (2.6%)	297 (95.5%)	
Housing item No.22									
Not pass	2 (1.1%)	16 (8.9%)	0.342*	0 (0.0%)	3 (5.4%)	1.000*	1 (0.3%)	32 (10.3%)	0.597*
Pass	10 (5.6%)	152 (84.4%)		9 (16.1%)	44 (78.6%)		7 (2.3%)	271 (87.1%)	
Housing item No.24									
Not pass	2 (1.1%)	20 (11.1%)	0.644*	0 (0.0%)	8 (14.3%)	0.329*	2 (0.6%)	26 (8.4%)	0.156*
Pass	10 (5.6%)	148 (82.2%)		9 (16.1%)	39 (69.6%)		6 (1.9%)	277 (89.1%)	
Housing item No.35									
Not pass	4 (2.2%)	65 (36.1%)	1.000*	1 (1.8%)	21 (37.5%)	0.074*	4 (1.3%)	94 (30.2%)	0.266*
Pass	8 (4.4%)	103 (57.2%)		8 (14.3%)	26 (46.4%)		4 (1.3%)	209 (67.2%)	
Housing item No.36									
Not pass	8 (4.4%)	138 (76.7%)	0.244*	7 (12.5%)	38 (67.9%)	1.000*	8 (2.6%)	228 (73.3%)	0.206*
Pass	4 (2.2%)	30 (16.7%)		2 (3.6%)	9 (16.1%)		0 (0.0%)	75 (24.1%)	
Housing item No.37									
Not pass	10 (5.6%)	130 (72.2%)	1.000*	6 (10.7%)	36 (64.3%)	0.676*	6 (1.9%)	225 (72.3%)	1.000*
Pass	2 (1.1%)	38 (21.1%)		3 (5.4%)	11 (19.6%)		2 (0.6%)	78 (25.1%)	
* Fisher's exact test coefficient, means more than 20% of the expected values in cells are less than 5; ** no statistics are computed because it is a constant, number of housing item corresponded to Table II Conditions of Housing Sanitation.									

Tab. SIII. The Correlation between Indoor Air Quality and Characteristics of the Elderly Workers and Housing Sanitation.

Characteristics	Bacteria in bedroom			Bacteria in kitchen			Fungi in bedroom			Fungi in kitchen		
	≤ 100 CFU/m ³ (227)	> 100 CFU/m ³ (76)	p-value	≤ 100 CFU/m ³ (193)	> 100 CFU/m ³ (97)	p-value	≤ 100 CFU/m ³ (218)	> 100 CFU/m ³ (72)	p-value	≤ 100 CFU/m ³ (214)	> 100 CFU/m ³ (73)	p-value
Gender												
Male	66 (21.8%)	17 (5.6%)	0.256	52 (17.9%)	23 (7.9%)	0.553	56 (19.3%)	26 (9.0%)	0.089	53 (18.5%)	19 (6.6%)	0.830
Female	161 (53.1%)	59 (19.5%)		141 (48.6%)	74 (25.5%)		162 (55.9%)	46 (15.9%)		161 (56.1%)	54 (18.8%)	
Education												
Primary school and below	151 (49.8%)	60 (19.8%)	0.041	131 (45.2%)	70 (24.1%)	0.455	140 (48.3%)	58 (20.0%)	0.010	140 (48.8%)	60 (20.9%)	0.007
Secondary school and higher	76 (25.1%)	16 (5.3%)		62 (21.4%)	27 (9.3%)		78 (26.9%)	14 (4.8%)		74 (25.8%)	13 (4.5%)	
Monthly income												
≤ 5,000 THB	79 (26.1%)	20 (6.6%)	0.219	60 (20.7%)	32 (11.0%)	0.946	70 (24.1%)	20 (6.9%)	0.789	68 (23.7%)	26 (9.1%)	0.714
5,001-10,000 THB	75 (24.8%)	33 (10.9%)		69 (23.8%)	34 (11.7%)		77 (26.6%)	27 (9.3%)		77 (26.8%)	27 (9.4%)	
≥ 10,000 THB	22 (7.3%)	9 (3.0%)		64 (22.1%)	31 (10.7%)		71 (24.5%)	25 (8.6%)		69 (24.0%)	20 (7.0%)	
Career												
Farmer/Fishery	67 (22.1%)	12 (4.1%)	0.000	53 (18.3%)	21 (7.2%)	0.009	64 (22.1%)	11 (3.8%)	0.000	63 (22.0%)	11 (3.8%)	0.000
Merchant	46 (15.2%)	18 (5.9%)		42 (14.5%)	21 (7.2%)		43 (14.8%)	18 (6.2%)		43 (15.0%)	19 (6.6%)	
Employee	50 (16.5%)	6 (2.0%)		44 (15.2%)	10 (3.4%)		49 (16.9%)	7 (2.4%)		48 (16.7%)	5 (1.7%)	
Self-employed	42 (13.9%)	31 (10.2%)		39 (13.4%)	29 (10.0%)		39 (13.4%)	29 (10.0%)		46 (16.0%)	24 (8.4%)	
Homemaker	22 (7.3%)	9 (3.0%)		15 (5.2%)	16 (5.5%)		23 (7.9%)	7 (2.4%)		14 (4.9%)	14 (4.9%)	
Religions												
Buddhism	190 (62.7%)	55 (18.2%)	0.030	165 (56.9%)	72 (24.8%)	0.019	186 (64.1%)	49 (16.9%)	0.001	178 (62.0%)	54 (18.8%)	0.084
Islam/Christianity	37 (12.2%)	21 (6.9%)		28 (9.7%)	25 (8.6%)		32 (11.0%)	23 (7.9%)		36 (12.5%)	19 (6.6%)	
Housing item No.2												
Not pass	6 (2.0%)	6 (2.0%)	0.081*	6 (2.1%)	6 (2.1%)	0.225*	3 (1.0%)	5 (1.7%)	0.025*	4 (1.4%)	6 (2.1%)	0.020*
Pass	221 (72.9%)	70 (23.1%)		187 (64.5%)	91 (31.4%)		215 (74.1%)	67 (23.1%)		210 (73.2%)	67 (23.1%)	
Housing item No.3												
Not pass	21 (6.9%)	9 (3.0%)	0.513	19 (6.6%)	11 (3.8%)	0.693	17 (5.9%)	10 (3.4%)	0.123	19 (6.6%)	9 (3.1%)	0.391
Pass	206 (68.0%)	67 (22.1%)		174 (60.0%)	86 (29.7%)		201 (69.3%)	62 (21.4%)		195 (67.9%)	64 (22.3%)	
Housing item No.4												
Not pass	21 (6.9%)	10 (3.3%)	0.331	15 (5.2%)	15 (5.2%)	0.042	16 (5.5%)	12 (4.1%)	0.020	14 (4.9%)	14 (4.9%)	0.002
Pass	206 (68.0%)	66 (21.8%)		178 (61.4%)	82 (28.3%)		202 (69.7%)	60 (20.7%)		200 (69.7%)	59 (20.6%)	
Housing item No.5												
Not pass	45 (14.9%)	20 (6.6%)	0.233	35 (12.1%)	28 (9.7%)	0.037	35 (12.1%)	28 (9.7%)	0.000	33 (11.5%)	28 (9.8%)	0.000
Pass	182 (60.1%)	56 (18.5%)		158 (54.5%)	69 (23.8%)		183 (63.1%)	44 (15.2%)		181 (63.1%)	45 (15.7%)	
Housing item No.9												
Not pass	25 (8.3%)	13 (4.3%)	0.165	19 (6.6%)	17 (5.9%)	0.061	22 (7.6%)	11 (3.8%)	0.230	23 (8.0%)	12 (4.2%)	0.199
Pass	202 (66.7%)	63 (20.8%)		174 (60.0%)	80 (27.6%)		196 (67.6%)	61 (21.0%)		191 (66.6%)	61 (21.3%)	
Housing item No.10												
Not pass	28 (9.2%)	13 (4.3%)	0.293	23 (7.9%)	17 (5.9%)	0.191	26 (9.0%)	11 (3.8%)	0.460	25 (8.7%)	13 (4.5%)	0.182
Pass	199 (65.7%)	63 (20.8%)		170 (58.6%)	80 (27.6%)		192 (66.2%)	61 (21.0%)		189 (65.9%)	60 (20.9%)	
Housing item No.11												
Not pass	4 (1.3%)	3 (1.0%)	0.373*	3 (1.0%)	4 (1.4%)	0.228*	2 (0.7%)	3 (1.0%)	0.100*	1 (0.3%)	5 (1.7%)	0.005*
Pass	223 (73.6%)	73 (24.1%)		190 (65.5%)	93 (32.1%)		216 (74.5%)	69 (23.8%)		213 (74.2%)	68 (23.7%)	
Housing item No.12												
Not pass	10 (3.3%)	13 (4.3%)	0.000	8 (2.8%)	14 (4.8%)	0.002	7 (2.4%)	13 (4.5%)	0.000	9 (3.1%)	11 (3.8%)	0.002
Pass	217 (71.6%)	63 (20.8%)		185 (63.8%)	83 (28.6%)		211 (72.8%)	59 (20.3%)		205 (71.4%)	62 (21.6%)	
Housing item No.13												
Not pass	17 (5.6%)	8 (2.6%)	0.405	12 (4.1%)	13 (4.5%)	0.040	14 (4.8%)	10 (3.4%)	0.046	13 (4.5%)	10 (3.5%)	0.038
Pass	210 (69.3%)	68 (22.4%)		181 (62.4%)	84 (29.0%)		204 (70.3%)	62 (21.4%)		201 (70.0%)	63 (22.0%)	
Housing item No.15												
Not pass	34 (11.2%)	11 (3.6%)	0.915	29 (10.0%)	14 (4.8%)	0.893	32 (11.0%)	11 (3.8%)	0.901	33 (11.5%)	10 (3.5%)	0.722
Pass	193 (63.7%)	65 (21.5%)		164 (55.6%)	83 (28.6%)		186 (64.1%)	61 (21.0%)		181 (63.1%)	63 (22.0%)	
Housing item No.19												
Not pass	4 (1.3%)	4 (1.3%)	0.112*	4 (1.4%)	4 (1.4%)	0.448*	3 (1.0%)	5 (1.7%)	0.025*	4 (1.4%)	3 (1.0%)	0.376*
Pass	223 (73.6%)	72 (23.8%)		189 (65.2%)	93 (32.1%)		215 (74.1%)	67 (23.1%)		210 (73.2%)	70 (24.4%)	
Housing item No.20												
Not pass	4 (1.3%)	2 (0.7%)	0.643*	3 (1.0%)	1 (0.3%)	1.000*	3 (1.0%)	3 (1.0%)	0.165*	2 (0.7%)	4 (1.4%)	0.038*
Pass	223 (73.6%)	74 (24.4%)		190 (65.5%)	96 (33.1%)		215 (74.1%)	69 (23.8%)		212 (73.9%)	69 (24.0%)	
Housing item No.22												
Not pass	18 (5.9%)	16 (5.3%)	0.002	14 (4.8%)	17 (5.9%)	0.008	18 (6.2%)	13 (4.5%)	0.020	16 (5.6%)	16 (5.6%)	0.001
Pass	209 (69.0%)	60 (19.8%)		179 (61.7%)	80 (27.6%)		200 (69.0%)	59 (20.3%)		198 (69.0%)	57 (19.9%)	
Housing item No.24												
Not pass	17 (5.6%)	12 (4.0%)	0.033	14 (4.8%)	13 (4.5%)	0.089	15 (5.2%)	11 (3.8%)	0.031	15 (5.2%)	11 (3.8%)	0.038
Pass	210 (69.3%)	64 (21.1%)		179 (61.7%)	84 (29.0%)		203 (70.0%)	61 (21.0%)		199 (69.3%)	62 (21.6%)	
Housing item No.35												
Not pass	65 (21.5%)	36 (11.9%)	0.003	51 (17.6%)	45 (15.5%)	0.001	55 (19.0%)	37 (12.8%)	0.000	53 (18.5%)	42 (14.6%)	0.000
Pass	162 (53.5%)	40 (13.2%)		142 (49.0%)	52 (17.9%)		163 (56.2%)	35 (12.1%)		161 (56.1%)	31 (10.8%)	
Housing item No.36												
Not pass	170 (56.1%)	63 (20.8%)	0.152	141 (48.6%)	80 (27.6%)	0.076	161 (55.5%)	62 (21.4%)	0.032	155 (54.0%)	64 (22.3%)	0.008
Pass	57 (18.8%)	13 (4.3%)		52 (17.9%)	17 (5.9%)		57 (19.7%)	10 (3.4%)		59 (20.6%)	9 (3.1%)	
Housing item No.37												
Not pass	167 (55.5%)	61 (20.1%)	0.242	137 (47.2%)	79 (27.2%)	0.054	154 (53.1%)	64 (22.1%)	0.002	150 (52.3%)	64 (22.3%)	0.003
Pass	60 (19.8%)	15 (5.0%)		56 (19.3%)	18 (6.2%)		64 (22.1%)	8 (2.8%)		64 (22.3%)	9 (3.1%)	

* Fisher's exact test coefficient, number of housing item corresponded to Table II Conditions of Housing Sanitation.

RESEARCH ARTICLE

Relationship of pupils' quality of life and academic achievement with the employment status of their mothers

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Keywords

Quality of life • Academic achievement • Mothers' employment

Summary

Introduction. One of the most important environmental factors affecting academic achievement and performance is the family especially mothers. The purpose of this study was to determine the relationship between quality of life (QOL) and the academic achievement of pupils with the employment status of their mothers.

Methods. This cross-sectional study was conducted on 9th-grade students in Shiraz. A sample of 400 individuals was selected through a multi-stage sampling method from among the 9th-grade students and a questionnaire on academic achievement and quality of life was completed for them. Then data was entered into spss23 software and analyzed. The value of $P < 0.05$ was considered a significant statistical level.

Results. There was no significant difference between students who have employed and Housewife mothers about the student's academic achievements and QOL score ($P > 0.05$). According to the results of multivariate analysis, none of the variables was a significant predictor of the QOL and academic achievement in the students.

Conclusion. In spite of lack of association between the quality of life and academic achievement of students with their mothers' occupation but it should be regarded that more attention to students and spent more time by students can be very helpful in the academic achievement of students.

Introduction

Pupils in any community comprise an efficient subpopulation and the builders of the future in any country. Pupils represent the subpopulation to whom most of the planning and budget in any country is allocated and whose academic achievement is greatly important to gaining success in the future; therefore, identifying the factors affecting academic achievement is a step towards sustainable development [1, 2]. Academic achievement refers to the amount of school learning or the degree to which students achieve educational goals that are measured by various examinations [3]. One of the most important environmental factors affecting academic achievement and performance is the family whose functional dimension has been investigated in various studies [4]. Another study indicated that the success of students in school has a significant relationship with the living conditions of parents such as their income and education level [5]. Investigating health-related quality of life (QOL) is used to predict health care needs for identifying the most important dimensions of children's health that are at risk, or for identifying children in need of support in the early stages of life [6]. Studies on healthy children are mainly necessary because the QOL of children and adolescents is directly related to their QOL in adulthood [7]. The results of Viira et al.'s study on Estonian adolescents to determine the difference in the QOL between boys and girls in physical, mental, and school-related

activities showed that the total score of adolescent females' QOL was lower than adolescent males' [8]. Several factors affect the QOL and the academic achievement of adolescents, including religion, social relationships, social participation, and mother-child attachment. Among these factors, the mother's employment, due to its growing growth, needs to be further explored. During adolescence, many behaviors affecting the health and lifestyle of individuals are shaped; attitudes and behaviors shaped during adolescence determine the healthy lifestyle habits of adulthood. Because of the behaviors and lifestyle of this period, leading to a huge burden of main diseases in the future, and because the pattern of illnesses has changed, and illnesses caused by the unhealthy lifestyle are the leading cause of death, and given the fact that by changing lifestyle, many risk factors that are one of the most important causes of mortality can be fought, the necessity of investigating the relationship of QOL and the academic achievement and mother's employment in pupils is intensified. Given the mentioned points the purpose of this study was to determine the relationship between quality of life (QOL) and the academic achievement of pupils with the employment status of their mothers.

Materials and methods

In this analytical-cross-sectional study, the number of schools and the 9th-grade students based on the divisions

of the Education Organization with considering the education quality and different districts of the Education Organization was obtained from the Education Department of Shiraz.

Multistage sampling was used to select participants. To this end, girls' and boys' schools were selected by convenience random sampling and then some classes were randomly selected from the ninth grade classes of selected schools.

Selected classes were considered clusters and all eligible pupils of the class who fulfilled inclusion criteria (lack of suffering from hard-to-treat diseases, living with both parents, and being natives to Shiraz) were studied and the relevant questionnaires were completed for them.

Considering that the maximum standard deviation of QOL domains, according to the study by Nik Azin et al., was 21.3, and to reach a significant difference of at least 6.50 in the mean value of the pupils' QOL between employed and unemployed mothers, the sample size was determined to be 360 that increased to 400 due to the probability of subject attrition [9].

Data collection instruments were a researcher-developed checklist (including variables such as gender, birth order, number of children, the age difference between the mother and her child, parental education, parental occupation, parental Work Experience, working hours of parents, and time spent by parents), and the standard questionnaires of educational attainment and health-related QOL.

The standard questionnaire of the academic attainment of high school students has 60 items and aims to measure the students' academic achievement. The items of the questionnaire are two-choice (Yes/No) questions, which are scored from 0 to 1. The reliability of the questionnaire has been estimated to be 0.82 [10].

The questionnaire used to investigate QOL was the *Kidscreen Health-related Quality of Life Questionnaire* consisting of 27 items. The questionnaire has 5 dimensions: 1) Physical well-being (5 items; measuring levels of physical activity, energy, and fitness); 2) Psychological well-being (7 items; measuring positive emotions, life satisfaction, and emotionally balanced feelings); 3) Parental communication and autonomy (7 items; measuring relationships with parents, home atmosphere, having adequate age-proportionate freedom and an adequate degree of satisfaction with financial resources; 4) Social and peer support (4 items; measuring the nature of the respondent's communication with other peers); 5) School environment (4 items; measuring child and adolescent perception of cognitive capacity, learning and concentration, and feelings about the school). In the study by Nick Azin et al., the validity and reliability of the questionnaire were approved in students in Yazd, Iran [9]. To observe ethical considerations, the data were analyzed anonymously after informed consent was provided by the parents of students.

After data collection, the data were entered into SPSS version 23. Descriptive statistics (e.g., mean and standard deviation) were used to describe the data by using a t-test, ANOVA, Pearson correlation coefficient, and

univariate and multivariate linear regressions. $P < 0.05$ was considered as a significance level.

Results

The mean score of academic achievement among students with employed and Housewife mothers was 27.24 ± 4.87 and 26.62 ± 5.42 respectively ($P = 0.25$). Also, the total score of quality of life among students with employed and Housewife mothers was 95.05 ± 0.76 and 95.65 ± 1.07 respectively ($P = 0.65$). About the different dimensions of quality of life, there was no significant difference between students who have Employed and Housewife mothers ($P > 0.05$) more details as shown in Table I.

In comparison student academic achievement score and Total quality of life score about different variables, in terms of student academic achievement, just the mean difference between different subgroup of mother education level (Primary: 27.96 ± 4.07 , Diploma: 27.81 ± 5.37 , Academic: 26.51 ± 5.05) about this score was showed a significant difference ($P = 0.03$). In other words, the students who had mothers with primary and diploma education levels had the highest academic achievement. But this index does not have a significant difference in the variables such as sex, birth order, Number of children, Mother's Work Experience, father's Work Experience, mother's education level, and father's education level.

About the total quality of life, the mean score of quality of life among males students was 93.98 ± 12.31 and among females was 96.53 ± 12.39 and this difference was significant ($p = 0.04$). But there was no statistically significant difference in the variables such as mother education level, birth order, Number of children, Mother's Work Experience, father's Work Experience, mother's education level, and father's education level. The comparison of different diminutions of quality of life about different variables was shown in Table II.

According to the results of multiple linear regression, the effect of father job status on the total quality of life score was statistically significant ($p < 0.05$). But the effect of other variables such as Time spent with mother, Mother's occupation status, Age difference with mother, Mother's occupation status, Birth order, Number of children, Mother's Work Experience, Mother working hours, Mother's education level and Father's education level not statistically significant ($p > 0.05$). Also the effect of father job status, Time spent with mother, Mother's occupation status, Age difference with mother, Mother's occupation status, Birth order, Number of children, Mother's Work Experience, Mother working hours, Mother's education level and Father's education level on students' academic achievement not statistically significant ($p > 0.05$) (Tab. III). In term of correlation between academic achievement and quality of life scores with some factors such as, Time spent with mother, Time spent with father, just the correlation between Parental communication and autonomy with Time spent with mother ($r = 0.12$, $P = 0.01$) and Time spent with mother ($r = 0.09$, $P = 0.04$) was statistically significant (Tab. IV).

Tab. I. Comparison of mean scores for quality of life and academic achievement of ninth-grade students at Employed and Housewife mothers in 2016.

Variable		Mean \pm SD		P
		Employed mothers (267)	Housewife mothers (133)	
Academic achievement		4.87 \pm 27.24	5.42 \pm 26.62	0.25
The total score of quality of life		0.76 \pm 95.05	1.07 \pm 95.65	0.65
Dimensions of quality of life	Physical well-being	4.06 \pm 17.99	18.22 \pm 4.09	0.6
	Psychological well-being	2.95 \pm 21.83	21.93 \pm 3.08	0.75
	Parental communication and autonomy	5.39 \pm 26.74	26.65 \pm 5.3	0.88
	Social and peer support	3.36 \pm 14.13	13.86 \pm 3.33	0.46
	School environment	3.03 \pm 14.37	14.98 \pm 2.88	0.06

Tab. II. Comparison of students' quality of life scores and academic achievement grade about some variables.

Variable		Mean \pm SD						
		Academic achievement	The total score of quality of life	Dimensions of quality of life				
				Physical well-being	Psychological well-being	Parental communication and autonomy	Social and peer support	School environment
Sex	Male	26.84 \pm 4.79	93.98 \pm 12.31	17.28 \pm 4.09	21.67 \pm 3.01	26.33 \pm 5.42	14.23 \pm 3.44	14.48 \pm 3.05
	Female	27.24 \pm 5.32	96.53 \pm 12.39	18.86 \pm 3.89	22.06 \pm 2.96	27.09 \pm 5.27	13.86 \pm 3.25	14.66 \pm 2.94
	P	0.44	0.04	0.001	0.193	0.15	0.27	0.55
Birth order	1	26.88 \pm 4.91	95.68 \pm 11.76	18.42 \pm 3.67	21.69 \pm 3.19	26.89 \pm 5.19	14.14 \pm 3.32	14.54 \pm 2.83
	2	27.04 \pm 5.44	96.14 \pm 12.37	18.22 \pm 4.28	22.11 \pm 2.69	26.93 \pm 5.12	14.13 \pm 3.5	14.75 \pm 3.16
	> 3	27.67 \pm 4.77	91.47 \pm 14.37	16.27 \pm 4.62	21.98 \pm 2.81	25.49 \pm 6.34	13.44 \pm 3.08	14.29 \pm 3.25
	P	0.58	0.05	0.002	0.44	0.19	0.36	0.62
Number of children	1	27.79 \pm 5.27	95.39 \pm 9.86	18.12 \pm 3.28	21.69 \pm 2.98	26.71 \pm 4.77	13.93 \pm 3.32	14.66 \pm 2.71
	2	26.75 \pm 4.96	96.02 \pm 12.64	18.38 \pm 3.95	21.74 \pm 3.09	27.09 \pm 5.34	14.26 \pm 3.28	14.56 \pm 2.96
	> 3	27.18 \pm 5.14	93.81 \pm 13.01	17.49 \pm 4.55	22.04 \pm 2.81	26.04 \pm 5.61	13.71 \pm 3.46	14.53 \pm 3.19
	P	0.35	0.29	0.15	0.64	0.22	0.34	0.97
Mother's work experience	0	26.89 \pm 4.57	95.19 \pm 12.04	17.82 \pm 3.94	21.69 \pm 2.93	27.03 \pm 5.11	14.12 \pm 3.37	14.53 \pm 2.93
	1-15	27.41 \pm 5.54	96.12 \pm 12.97	18.69 \pm 4.19	22.41 \pm 3.22	26.52 \pm 5.75	14.23 \pm 3.37	14.27 \pm 3.07
	> 16	26.95 \pm 5.51	94.52 \pm 12.61	17.94 \pm 4.16	21.66 \pm 2.83	26.28 \pm 5.42	13.7 \pm 3.29	14.94 \pm 3.03
	P	0.56	0.29	0.49	0.89	0.35	0.77	0.91
Mother working hours	0	26.89 \pm 4.57	95.19 \pm 12.04	17.82 \pm 3.94	21.69 \pm 2.93	27.03 \pm 5.11	14.12 \pm 3.37	14.53 \pm 2.93
	1-7	27.21 \pm 5.87	94.82 \pm 12.54	18.18 \pm 4.16	21.88 \pm 2.96	25.31 \pm 5.42	13.93 \pm 3.35	14.53 \pm 3.07
	> 8	27.11 \pm 4.69	96.38 \pm 13.33	15.59 \pm 4.26	22.38 \pm 3.2	26.59 \pm 5.93	14.05 \pm 3.32	14.78 \pm 3.06
	P	0.08	0.58	0.41	0.87	0.43	0.84	0.19
Mother's education level	Primary	27.96 \pm 4.07	93.02 \pm 14.45	17.06 \pm 4.65	21.88 \pm 3.22	25.6 \pm 5.86	13.58 \pm 3.88	14.36 \pm 3.36
	Diploma	27.81 \pm 5.37	94 \pm 11.52	17.53 \pm 3.99	21.83 \pm 2.96	26.22 \pm 5.49	13.75 \pm 3.09	14.67 \pm 2.57
	Academic	26.51 \pm 5.05	96.25 \pm 12.27	18.39 \pm 3.95	21.88 \pm 2.97	27.15 \pm 5.15	14.26 \pm 3.34	14.57 \pm 3.09
	P	0.03	0.12	0.13	0.99	0.09	0.25	0.83
Father's education level	Primary	27.79 \pm 4.47	93.15 \pm 14.35	17.85 \pm 4.47	22.04 \pm 3.13	25.29 \pm 6.01	13.49 \pm 3.74	14.47 \pm 2.95
	Diploma	27.37 \pm 4.86	95.33 \pm 11.93	17.89 \pm 4.14	21.92 \pm 2.82	26.98 \pm 5.34	14.09 \pm 3.26	14.44 \pm 2.99
	Academic	26.67 \pm 5.28	95.65 \pm 12.25	18.21 \pm 3.94	21.79 \pm 3.07	26.85 \pm 5.19	14.12 \pm 3.32	14.67 \pm 3.01
	P	0.25	0.45	0.72	0.85	0.15	0.49	0.76

Discussion

This study aimed to identify the effective factor in students' QOL and academic achievement in Shiraz city in Iran.

The results showed that the student's QOL and academic achievement had no significant association with the mother's occupation.

The physical well-being dimension of QOL was significantly associated with students' sex, the age

Tab. III. Effective factors on student's quality of life score and the academic achievement of the ninth grade students.

Variable		The total score of quality of life			Academic achievement		
		B	95% CI	P	B	95% CI	P
Time spent with mother		0.31	-0.21-0.83	0.24	0.08	-0.13-0.29	0.44
Age difference with mother		0.002	-0.28-0.28	0.99	0.03	-0.08-0.14	0.63
Mother's occupation status	Housewife	3.55	-1.71-8.81	0.19	-1.84	-3.97-0.29	0.09
Birth order	1						
	2	1.33	-1.82-4.48	0.41	0.12	-1.15-1.39	0.85
	> 3	-0.78	-6.32-4.75	0.78	0.13	-2.11-2.37	0.91
Number Of children	1						
	2	0.003	-3.79-3.79	0.99	-1.11	-2.65-0.42	0.15
	> 3	-0.62	-5.49-4.2	0.8	-1.23	-3.19-0.74	0.22
Mother's work experience	0						
	1-15	0.03	-6.27-6.32	0.99	2.39	-0.15-4.94	0.07
	> 16	-2.89	-9.69-3.89	0.4	2.42	-0.33-5.17	0.08
Mother working hours	0						
	1-7	-1.43	-5.29-2.43	0.47	-0.26	-1.83-1.29	0.74
	> 8	0	-	-	-	-	-
Mother's education level	Elementary						
	Diploma	-0.16	-5.04-4.72	0.95	-0.36	-2.33-1.61	0.72
	Academic	-1.2	-6.71-4.31	0.68	-0.47	-2.69-1.76	0.68
Father's education level	Elementary						
	Diploma	1.45	-3.31-6.22	0.55	0.15	-1.78-2.08	0.88
	Academic	4.7	-0.53-9.94	0.08	-0.68	-2.79-1.44	0.53
Father's job status	Jobless						
	worker	3.85	-0.4-8.09	0.08	-0.82	-2.54-0.89	0.35
	Employee	5.92	1.86-90.98	0.004	-0.07	-1.71-1.57	0.94
	Free	7.13	0.52-13/75	0.04	1.17	-1.51-3.85	0.39

Tab. IV. Correlation between academic achievement and quality of life with some factors.

Variables		Time spent with mother	Time spent with father
Academic achievement score	r*	0.002	-0.040
	P	0.969	0.430
	n	400	400
The total score of quality of life	r	0.084	0.065
	P	0.095	0.196
	n	400	400
Physical well-being	r	0.040	0.077
	P	0.425	0.122
	n	400	400
Psychological well-being	r	-0.079	-0.081
	P	0.113	0.108
	n	400	400
Parental communication and autonomy	r	0.120*	0.099
	P	0.016	0.048
	n	400	400
Social and peer support	r	0.082	0.010
	P	0.102	0.839
	n	400	400
School environment	r	0.066	0.055
	P	0.191	0.268
	n	400	400

* Correlation coefficient.

difference between mother and child, birth order, and the average time spent by the mother. Also, there was a significant association between the parental communication and autonomy dimension and the average time spent by the mother and father's occupation.

Educational achievement had a significant association with the father's education level and occupation.

Some scholars consider the QOL of children and adolescents to be subjective and alterable in their health and believe that this feeling reflects their desires, hopes, expectations concerning their present and future life.

The results of various studies showed that physical and psychological health and QOL of female adolescents were more unfavorable than those of male adolescents [8, 11, 12], which is consistent with the results of our study.

In this study, students in the autonomy dimension attained the highest score. The autonomy domain addresses the freedom of choice, self-sufficiency, and independence of the adolescent, and considers the individual's opportunities for recreation and social activity. Contrary to the results of this study, Arsanjani et al reported the lowest score on the autonomy dimension [13]. the differences between the studies may be due to different study population also different socio-economic status and so on.

The results of a study showed that while parental education and occupation were associated with academic achievement significantly, the mother's occupation was significantly associated with students' academic achievement [14]. In the current study, there was no relationship between the mother's occupation and the students' QOL and academic achievement, but there was a significant association between father's occupation and academic achievement of students.

Alipour investigated the health-related QOL in high school students, according to their results, the understudied student's moderate QOL score.

In the current study, the highest mean value was related to the relationship with parents and the least for the physical well-being and psychological well-being dimensions. Based on the current study results there was a significant association between gender and physical well-being. The gender and selection of family members for living variables were an effective factor in psychological well-being. The mother's education, selection of family members for living, and composition of family members variables were significantly associated with parental communication. Father's occupation was a significant predictor for social support and age. According to another study results, the selection of family members for the living variable was a significant predictor of the school environment [15]. In comparison to our results, the study of Atadokht showed that neglect of academic work among male students was more than in female students [16].

In the study by Alipour et al., parents' education level had a significant impact on students' academic achievement and Students who living in fewer literate levels and illiterate families had academic procrastination [1]. Mohammadi et al. argued that the father's education level did not cause of the difference in the academic achievement among pre-high school, high school, and university students, but mother's education had a significant effect on students' success, the effect of mother education level on children academic success may be due to the greater control and more sensitivity of mothers to their children's education [17].

According to the results of the current study, the father's job status had a significant effect on the academic achievement of students. It seems the better job status of the father can improve the socio-economic status of the family and it can provide better conditions for the students.

In this study, academic achievement was correlated with Parental communication and autonomy.

The results of some studies have shown that there is a significant correlation between academic procrastination and QOL [18, 19], which is consistent with the results of the current study.

The main reason for the inconsistency in the results of the current study and similar studies is due to use of research instruments, the difference about the students' age and grade, the available facilities, and how they are managed in schools, as well as the differences in parental relationships among different societies.

According to the results of our study, students should pay more attention to improving their QOL in schools to increase their academic achievement.

Conclusions

The results of this study showed that there was no significant association between quality of life and academic achievement of students with their mothers' occupation status. But this point should be considered that more attention to students and spent more time by students can be very helpful in the academic achievement of students. Finally, it should be considered that the mentioned association may be affected by different factors so it recommended similar studies by controlling the effect of a more probable confounder.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

FP and MHL carried out the study, participated in the analysis and manuscript drafting, participated in analysis and manuscript drafting, collaborated in Collecting the raw data. MF and HF coordinated the study and participated in the analysis and manuscript drafting. All authors read and approved the final manuscript.

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RESEARCH ARTICLE

Fungal carriage on healthcare workers' hands, clothing, stethoscopes and electronic devices during routine patient care: a study from a tertiary care center

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Keywords

Fungal surveillance • Health care workers • *Candida auris* • Hands • Electronic devices

Summary

Background. Invasive fungal infections are a constant threat to immunocompromised and critically ill patients. Healthcare workers caring for such patients act as conduits of transmission through their contaminated hands and belongings causing nosocomial infections. Although bacterial contamination of healthcare workers is known, our knowledge about fungal carriage is sparse. Among the fungi, candida species colonization of hands of healthcare workers is known however it would be interesting to know the type of fungal carriage on their inanimate belongings.

Aim. To study the prevalence and type of fungal carriage on healthcare workers hands, aprons/hospital scrubs, electronic devices, and stethoscopes.

Methods. Healthcare workers working in Medicine ward and ICU during November and December 2019 were sampled. Hand washes were collected in Brain Heart Infusion (BHI) broth with gentamycin. Direct impression smears on blood agar were taken

from aprons/hospital scrubs. Electronic devices and stethoscopes were sampled using moist cotton swabs. Subculture and plating was done on Sabarouds Dextrose Agar (SDA). Yeasts were identified using Matrix Assisted Laser Desorption Ionisation Time of Flight (MALDI TOF) and moulds were identified using microscopy.

Findings. Out of 60 health care workers, 20 (33.3%) had fungal carriage. Aprons/hospital scrubs and hands were contaminated in 17 (28.3%) and 3 (5%) respectively. Aprons/hospital scrubs mainly constituted moulds belonging to species of *Aspergillus*. Hands were contaminated with *Candida tropicalis*, *Candida parapsilosis* and *Candida auris*. Electronic devices and stethoscopes had no fungal contamination.

Conclusions. Active fungal surveillance provides prevalent carriage rates and serve as a feedback to improve our disinfection and hand hygiene practices. It also aids in identification of potential source of hospital outbreaks.

Introduction

Fungal nosocomial infections continue to be a serious problem among hospitalized patients causing increasing morbidity, mortality and healthcare costs [1]. A study done at a tertiary care center in India reported 15% invasive fungal infections in ICU, including invasive aspergillosis, invasive candidiasis and mucormycosis [2]. Most of the fungal nosocomial infections are due to exogenous acquisition of the fungus which shows a marked tendency to colonize hospital environments. These fungal pathogens flourish on their surfaces and form biofilms causing plethora of hospital acquired infections. The presence of biofilms proves to be therapeutic challenge and thus complicates the clinical scenario [3, 4]. The major implicated agent involved in spread of fungal infections are the hands of healthcare workers (HCWs) which are vulnerable to colonization and infection by fungal pathogens, especially with *Candida species* [5, 6]. Recent studies have observed, *Candida parapsilosis* represents the most frequently isolated fungus from the hands of healthy people and healthcare workers thus highlighting the importance of hand washing to prevent the horizontal transmission of

this pathogen [7, 8]. The other modes of transmission of nosocomial infections are less studied in fungal pathogens, hence this study was undertaken to assess the frequency and type of carriage of fungal pathogens on health care workers hands, apron/hospital scrubs, electronic devices and stethoscopes and their role as conduits of transmission.

Methods

A cross sectional study was conducted over a period of two months (November and December 2019) among health care workers working in wards and ICU of medicine department AIIMS, New Delhi after receiving ethical approval from institute ethics committee. The health care workers included were doctors, nursing officers and other support staff (OT technicians, hospital attendants and sanitary attendants)

Samples from hands were taken using Brain Heart Infusion (BHI) broth with gentamycin, in which the hands were washed, and samples were collected as hand washes. The hand wash broths were further incubated

at 38 degree Celsius for 48 hours and later was sub-cultured on Sabarouds Dextrose Agar (SDA).

Samples from apron/hospital scrubs sleeves and side pockets were taken as direct impression smears on blood agar plates. Stethoscopes and electronic devices were swabbed using moist cotton swabs and were further cultured on SDA and incubated.

SDA and blood agar plates were incubated at 38 degree Celsius for a maximum of five days to look for any growth. The growth was identified using gram stain and Matrix Assisted Laser Desorption Ionisation Time of Flight (MALDI TOF) for yeast like colonies. Moulds were identified by microscopy based on morphology on Lactophenol Cotton Blue (LPCB) mount.

This pilot study was carried out on healthcare workers working in medicine wards and ICU. A total of 60 healthcare workers were sampled based on convenience and available resources. A descriptive statistical analysis was performed in the form of frequency and percentages to assess the nature of fungal carriage on healthcare workers hands, aprons/hospital scrubs, stethoscopes, and devices.

Results

Sixty healthcare workers in medicine wards and ICU were sampled during the study period. It included 43 males and 17 females. They were further stratified based on their designation, 36.7, 26.7, 25, 10 and 1.7% were Junior Residents, Nursing staff, Senior Residents, Support staff and interns, respectively. 75 and 25% of the healthcare workers included were working in medicine wards and ICU respectively (Tab. I). A total of 41 stethoscopes, 66 devices (Mobile phones, tablets, pulse oximeters), everyone's hands and aprons were sampled, totalling up to 227 samples. Fifty-four (90%) had a single device while 6 (10%) had two devices.

Twenty (33.3%) out of the 60 healthcare workers had one or the other fungi isolated. None of the stethoscopes or the devices swabbed had any fungal growth while growth was seen mainly in the aprons and hands. Out of the 20 fungi isolated, 17 were from aprons, 3 were from hands (Tab. II). Amongst the fungi isolated from apron, 15 were *Aspergillus* species, one *Rhizopus oryzae* and one *Lichthemia corymbifera*. Only *Candida* species was isolated from hands which included one each of *Candida tropicalis*, *Candida parapsilosis* and *Candida*

Tab. I. Demographic profile.

Demographic characteristic		Number (%), N = 60
Male		43 (71.7%)
Designation	Senior resident	15 (25%)
	Junior resident	22 (36.7%)
	Intern	1 (1.7%)
	Nursing staff	16 (26.7%)
	Support staff	6 (10%)
Unit of surveillance	Ward	45 (75%)
	ICU	15 (25%)

Tab. II. Fungal isolates from different samples.

Sample (N)	Number of fungal isolates (n = 20) (%)
Stethoscope (41)	0
Devices (66)	0
Aprons (60)	17 (28.3%)
Hands (60)	3 (5%)

Tab. III. Species of fungi isolated from various samples.

Sample	Fungal isolate	Number (n = 20) (%)
Aprons/hospital scrubs	<i>Aspergillus fumigatus</i>	10 (50%)
	<i>Aspergillus flavus</i>	2 (1%)
	<i>Aspergillus terreus</i>	1 (0.5%)
	<i>Aspergillus nidulans</i>	1 (0.5%)
	<i>Aspergillus sydowii</i>	1 (0.5%)
	<i>Rhizopus oryzae</i>	1 (0.5%)
	<i>Lichthemia corymbifera</i>	1 (0.5%)
Hand	<i>Candida auris</i>	1 (0.5%)
	<i>Candida tropicalis</i>	1 (0.5%)
	<i>Candida parapsilosis</i>	1 (0.5%)

Tab. IV. Fungal isolates in different surveillance units.

Surveillance unit (N)	Number of fungal isolates (n = 20) (%)	
Ward (45)	12 (26.7%)	Apron - 11
		Hands - 1
ICU (15)	8 (53.3%)	Apron - 6
		Hands - 2

auris (Tab. III). Electronic devices and stethoscopes had no fungal contamination. Eight out of 15 (53.3%) and 12 out of 45 (26.7%) of healthcare workers working in wards and ICU respectively were contaminated with fungi (Tab. IV).

Discussion

Our study was conducted to analyse the fungal carriage among healthcare workers by active surveillance. Wide spectrum of healthcare workers were sampled including senior residents, junior residents, interns, nursing staff and support staff working in wards and ICU. All potential sites of contamination including hands, aprons/hospital scrubs, devices and stethoscope of healthcare workers were sampled. The total fungal carriage among healthcare workers was 33.3% in our study, which accounts for one third of the healthcare workers sampled. Single studies which have comprehensively investigated all possible sites for fungal carriage in a healthcare worker are sparse. Most of the studies have focussed on bacterial carriage, however the present study has shown a significant proportion of fungal carriage.

Aprons/hospital scrubs and hands were the major sources of contamination accounting for 28.3% and 5% respectively. Varying levels of fungal isolation have been reported from hands. A surveillance study on yeast carriage on hands reported a prevalence of 61% from healthcare workers out of which 57% were *Candida* species [5]. While another study revealed a prevalence

of 16.6% *Candida* species [9]. Our rates of carriage were much lower, the probable reason could be good adherence to hand hygiene practices. However, among the three *Candida* species isolated one of them was *Candida auris*. It is known to cause hospital outbreaks. Its multidrug resistant nature and persistent colonization makes it difficult to treat in critically ill patients. Health care workers can have transient colonization and can act as conduits of transmission as reported in a study which had a *Candida auris* carriage rate of 2.8% [10]. With the isolation of *Candida auris*, ICU staff were alerted, and strict hand hygiene measures were employed. Repeat testing after 2 weeks did not show any growth. Emphasizing the need for handwashing.

Aprons/hospital scrubs were the major source of fungal contamination, accounting up to 28.3% in our study which mainly included various species of *Aspergillus*. Fungal isolation was seen 1.9% in a study, which included *Mucorales* [11]. Swabbing was their method of surveillance which markedly differed from ours wherein blood agar plates were directly inoculated from the scrubs. Fungal spores are ubiquitous in the environment and can readily contaminate the scrubs and thus can act as potential sources of transmission. In the absence of HEPA filters, fungal spores can cause invasive infections in immunocompromised patients.

Bacterial contamination of cell phones has been documented however moulds and yeasts have been infrequently isolated from electronic devices used by healthcare workers [12-14]. Similarly, we were also not able to isolate any fungal growth from both stethoscope and electronic devices which mainly included mobile phones. That does not mean that they cannot be a source of contamination and it probably requires better method of surveillance.

This study emphasizes the need for active fungal microbiological surveillance among healthcare workers. Neutropenic and critically ill patients are at an increased risk of invasive fungal infections. Most of the surveillance currently focuses on isolation of bacteria, however fungal surveillance can help in recognizing healthcare workers as a source of transmission and thus prevent an outbreak as evidenced in this study by isolation of *Candida auris* and a potential outbreak could be averted. This study also provides insight into novel surveillance methods which can be tried in contrast to the usual swabbing technique. A significant fungal carriage was reported in this study, but does this carriage translate into transmission and disease in patients requires additional studies.

Conclusions

Fungal carriage among healthcare workers is significant. They can serve as a potential source of transmission. Active surveillance, adequate disinfection of hospital scrubs and compliance to hand hygiene can go a long way in reducing invasive fungal infections.

Abbreviations

ICU: Intensive Care Unit

BHI: Brain Heart Infusion

SDA: Sabarouds Dextrose Agar. Yeasts were identified using

MALDI TOF: Matrix Assisted Laser Desorption Ionisation Time of Flight

LPCB: Lactophenol Cotton Blue

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

VCK, AK and GS conceived the study. VCK, NR and MS were involved in collection of samples and processing under the guidance of GS. VCK wrote the manuscript and was guided by AK. MAK was involved in statistical analysis and script editing. NW and IX were involved in script editing and script critical review. All authors read and approved the final version of the manuscript.

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RESEARCH ARTICLE

Worldwide incidence and mortality of ovarian cancer and Human Development Index (HDI): GLOBOCAN sources and methods 2018

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Keywords

Incidence • Mortality • Ovarian cancer • Human development index

Summary

Objective. Ovarian cancer is known as the seventh most common cancer among women, accounting for about 4% of all cancers associated with the females.

Method. This is a descriptive cross-sectional study based on cancer incidence data and cancer mortality rates from the Global Cancer Data in 2018. The incidence and mortality rates were estimated and ovarian cancer distribution maps for world countries were drawn. To analyze data, correlation and regression tests were used to evaluate association between its incidence and mortality with human development index (HDI)

Results. Results revealed a direct and significant correlation between ovarian cancer incidence ($R = 0.409$, $P < 0.0001$) and mortality ($R = 0.193$, $P < 0.05$) with HDI. It also projected a direct

and significant correlation between incidence with Gross National Income per 1,000 capita (GNI), mean years of schooling (MYS), life expectancy at birth (LEB) and expected years of schooling (EYS) ($P < 0.0001$). The findings also demonstrated a direct and significant correlation between mortality and GNI, MYS, LEB as well as EYS ($P < 0.05$). The linear regression model showed that a higher MYS [$B = 0.2$, CI 95%: (-0.03, 0.5)] can significantly augment the incidence of ovarian cancer while an increased MYS [$B = 0.2$, CI 95% (0.03, 0.4)] can induce mortality.

Conclusions. Given the direct and significant correlation between ovarian cancer incidence and mortality with HDI, attention to risk factors in these countries can be effective in curbing its incidence and mortality.

Introduction

Non-communicable diseases (NCDs) are among the leading causes of death around the globe. Due to major changes in fertility and life expectancy, the world's population is growing rapidly and non-communicable diseases including cancers are accordingly increasing significantly [1]. According to WHO estimates in 2015, cancer is the first or second leading cause of mortality before the age of 70 in most countries. Population growth, aging, and economic development are among the reasons for the growing prevalence of cancer worldwide. Cancers are the leading cause of death in some developed countries and the second leading cause of death after cardiovascular disease in the developing countries [2]. Ovarian cancer is ranked seventh of the most common cancers among women thus accounting for about 4% of all cases associated with the females; it is the sixth malignant cause of cancer deaths in women [3]. As for its high prevalence, high mortality rate and its impact on patients' quality of life and economic costs, ovarian cancer is known to be one of the important abnormalities that require special attention [4].

Among the most significant factors triggering the incidence of ovarian cancer is family history, pregnancy, childbirth

and age [5, 6]. Environmental and socioeconomic factors also affect ovarian cancer mortality rate. The overall growing trend of ovarian cancer incidence and mortality can be observed in all regions of the world across different social and economic levels. Variations in ovarian cancer incidence rate in the world is not restricted to the above factors. It can also be due to differences in the cancer registration system in different countries [7].

Socio-economic developments can bear profound impact on the scale and features of cancer. The epidemiological transmission of cancer distribution around the world has virtually changed. Compared to high-income nations, the prevalence of global demographic and epidemiological trends in middle- and low-income countries has shown a crucial cancer decline in recent decades. In some regions of Africa, the standardized prevalence of ovarian cancer is lower than 5 per 100,000 whereas in eastern and central Europe it proves to be higher than 11 per 100,000 among women [4, 8].

Annually, 225,000 new cases of ovarian cancer are diagnosed 140,000 of whom die out [9]. The risk of complications resulting from this cancer is 1 in 71 and the chance of death amounts to 1 in 95 [9, 10]. Moreover, estimates of the disability-adjusted life-years (DALYs)

lost in ovarian cancer are on the rise [11]. Ovarian cancer is more common in industrialized than in the developing countries. However, the highest proportion of age-specific mortality in ovarian cancer is seen in the developing countries [12]. According to the United Nations record on HDI, the disease burden associated with ovarian cancer in areas with a high HDI proves higher. HDI is a summary index for human development measurements; it measures the mean achievement of a country in three main dimensions of human development: long and healthy life, access to knowledge and living standards [13].

In regard with the global trend of ovarian cancer and its progress in recent years, awareness to its incidence and mortality and its relation to the HDI can be effective in planning and managing financial and human resources for its prevention. Despite the increasing burden of cancers in the developing countries, only 5% of global resources are appropriated for these countries [14]. It thus seems a requisite for all nations to conduct further research so as to uncover how socioeconomic conditions can affect the cancer risk factors.

The purpose of this study is to assess the impact of socioeconomic development (based on HDI) on the global trend of incidence and mortality resulting from ovarian cancer in the world based on Global Cancer Data for 2018. We intend to measure the key characteristics of ovarian cancer transmission in the world by examining the relationship between the incidence rate and the HDI, which consists of life expectancy, education, and gross national income.

Material and methods

Methods used for measuring incidence rate in terms of age and gender for each country are touched upon broadly as follows: 1) national incidence rate observed by 2018 (45 countries); 2) the most recent (national or regional) incidence rates on the basis of the population in 2018 (50 countries); 3) rates calculated using national mortality data through modeling and the ratio of mortality to incidence rate obtained from cancer records of countries (14 countries); 4) rates calculated using national mortality data through modeling and the ratio of mortality to incidence rate obtained from cancer records of neighboring countries (37 countries); and 5) national incidence rates in terms of age and gender for all cancers obtained by averaging the overall incidence rates from neighboring countries. These values were then analyzed to obtain the national incidence for each specific site using relative cancer frequency data (7 countries). Further, the rates were calculated as the median of selected neighboring countries.

MORTALITY

The methods deployed for measuring incidence rate for each country as to age and gender are ranked as follows: 1) the national mortality rate observed and published by 2018 (81 countries); 2) recent national mortality rates according to population in 2018 (20 countries); 3) rates

calculated using national mortality data through modeling and the ratio of mortality to incidence rate obtained from cancer records of neighboring countries (81 countries); 4) the rates calculated as the median of selected neighboring countries (three countries).

HUMAN DEVELOPMENT INDEX (HDI)

Since 1990, a report called Human Development Report is published annually by the United Nations Development Program in which countries are compared on various indicators including education, health, as well as economic, social, environmental, political factors and the like. In the Human Development Report, countries are divided into groups of very high, high, moderate and low human development based on the Human Development Index [15].

The HDI numerical value is known to be between 0 and 1. This value reveals how much a country has attempted to achieve the highest possible value of 1 and also allows comparisons among the countries. The Human Development Index (HDI) is a summary measure of the average achievement in three dimensions of human development: having a long and healthy life, being knowledgeable and bearing a decent standard of living. The HDI is the geometric mean of normalized indices for each of the three dimensions, which measures the success of each dimension. Life expectancy is measured by life expectancy at birth, the education dimension is estimated by mean of years of schooling (elementary, secondary, and higher education), and living standard is measured by gross national income (GNI) per capita [16, 17].

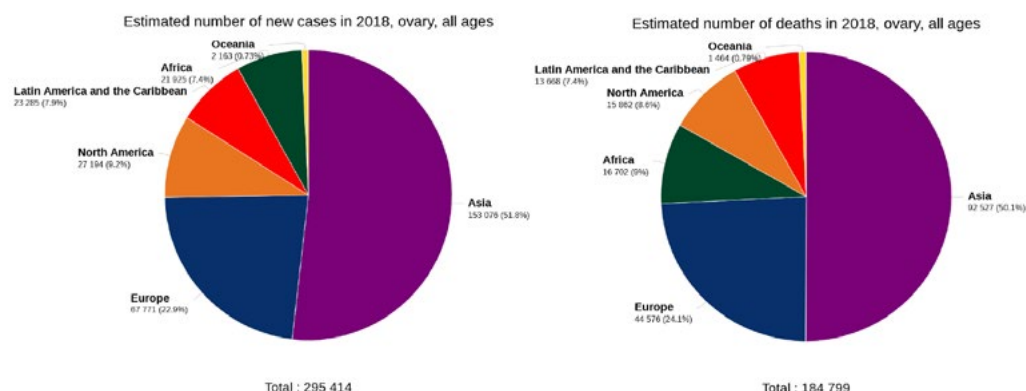
STATISTICAL ANALYSIS

In this study, the correlation bivariate method was used to assess the correlation between the incidence and mortality rates of ovarian cancer and the HDI. Linear regression models were also used to assess the HDI effect on the incidence rate of ovarian cancer. Significance level was considered lower than 0.05. Data analysis was conducted by Stata software version 14.

Results

Based on cancer record results in 2018, 8,622,539 new cancer cases and 4,169,387 cancer deaths were recorded in women; 1.72 were new cases (4.4%) while 184,799 (2.08%) deaths were due to ovarian cancer. The highest number of new cancer cases and the highest death cases from ovarian cancer reported for Asia amounted to 153,075 (51.8%) and 92,527 (50.01%), respectively (Fig. 1).

Table I sets out the incidence and mortality rate of ovarian cancer in each continent. The results indicated the highest ovarian cancer incidence in the world being in Serbia (16.6 per 100,000), Brunei (16 per 100,000) and Belarus (15.4 per 100,000), respectively. The highest mortality rates for ovarian cancer were identified in Samoa (12 per 100,000), Solomon Islands (8.4 per 100,000) and Poland (8.7 per 100,000) (Tab. I, Fig. 2).

Fig. 1. Pie charts presenting the distribution of new cases and deaths due to ovarian cancer in 2018 for all age groups in different continents [source: GLOBOCAN 2018].**Tab. I.** Estimated age-standardized incidence and mortality rates due to ovarian cancer in the world in 2018 [source: GLOBOCAN 2018].

Country	Incidence				Mortality			
	Age group				Age group			
	0-49		50-85		0-49		50-85	
	CR	ASR	CR	ASR	CR	ASR	CR	ASR
Afghanistan	1.5	2.2	13.1	13.1	0.93	1.5	12.4	12.5
Albania	2.1	1.6	12.6	12.7	0.53	0.42	7.1	6.6
Algeria	2.6	2.4	14.6	15	0.87	0.82	11.5	11.9
Angola	0.83	1.2	10.4	10.6	0.47	0.8	10.2	10.5
Argentina	3.8	3.3	27.2	25.9	1.1	0.94	18.3	16.1
Armenia	2.5	1.9	20.9	20.4	1.2	0.95	18.8	18.2
Australia	2.9	2.2	29.2	25.8	0.7	0.53	21.9	17.3
Austria	3.9	2.6	34.4	30.8	0.87	0.53	25.8	19.7
Azerbaijan	2.8	2.3	17.3	17.7	1.2	1	15.5	16.3
Bahamas	2.7	2	15.6	14.6	0.69	0.5	19	18.1
Bahrain	2.3	2.2	28	33	1	0.96	23.3	29.1
Bangladesh	2.4	2.2	10.5	10.8	1.5	1.4	9.1	9.5
Barbados	6.4	4.3	26.8	21.8	3.2	2.2	25	20
Belarus	11.4	7.9	44.3	45.6	1.9	1.3	18.4	17.7
Belgium	2.4	1.8	25.8	23.4	0.61	0.43	24.7	17.9
Belize	1.2	1.5	0	0	0.61	0.74	0	0
Benin	1.3	1.8	6.9	6.9	0.76	1.1	6.8	6.8
Bhutan	2.1	2.3	21.5	21.3	0.91	1.1	19.7	19.7
Bolivia, Plurinational State of	1.6	1.7	10.5	11.3	0.58	0.7	7	7.4
Bosnia and Herzegovina	6.6	4.4	34.3	34.5	1.4	0.93	23.6	22.2
Botswana	0.99	1.1	8.6	8.9	0.3	0.37	8.6	8.9
Brazil	2.6	2.1	16.6	15.9	0.94	0.76	12.4	11.7
Brunei	9.5	7.8	52.7	48.6	1.8	1.3	26.4	25.7
Bulgaria	7.9	5	34.6	34.8	3	1.9	25.1	22.9
Burkina Faso	1.3	1.8	9.9	9.9	0.85	1.3	9.8	9.8
Burundi	1	1.6	13.3	13.5	0.74	1.3	13.1	13.3
Cabo Verde	0	0	6.5	6.1	0	0	6.5	6.1
Cambodia	2.4	2.5	14.9	14.9	1	1.1	11.9	12.1
Cameroon	2.2	3.1	11.4	11.4	1.4	2.1	10.8	10.8
Canada	3.9	2.9	30.9	28.1	0.91	0.65	23.7	19.3
Central African Republic	1.7	2.5	14.8	14.9	1.3	2.1	14.8	14.9
Chad	2	3.2	17	17	1.4	2.5	17	17
Chile	3.5	2.8	22	21.5	0.96	0.75	14.5	13.4
China	4	2.8	15.4	15.5	1.1	0.72	11.5	11.4
Colombia	4.1	3.5	26.3	26.2	1.3	1.1	16.3	16.1

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Tab. I. Estimated age-standardized incidence and mortality rates due to ovarian cancer in the world in 2018 [source: GLOBOCAN 2018].

Country	Incidence				Mortality			
	Age group				Age group			
	0-49		50-85		0-49		50-85	
	CR	ASR	CR	ASR	CR	ASR	CR	ASR
Comoros	0	0	6.5	6.1	0	0	6.5	6.1
Congo, Democratic Republic of	0.81	1.3	11.5	11.6	0.52	0.88	10.2	10.3
Congo, Republic of	1	1.4	13.1	13.2	0.46	0.64	12.7	12.9
Costa Rica	2.2	1.8	16.1	15.5	1	0.87	12	11
Croatia	7.3	4.9	42.3	40.6	2.1	1.4	30.9	26
Cuba	4.3	3.1	16.5	16.4	1.4	0.89	12.8	12.2
Cyprus	2.2	1.6	30.2	27.9	1.5	1.1	33.8	28.2
Czech Republic	4.9	3.1	38.7	35.3	1.8	1.1	34.9	29.1
Côte d'Ivoire	1	1.5	15.6	16.1	0.66	1	15.3	15.9
Denmark	2.5	1.8	33.1	29.5	0.99	0.69	30.7	24
Djibouti	3.1	3.2	21.8	21.9	1.7	1.8	21.8	21.9
Dominican Republic	1.3	1.3	7.9	7.9	0.34	0.34	6.7	6.6
Ecuador	2.9	2.7	22	21.3	0.98	0.95	14.8	13.9
Egypt	2.4	2.5	20.8	20.7	0.94	1	18.9	18.9
El Salvador	4.8	4.5	22	20.2	1.5	1.5	16.1	13.9
Equatorial Guinea	1.9	2.8	15.9	15.5	0.76	1.3	15.9	15.5
Eritrea	2.7	3.5	23.4	23.2	1.8	2.7	23.4	23.2
Estonia	5.4	3.6	41.6	36.9	1.6	1	36.8	28.5
Ethiopia	3.1	4.1	23.8	23.8	1.9	2.8	23.5	23.6
Fiji	8.8	8.3	27.6	27.9	2.8	2.8	21.5	21.6
Finland	2.9	2.3	32.2	27.9	0.76	0.58	25.6	19.2
France	2.8	2.1	32.5	27.4	0.74	0.54	27.7	19.5
France, Guadeloupe	3.5	2.7	25.3	25.8	1.4	0.78	16.2	13.6
France, La Réunion	2.9	2.3	25.6	24.8	0.64	0.49	12.4	11.3
France, Martinique	2.5	1.4	21	19.8	0.84	0.44	13.2	11.9
France, New Caledonia	5	3.9	36.7	37.2	0.99	0.73	15.7	16.9
French Guyana	0.84	0.85	38.4	39.1	0	0	23	22.9
French Polynesia	3.8	3.4	14.5	14.5	0	0	14.5	14.7
Gabon	2.1	2.5	13.1	12.2	1	1.3	13.9	12.8
The Gambia	0.1	0.16	2.1	2.1	0	0	2.1	2.1
Gaza Strip and West Bank	1.4	1.8	17.2	17.7	0.67	0.91	15.3	15.9
Georgia	2.9	2	21.9	21.4	1.3	0.93	19.6	18.5
Germany	3.2	2.2	31.1	27	1	0.66	26.5	20.1
Ghana	2.6	3.1	29.3	30	1.3	1.7	28.2	29.1
Greece	5.6	3.6	29.3	26.5	1.4	0.83	22.2	17.4
Guam	1.7	1.5	31.6	32.2	1.7	1.5	31.6	32.2
Guatemala	1.9	2.1	9.8	9.6	0.57	0.66	7.3	7
Guinea	0.88	1.2	7.9	7.9	0.59	0.89	8.1	8
Guinea-Bissau	1.3	1.8	11.8	11.6	0.81	1.2	11.8	11.6
Guyana	3.2	3.2	26.8	27.2	1.3	1.3	18.8	19.3
Haiti	2.8	2.8	7.7	7.8	1.8	1.8	7.4	7.6
Honduras	2.8	2.8	7.6	7.4	1.3	1.3	5.9	5.9
Hungary	8	5.1	49.7	45.6	2.3	1.4	33	27.6
Iceland	1.8	1.4	33.1	30.7	0	0	26.1	19.3
India	2.9	2.7	16.5	16.5	1.2	1.1	14	14.1
Indonesia	5	4.4	30.6	31.1	1.8	1.6	22.8	23.7
Iran, Islamic Republic of	2.2	1.9	13.8	14	0.59	0.54	8.9	9.3
Iraq	1.6	2	11.6	11.6	0.81	1	10.3	10.4
Ireland	4.3	3	49.1	45.1	1.2	0.88	35.5	28.5
Israel	1.9	1.7	22.6	20.9	0.87	0.81	25.5	21.2
Italy	5.5	3.5	28.4	26.1	1.3	0.74	21.1	16.7
Jamaica	4.2	3.7	27.1	25	1.5	1.3	23	20.3
Japan	8.7	5.7	24.5	25	1.8	1.1	14.6	12.2

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Tab. I. Estimated age-standardized incidence and mortality rates due to ovarian cancer in the world in 2018 (source: GLOBOCAN 2018).

Country	Incidence				Mortality			
	Age group				Age group			
	0-49		50-85		0-49		50-85	
	CR	ASR	CR	ASR	CR	ASR	CR	ASR
Jordan	1.9	2.1	18.5	19.2	0.7	0.8	16.2	17
Kazakhstan	4.5	4	30.7	31	1.8	1.6	21.5	21.8
Kenya	1.6	2.1	23.8	24.7	0.79	1.1	23.4	24.3
Korea, Democratic Republic of	3.4	2.5	17.1	17.4	1.1	0.78	10.8	10.3
Korea, Republic of	5.4	3.7	18	17.8	1	0.62	10.6	9.5
Kuwait	1.7	1.3	14.3	17.7	0.65	0.49	11.9	16
Kyrgyzstan	3.7	3.8	24	24.3	1.4	1.6	19.3	19.9
Lao People's Democratic Republic	2.6	2.8	17.5	17.6	1	1.2	13.6	13.9
Latvia	9.6	6.1	48.4	47	3	1.9	37	31.3
Lebanon	3.6	3.5	31.9	30.9	1.3	1.3	27.7	26
Lesotho	1	1.4	10.5	10.2	0.5	0.8	10.5	10.2
Liberia	1	1.4	12.5	12.5	0.65	0.95	12.5	12.5
Libya	2.5	2.2	15.3	15.3	0.59	0.51	11.1	11.3
Lithuania	7.7	5.1	42.8	40.6	3	1.9	36.3	31.3
Luxembourg	3.2	2.1	42.5	32.5	1.6	1	30.9	21.2
Madagascar	0.47	0.59	6.7	6.8	0.28	0.42	6.6	6.7
Malawi	1.6	2.2	8.1	8.2	0.96	1.5	8	8.1
Malaysia	3.7	3.4	26.3	26.3	1.5	1.4	19.9	20
Maldives	4.3	4	29.7	30.9	1.2	1.4	23.1	23.6
Mali	1.6	2.4	12.2	12.2	1	1.7	12.1	12.1
Malta	4	2.7	33.8	28.3	0	0	34.9	25.1
Mauritania	1.5	1.8	11.5	11.5	0.7	0.95	11.5	11.5
Mauritius	3.7	2.8	23.4	22.9	1.4	1	16.7	16.5
Mexico	4	3.5	20.2	20.2	1.4	1.2	15.5	15.2
Mongolia	2.5	2.3	14.6	14.7	1.1	1	10.3	11.2
Montenegro	1.5	1.1	24.7	24.6	0.5	0.37	15.3	13.4
Morocco	2.5	2.2	18.8	19.1	0.84	0.79	16.5	16.9
Mozambique	0.38	0.44	5.5	5.6	0.24	0.37	5.4	5.5
Myanmar	3.5	3.1	15.5	15.2	1.6	1.4	11.7	11.7
Namibia	0.86	1.1	11.8	12.2	0.35	0.47	11.2	11.7
Nepal	3.5	3.5	15.7	16.1	1.7	1.8	14.1	14.3
New Zealand	2.5	1.9	28.1	25.2	0.84	0.63	19.2	15.9
Nicaragua	2.9	2.7	13.1	13.1	1.1	1.1	11.7	11.6
Niger	2.5	4.1	21.9	22.4	1.9	3.4	22.1	22.5
Nigeria	1.8	2.5	12.5	12.2	1	1.5	12.1	11.8
Norway	2.7	2	29.1	26.8	0.89	0.64	29.5	24.3
Oman	1.6	1.7	9	9.7	0.62	0.69	9	9.7
Pakistan	2.4	2.8	18.1	18.2	1.3	1.6	16.3	16.5
Panama	2.4	2.1	16.4	15.5	0.8	0.73	12.6	11.4
Papua New Guinea	4.2	4.6	16.7	16.6	2.3	2.7	16.2	16.1
Paraguay	2.3	2.4	21.2	20.6	0.82	0.94	15.9	15.1
Peru	3.3	3	26.4	26	1.2	1.1	14.9	14.2
Philippines	4.5	4.7	34.1	34.3	1.6	1.7	25.9	26.4
Poland	9.5	6.4	49.8	47.9	2.6	1.7	36.4	32.4
Portugal	3.2	2.1	19.7	17.4	0.9	0.53	15.8	12.5
Puerto Rico	3.7	2.8	24.8	21.7	0.74	0.53	15.9	13.3
Qatar	1.8	1.8	19	23.4	0.82	0.82	17.4	22.4
Republic of Moldova	8.6	6.2	30.6	30.9	2.2	1.6	19.5	19.3
Romania	7.1	4.6	34.2	33.7	2	1.2	23.5	21.2
Russian Federation	7.4	5.2	34.3	34.8	2.1	1.5	23.1	22
Rwanda	0.67	0.92	9.9	10.1	0.39	0.61	9.6	9.8
Saint Lucia	0	0	15.9	16.1	0	0	11.9	12.1

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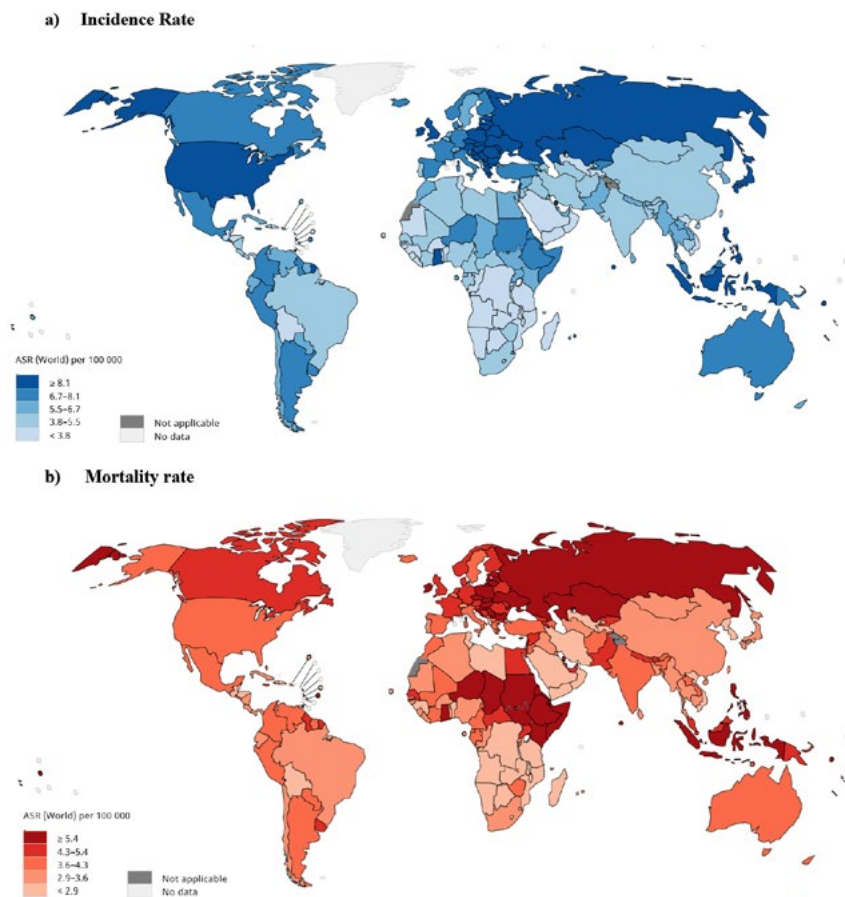
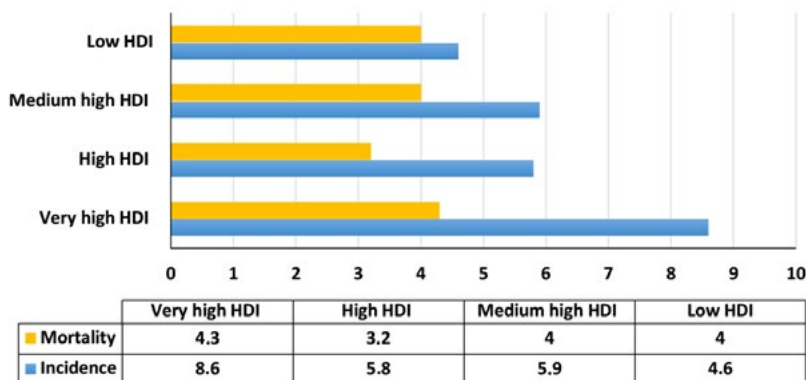
Tab. I. Estimated age-standardized incidence and mortality rates due to ovarian cancer in the world in 2018 [source: GLOBOCAN 2018].

Country	Incidence				Mortality			
	Age group				Age group			
	0-49		50-85		0-49		50-85	
	CR	ASR	CR	ASR	CR	ASR	CR	ASR
Samoa	1.3	1.7	23.1	25.3	1.3	1.7	69.4	53.2
Sao Tome and Principe	5.3	6.4	9.3	7.5	2.1	2.2	9.3	7.5
Saudi Arabia	1.5	1.3	12.2	13	0.54	0.48	9.6	10.5
Senegal	1.6	2.1	16.5	16.7	0.93	1.4	16.2	16.5
Serbia	10.5	7.4	51.4	53.1	2.4	1.6	29.9	27.3
Sierra Leone	1.3	1.8	11.5	11.7	0.82	1.2	11.5	11.7
Singapore	7	4.6	38.9	34	1.8	1.1	24.1	22.6
Slovakia	6.5	4.3	43.7	40.6	1.3	0.87	32.7	28
Slovenia	4.2	2.8	29.9	26.8	1.5	0.93	28.2	23
Solomon Islands	4.8	5.3	19.9	20.6	4.8	5.3	19.9	20.6
Somalia	2.3	3.5	23.4	23.9	1.8	3	23.7	24.2
South Africa	1.9	1.8	16.7	16.5	0.71	0.7	14.6	14.4
South Sudan	1.9	2.6	20.3	20.5	1.3	1.9	20.2	20.4
Spain	5.2	3.2	26.9	24.9	1.3	0.75	19.1	15.6
Sri Lanka	3.7	3.1	18.4	18.6	1.4	1.2	13	13
Sudan	2.1	2.7	23.4	23.8	1	1.5	23.1	23.6
Suriname	1.8	1.6	22.9	22.7	0	0	19.8	19.1
Swaziland	1.3	1.8	8.6	8.7	0.47	0.71	8.6	8.7
Sweden	2.5	1.9	25.7	24.4	0.3	0.21	26.2	18.2
Switzerland	3.1	2.1	27.2	21.2	0.83	0.53	23.1	15.2
Syrian Arab Republic	2.2	2.6	20.4	20.6	1	1.3	18.8	19.1
Tajikistan	1.2	1.3	8	8	0.41	0.49	7	7.3
Tanzania, United Republic of	0.55	0.77	7.9	8.1	0.31	0.52	7.8	8
Thailand	4.8	3.3	17.6	17.5	2.4	1.6	11.3	11.3
The Netherlands	2.1	1.6	31.2	25.6	0.87	0.61	28.5	22.6
The former Yugoslav Republic of Macedonia	6.6	4.8	26.3	26.2	1.5	1	15.4	14.2
Timor-Leste	1.9	2.8	17.6	17.7	0.86	1.5	14.9	15.2
Togo	1.5	2	13.3	13.3	0.86	1.2	13.1	13.1
Trinidad and Tobago	5.7	4.5	25	24.6	2	1.6	33.6	32.2
Tunisia	1.8	1.5	12.8	12.6	0.61	0.51	10.8	10.7
Turkey	3.7	3.1	25.5	25.1	1.1	0.94	18.3	17.5
Turkmenistan	3.4	3.3	10.1	9.8	1.6	1.6	9.8	9.6
Uganda	1.3	2.3	19.2	19.2	0.9	1.7	18.4	18.6
Ukraine	9.3	6.3	34.6	36.4	2.7	1.8	23.2	23.1
United Arab Emirates	1.5	1.3	23.3	27.7	0.58	0.5	17.8	22.2
United Kingdom	3.7	2.7	42.9	37.5	0.78	0.56	30.3	22.4
United States of America	3.6	2.8	34.3	31.1	0.78	0.61	21.8	17.9
Uruguay	3.2	2.6	30.3	27.2	1.5	1.2	24.9	21.4
Uzbekistan	1.6	1.5	11.2	11.4	0.64	0.63	7.8	8
Vanuatu	1.7	1.7	9.9	10.4	1.7	1.7	9.9	10.4
Venezuela, Bolivarian Republic of	3.2	3	21	21	1.1	1.1	14.7	14.6
Viet Nam	1.8	1.5	7	7.4	0.64	0.55	5.1	5.4
Yemen	1.2	1.5	7	6.9	0.68	0.97	6.7	6.6
Zambia	0.82	1.1	6.5	6.5	0.41	0.65	6.2	6.3
Zimbabwe	1.2	1.5	16.9	17	0.55	0.83	16.6	16.8

Based on the reported results for cancer in 2018, the highest incidence (8.6 per 1,000,000) and mortality (4.3 per 100,000) of the ovarian cancer are related to the very high HDI areas (Fig. 3).

The variance analysis detected the highest mean incidence (8.4 out of 100,000) being related to very high HDI areas and the lowest incidence (3.4 out of

100,000) related to low HDI areas, which was statistically significant ($P < 0.0001$). Moreover, the highest mortality rate (4.8 per 100,000) was pertinent to very high HDI areas while the lowest (3.6 per 100,000) was found for medium HDI areas; this difference was also statistically significant ($P < 0.0001$) (Tab. II).

Fig. 2. Map presenting (A) incidence and (B) mortality rates of ovarian cancer among women in the world in 2018 [source: GLOBOCAN 2018].**Fig 3.** Distribution of incidence and mortality rates of ovarian cancer in terms of HDI [source: GLOBOCAN 2018].

Displayed by the results, there is a positive and significant correlation between incidence ($r = 0.409$, $P < 0.05$) and ovarian cancer mortality ($r = 0.193$, $P < 0.05$) with HDI (Fig. 4).

The results demonstrated a positive and significant correlation between incidence with GNI ($r = 0.326$, $P < 0.0001$), MYS ($r = 0.503$, $P < 0.0001$), LEB ($r = 0.42$, $P < 0.0001$) and EYS ($r = 0.439$, $P < 0.0001$). Also a positive and significant correlation was identi-

fied between the ovarian cancer mortality with GNI ($r = 0.169$, $P < 0.05$), MYS ($r = 0.249$, $P < 0.05$), LEB ($r = 0.163$, $P < 0.05$) and EYS ($r = 0.118$, $P < 0.05$) (Tab. III).

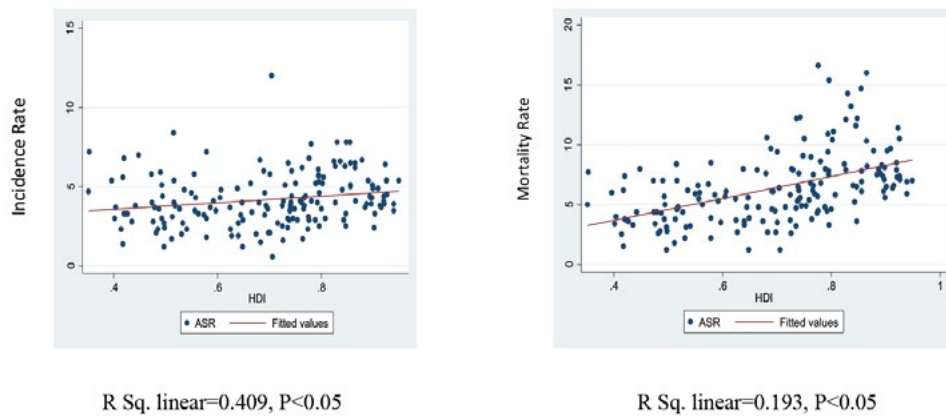
The results of linear regression analysis illustrated that boosting one standard unit in mean years of schooling would escalate the incidence and mortality of ovarian cancer by 0.2 ($P < 0.05$). However, no statistically significant relationship was identified between gross na-

Tab. II. Ovarian cancer incidence and mortality rate in different HDI regions in 2018.

HDI levels	Incidence rate		Mortality rate	
	CR	ASR	CR	ASR
Very high human development	14.7	8.4	10.1	4.8
High human development	8.7	6.7	5.6	4.1
Medium human development	4.5	5.1	2.9	3.6
Low human development	2.9	4.4	2.3	3.8
P-value (F-test)	P < 0.0001		P < 0.0001	

CR: Crude Rate; ASR: Age-Standardized Rates per 100,000.

Fig 4. Human Development Index, incidence and mortality rates of ovarian cancer in the world in 2018.



Tab. III. Pearson correlation between HDI components and dependent variable.

HDI components	ASIR*		ASMR*	
	r	P-value	r	P-value
Gross national income per 1,000 capita	0.326	P < 0.0001	0.169	P < 0.05
Mean years of schooling	0.503	P < 0.0001	0.249	P < 0.05
Life expectancy at birth	0.420	P < 0.0001	0.163	P < 0.05
Expected years of schooling	0.439	P < 0.0001	0.118	P > 0.05

* Dependent variables: ASIR and ASMR.

Tab. IV. Effect of HDI components on ovarian cancer incidence and mortality in the world in 2018.

HDI components	Incidence			Mortality		
	B	CI 95%	P-value	B	CI 95%	P-value
HDI	7.6	(-5.6, 21)	0.2	1.1	(-7.1, 9.5)	0.7
Gross national income per 1,000 capita	-0.004	(-0.04, 0.002)	0.7	-0.004	(-0.0001, 0.002)	0.6
Mean years of schooling	0.2	(-0.03, 0.5)	0.03	0.2	(0.03, 0.4)	0.02
Life expectancy at birth	-0.01	(0.1, 0.09)	0.7	0.006	(0.06, 0.08)	0.8
Expected years of schooling	-0.1	(0.4, 0.2)	0.4	-0.2	(-0.4, -0.01)	0.04

Tab. V. Incidence and mortality rates of ovarian cancer for different age groups in the world in 2018.

Variable		Incidence				Mortality			
		CR		ASR		CR		ASR	
		Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value
Age group	0-49	3.1 ± 2.1	P < 0.0001	2.7 ± 1.4	P < 0.0001	1.1 ± 0.6	P < 0.0001	1 ± 0.04	P < 0.0001
	50-85	21.6 ± 10.8		21.05 ± 10		17.7 ± 8.8		16.4 ± 8.1	

CR: Crude Rate; ASR: Age-Standardized Rates.

tional income per 1,000 capita, life expectancy at birth and expected years of schooling with the incidence and mortality of ovarian cancer (Tab. IV).

The results demonstrated the mean incidence and mortality rates in women over 50 being significantly higher than in those under 50 (P < 0.05) (Tab. V).

Discussion

The results uncovered the highest ovarian cancer incidence in the world pertaining to Serbia (16.6 per 100,000), Brunei (16 per 100,000) and Belarus (15.4 per 100,000), respectively. In addition, the highest death rate for ovarian cancer was related to Samoa (12 per 100,000), Solomon Islands (8.4 per 100,000) and Poland (7.8 per 100,000), respectively. The highest ovarian cancer incidence reported for Asia amounts to (51.8%), followed by Europe (22.9%), North America (9.2%), Latin America (7.9%), Africa (7.4%) and Oceania (0.73%). The lowest incidence is pertinent to Oceania.

Differences in the incidence of cancer in these areas can be attributed to variation in the economic situation of the individuals. An indicator for measuring a country's condition is the human development index (HDI). This index examines the conditions of a country in three fundamental aspects of development including life expectancy, education and living standard. Life expectancy is measured with life expectancy at birth, and years of potential education, and standards of living with per capita income or GDP. In countries with high levels of HDI, ovarian cancer incidence and mortality proves to be higher. Causes of high incidence include environmental and genetic factors, early screening, proper health care, early-stage disease diagnosis, and accurate registration systems [18].

The incidence of ovarian cancer in the United States in 2015 was 21,290 whereas the death rate levelled at 14,180. The cancer is reported as 11.4 percent for Eastern Europe and 6% for Central Europe [18]. Eighty-four percent of cancerous cases are reported for Asian countries. The highest standardized rate of ovarian cancer incidence is related to Asian countries such as Singapore and Kazakhstan. Standardized ovarian cancer mortality comprises five countries including India, China, Indonesia, Japan and Pakistan bearing the highest rate of ovarian cancer mortality [16].

The results of our study identified a positive correlation between human development index and the incidence and mortality of ovarian cancer.

The results of Rahmani's et al. study in 2018 revealed a significant positive relationship between the prevalence of ovarian cancer and HDI ($p < 0.001$) [12]. A study by Momenimovahed et al. (2019) demonstrated that although the prevalence of ovarian cancer is higher in areas with higher HDI, it is inversely proportional to the mortality rate [19]. Moreover, a 2016 study by Razi et al. identified a significant positive relationship between HDI levels and ovarian cancer. Ovarian rates appear to be greater in high-income individuals. The findings of the above study are in line with those of ours [1]. As these investigations project, cancer is still a global issue thereby requiring more extensive and comprehensive probes [4].

Socio-economic changes have had profound effects on cancer incidence and mortality. In countries with low or average income, the risk of cancer exhibits a rising trend. Cancer-induced infections account for about 26% of cancers in low-income countries. Low physical activity levels, obesity, malnutrition, infant lactation and the affluent social class are known as some of the risk factors for ovarian cancer [19]. The disease is associated with the industrialization

of societies, and statistics have constantly shown that most of the deaths from cancer occur in the developing countries. Our results also disclosed a positive correlation between HDI and ovarian cancer incidence ($r = 0.409$, $P < 0.0001$) as well as mortality ($r = 0.0771$, $P < 0.05$) in 2018.

Global cancer rates and the distribution of different types of cancer are clearly linked to HDI, and planners need to be vigilant about the continually changing features and priorities of cancer as countries move toward higher levels of human development.

The incidence of cancer in different geographical areas can partly be attributed to differences in lifestyle-related risk factors. Related risk factors in the developed countries include smoking, pattern of nutritional and reproductive behaviors, and infectious agents in the developing countries; however, the pattern of the disease is being under change [20].

The greater ovarian cancer incidence in countries with higher HDIs could be ascribed to appropriate infrastructure, optimal health care, use of modern medical equipment, high standards of living and screening for early detection of the disease. The reason for higher mortality in the developing countries pertains to lack of access to optimal health care, changing lifestyle and high diagnostic and therapeutic costs. HDI is the mean for normal indexes, which measures optimal lifestyle, knowledge, and life expectancy.

The results of our study manifested a significant positive correlation between the incidence and mortality of ovarian cancer and GDP (living standards) ($P < 0.05$). In a study by Leitzmann et al., the findings revealed that obesity with its hormonal mechanism elevates the risk of ovarian cancer, and hence escalates death [21].

Socioeconomic status is one of the predictors of ovarian cancer incidence and maintenance. Access to health care, patient awareness of ovarian cancer symptoms, timely response to symptoms, lifestyle and underlying diseases justify the link between socioeconomic status and ovarian cancer [22, 23].

Our study could also indicate a positive and significant correlation between life expectancy index and the incidence and mortality of ovarian cancer ($P < 0.05$).

Most cancers seem to be more common in the elderly. Cancer is also associated with population aging and socio-economic development. Further, the United Nations Development Program (UNDP) has now considered life expectancy as important [24, 25]. The Human Development Index (HDI) has also been taken into account to assess the impact of social development on health issues (including cardiovascular diseases and cancer) in different countries. Despite augmenting life expectancy and shrinking standardized mortality in men and women, the incidence of cancer has relatively remained stable [26]. The relationship between cancer and life expectancy in the general population has also been extensively studied [17, 27]

In addition to what was explained, the greater incidence of ovarian cancer in areas with higher life expectancy than those with lower and moderate levels could possibly indicate an improvement in diagnosis. Nevertheless, over-diagnosis of the ovarian cancer can also play a role [26]. Our findings, additionally, demonstrated a significant positive correlation between education level and the incidence and

mortality of the ovarian cancer ($p < 0.05$). Furthermore, in some investigations by Keng et al. [28] and Fallowfield et al. [29] a positive relationship was observed between ovarian cancer awareness and education level.

Because there is to date no effective way to prevent or screen ovarian cancer, early detection of the symptoms is of crucial importance. In countries where women enjoy greater levels of knowledge and education, there may be higher report of ovarian cancer incidence and mortality resulting from diagnosis of the disease, hence justifying this correlation.

As for some recent advancements and the fact that the true purpose of any development plan is achieving a healthy creative and happy life, HDI is needed to be considered. Genetic factors are known as the major causes of ovarian cancer. Therefore, early prevention strategies for the disease can be effective in reducing its incidence. Despite the relationship between these factors, caution must be taken regarding the interpretation and generalizability of the findings. In addition to the epidemiological risk factors of ovarian cancer, the inherent constraints of ecological studies should also be considered. On balance, it can be said that ovarian cancer incidence and mortality rate has seen a growing trend in many countries. Through adopting preventive measures, conducting epidemiological studies, performing timely treatment, and monitoring patients affected with ovarian cancer particularly with individuals residing in less-developed countries, the burden of the disease could very likely be reduced and effective steps could also be taken to improve the health systems of these countries.

Conclusions

Given the positive and significant correlation between ovarian cancer incidence and mortality with HDI, exercising attention to risk factors in these countries can be effective in containing its incidence and mortality. Higher incidence in these countries may be due to better and earlier detection of the disease. It can, therefore, be said that life expectancy, education, and GDP are the factors virtually associated with the disease accordingly contributing to depress its incidence and mortality.

Global cancer rates and the distribution of different types of cancer are clearly linked to HDI thus planners need to be vigilant about proceeding to change cancer features and priorities as countries move toward higher levels of human development.

LIMITATIONS OF THE STUDY

Limitations associated with our study largely comprise the data sources deployed. This is an ecological study special limitation of which include ecological misleading and lack of linkage between group results and the subjects.

RECOMMENDATIONS

Further research into the association between cancer (incidence, mortality, and survival) and HDI is warranted, and research using specific HDI components may provide meaningful insights into the relative importance of each factor pertinent to cancer. In addition, examining the incidence and mortality of cancer with increasing human

development index can lead to a better understanding of cancer patterns and the way they change in terms of the rate of human development. Research on cancer changes considering human development at the regional and national levels can shed light on the relative importance of social, economic, cultural, and environmental factors playing a role in the scale and characteristics of the disease.

List of abbreviations

HDI: Human development Index
NCDs: Non-communicable diseases
GNI: Gross national income per 1000 capita
MYS: Mean years of schooling
LEB: Life expectancy at birth
LYS: Expected years of schooling
ASIR: Age Standard Incidence Rate
ASMR: Age Standard Mortality Rate
CR: Crude Rate
ASR: Age-Standardized Rate

Ethical statement

Code of Ethics: IIR.SSU.SPH.REC.1398.141.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

EG and ZKH data extraction, performed data analysis and prepared the original manuscript. EG, ZKH, SMN and RB extracted Data, summarized and interpreted data and wrote the first draft of the manuscript. HN, SMB, EG and ZKH contributed to consultations and data collection and supervised the project. They also monitored the implementation of study and were involved in the preparation of the manuscript. All author(s) read and approved the final manuscript.

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RESEARCH ARTICLE

The level of fibroblast growth factor-2 prepared from Advanced Platelet Rich Fibrin (A-PRF) in obese Saudi subjects compared to healthy subjects

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Keywords

Fibroblast growth factor • Obesity • Periodontitis • Platelet Rich Fibrin

Summary

Background. The prevalence of obesity has increased substantially in the last few decades. World Health Organization (2020) estimated that around 600 million obese adults worldwide were obese, and a further increase is expected in the future due to increased consumption of high-calorie diets and a sedentary life-style as per the evidence.

Aim. To evaluate and compare the level of fibroblast growth factor platelet rich fibrin (A-PRF) in obese subject compare to healthy weight subject.

Methods. Blood samples were collected from 23 volunteers, 15 obese subject (test group) and 8 non-obese (control group) at Riyadh Elm University. Considering the smaller sample size of our study, the results are to cautiously be interpreted for generalizability. Studies employing larger sample size are recommended

to overcome this point. But considering the meticulous study procedure adhering to the study protocol and set criteria, the study pronounces greater internal validity in the sample chosen. The medical, dental histories, an interview and clinical examination was performed to check the eligibility of the participants to be involved in this study. Blood sample was collected in 10 ml syringe, then being processed using A-PRF centrifugation protocols. Ten milliliters of whole blood without anticoagulant was centrifuged at 1,300 rpm for 14 minutes.

Results. The level of FGF-2 released from (A-PRF) concentration was significantly lower on obese which was measured on 4 different times (day 1, day 7, day 14 and day 28), compared to healthy.

Conclusions. There was decrease in FGF-2 level released from (A-PRF) from obese compared to healthy.

Introduction

Periodontal regeneration is challenging and yet interesting arena of treatment strategy for the periodontitis [1]. Multiple cells and cell signaling cascades involved in the treatment of periodontal regeneration makes it still as a better treatment modality, where results and clinical outcomes are difficult to predict. However, challenge of periodontal regeneration is being addressed part by part and results are promising with available array of multiple treatment modalities [2, 3].

One of the well dealt regeneration strategies commonly utilized in the field of periodontics is the use of platelet concentrate [4]. Last decade has seen a tremendous growth in the platelet concentrate, with several modifications. First generation platelet concentrate Platelet Rich Plasma (PRP), was popular and remained in this field for few years, with natural phenomena to change with better understanding of the methods and concepts, which gave the way to the development of second generation concentrate Platelet Rich Fibrin (PRF) [5, 6]. Platelet rich fibrin a modification of platelet concentrate is a boon to the periodontal regeneration has seen various applications in the field of dentistry. Its simplicity and chair side technique attracted naturally many periodontist, oral

surgeons, dermatologists, orthopaedics professionals and others in the field of medicine and dentistry with open hands. Several changes in the methodology in terms of speed and material used resulted in the development of newer PRF techniques with superior results in terms of regeneration. However there is definite variation in the final outcome or clinical results when PRF is used for the regeneration, which made the researchers to search for the factors affecting the same [7, 8]. With the methodological factors and materials used, impacting the clinical result, there are systemic factors may also contribute to the regenerative capability of PRF.

The first report on the relationship between obesity and periodontal disease appeared in 1977, when Perlstein et al. observed histopathologic changes in the periodontium of hereditary obese Zucker rats (Zucker and Zucker, 1962; Perlstein and Bissada, 1977). Using ligature induced periodontitis; they found alveolar bone resorption to be greater in obese animals compared with non-obese rats (Perlstein and Bissada, 1977).

The role of obesity in periodontal disease progression is interesting and manifolds [9]. In humans, systemic diseases have always been considered as a risk factor for the periodontitis. Obesity is a major independent risk factor for hypertension, coronary heart disease, osteoarthritis, and, in particular, type 2 diabetes. Among

the commonly associated systemic disease diabetes and obesity are taking the front row, which has been shown to alter the periodontal disease progression and clinical outcome in many evidence-based studies. The presence of periodontal disease in a diabetic individual is a serious health hazard. Based on few studies done, there appears to be stronger obesity-periodontitis association in women, non-smokers, and younger individuals than in the general adult population [1].

Obesity has impact on the host cells and molecular signaling. PRF, derived from the platelets is a host of several growth factors. Growth factors which are the key component of initial and later stages of healing process are released by several hematopoietic cells, including platelets. Growth factors always function in an order or in a cycle with the help of other growth factors and cytokines. Functioning of many inflammatory cells are expected to change the obesity, platelet derived growth factors are not immune to this [10].

Thus, the present study is expected to explore the PRF derived growth factors in obese patients compare to non-obese patients, so that the outcome of the study is utilized in the regenerative strategy to be employed in the obese patients.

Methods

This was a descriptive, cross sectional study conducted on 23 subjects, chosen randomly from post-graduate residents in dentistry programs at Riyadh Elm University. For this, both the medical and dental histories were retrieved with an interview and clinical examination, which was performed to check the eligibility of the participants. For randomization, an electronic mail was sent to all residents with a detailed explanation of the procedure asking them to respond in case if they are willing to volunteer for the study. They were asked to get the Body Mass Index (BMI) done, and it should be above 30 (obese). After that, the positive responses were matched with the study criteria to determine the group of the participants that we can take our final sample from. Each of matched responses was given a number. The final sample was chosen from the sorted group. One trained person extracted the blood from all participants who was not a part of the research team but involved for the expertise skill that performed the centrifugation process for all samples. Ethical approval was obtained from research committee in Riyadh Elm University with registration number FPGRP/43831005/340.

PREPARATION OF PRF

Blood samples were collected from our volunteers, (23 total samples). 15 obese (test group) and 8 normal weight (control group). Blood was extracted by 10 ml syringe, which was then processed using A-PRF centrifugation protocols. Ten milliliters of whole blood without anticoagulant was centrifuged at 2,700 rpm (708 g) for 12 minutes, the fibrin clots were collected after centrifuging from the top of the centrifuge tubes. The PRF clots was placed into prepared dishes. For

each sample, 5 ml of culture medium was added. Dulbecco's modified eagle medium (DMEM) was used for this purpose. We used PRF kit and tubes provided by PROCESS for PRF Company in France with U.S. FDA registration number 3007006186. The centrifuge machine used is HERMLE Z 206 A. This machine manufactured by HERMLE Labortchnik GmbH, Wehingen-Germany.

PROTEIN QUANTIFICATION WITH ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA)

Principle of the assay

The kit is based on sandwich enzyme-linked immunosorbent assay technology. An antibody specific to FGF2 is pre-coated on to a 96-well plate. The standards and samples are added to the wells, incubated and washed with wash buffer. A biotin conjugated antibody specific to FGF2 is used for detection. TMB substrate is used to visualize HRP activity. TMB is catalyzed by HRP to produce a blue color product that changes into yellow after adding stop solution. The intensity of yellow is proportional to the FGF2 amount bound on the plate and then the concentration of FGF2 can be calculated.

To determine the amount of growth factors released from PRF at one day, seven days, 14 days, 28 days, samples will be kept at 37 C to allow for growth factor release. Protein quantification was carried out using ELISA machine. At desired time points, FGF-2 was quantified using an ELISA kit according to manufacturer protocol. Absorbance measured at 450 and 570 nm using a micro plate reader and the measurement at 570 nm were subtracted from the reading at 450 nm. Also, all samples were measured in duplicate.

STATISTICAL ANALYSIS

Data analyses were carried out using Statistical Packages for Social Sciences (SPSS) version 21 (SPSS, Chicago, IL, USA). Descriptive statistics of FGF2 experiments were summarized using mean and standard deviation or median (range) whenever appropriate. Normality of test was also conducted using Kolmogorov-Smirnov and Shapiro Wilk test, p-value < 0.05 were considered as non-parametric. Correlation procedure had also been conducted using Pearson correlation. The statistical association of mean FGF-2 measured over time among obese and non-obese was conducted using independent t-test. Paired t-tests were also conducted to measure the mean differences among FGF-2 measured over time between each group (obese and non-obese). A p-value < 0.05 was considered statistically significant and a p-value < 0.01 was considered highly statistically significant.

RELIABILITY ANALYSIS

Interclass Correlation Coefficient (ICC) was applied to determine the internal consistency of the study data. Based on the results the reliability analysis measured among four items (FGF-2 day to day 28) was 0.814 or 81.4% which indicates a very good internal consistency.

Results

We collected blood samples from 23 volunteers at Riyadh Elm University, 15 of them were classified into obese group (test group) and 8 participants were non-obese (control group). Table I presented the comparison between mean FGF-2 measured over time among obese and non-obese. It was found that, compared to non-obese patients, the level of FGF-2 measurement was significantly lower on obese which was measured on 4 different occasions (day 1 to day 28) ($p < 0.05$; 95% CI). The outcome indicated that the lower FGF2 concentration was associated with obese patients

whereas higher FGF-2 concentration was associated with the normal group (non-obese).

Figure 1 depicted the distribution of mean FGF-2 which was measured in 4 different times (day 1, day 7, day 14 and day 28) between obese and non-obese. It can be shown that FGF-2 measurement among 4 different occasions were significantly lower in obese patients ($p < 0.05$).

Figure 2 depicted the trend line of FGF-2 which was measured in different times. As revealed, the mean FGF-2 measurement of non-obese was significantly lower at day 1 (mean 2.55) while day 28 was significantly higher (mean 2.74). In obese group, mean FGF-2 was

Tab. I. Comparison between obese and non-obese according to the mean FGF2 measured overtime (n = 23).

Factor	FGF2 measurement			
	Day 1 Mean \pm SD	Day7 Mean \pm SD	Day 14 Mean \pm SD	Day 28 Mean \pm SD
Study group				
Obese	1.46 \pm 0.52	1.07 \pm 0.79	1.53 \pm 1.29	0.52 \pm 0.66
Non-obese	2.55 \pm 0.29	2.59 \pm 0.24	2.67 \pm 0.43	2.74 \pm 0.59
T-test	-5.478	-5.209	-2.391	-8.004
P-value §	< 0.001 **	< 0.001 **	0.026 **	< 0.001 **

§ P-value has been calculated using independent t-test; ** Significant at $p < 0.05$ level.

Fig. 1. Distribution of Mean FGF2 measured over time comparing obese vs non-obese.

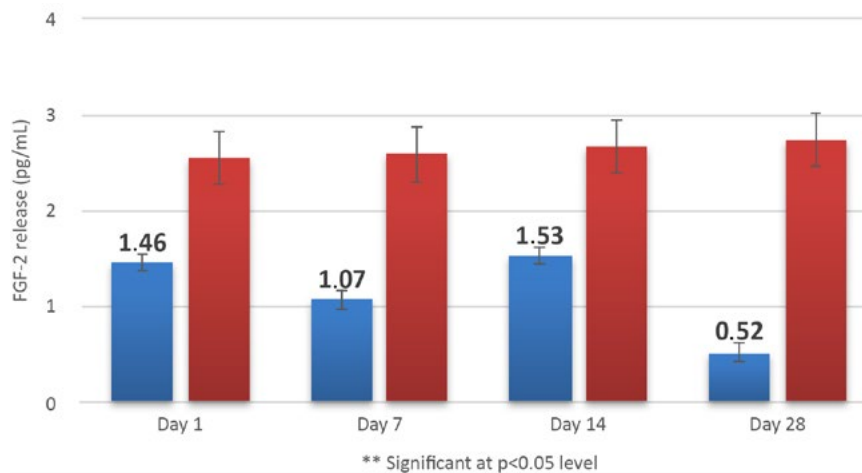
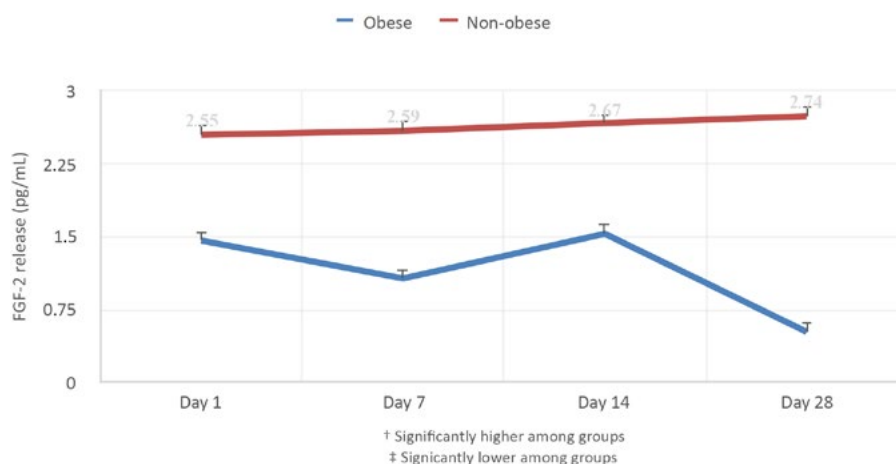


Fig. 2. FGF-2 trend line measured over time between obese and non-obese.



significantly lower on day 28 (mean 0.52) whereas day 14 was significantly higher (mean 1.53).

Table IIA described the Pearson correlation between FGF-2 concentration which was measured on different occasions such as; day 1, day 7, day 14 and day 28 among obese patients. It was determined that, no significant correlation was found among day1, day 7, day 17, and day 28 in relation to FGF-2 concentration.

In Table IIB where we also conducted Pearson correlation in regard to non-obese group. It was determined that

Tab. IIA. Correlation (Pearson – R) between FGF-2 measured over-time among obese group (n = 15).

FGF-2	Day 1	Day 7	Day 14	Day 28
Day 1	1			
Day 7	0.282	1		
Day 14	-0.122	0.112	1	
Day 28	0.030	0.101	0.455	1

Tab. IIB. Correlation (Pearson – R) between FGF-2 measured over-time among non-obese group (n = 8).

FGF-2	Day 1	Day 7	Day 14	Day 28
Day 1	1			
Day 7	0.981 **	1		
Day 14	-0.251	-0.301	1	
Day 28	-0.302	0.589	0.632	1

** Significant at p < 0.01 level.

the correlation between day 7 and day 1 was highly statistically significant ($r = 0.981$, $p < 0.001$).

Paired t-test was conducted at Table IIIA to assess the mean differences of FGF-2 which was measured over time among obese group. It can be seen that the paired t-test between day 1 and day 28 was statistically significant ($p = 0.001$). The difference was also statistically significant between day 7 and day 28 ($p = 0.048$) while the paired t-test between day 14 and day 28 was also statistically significant ($p = 0.004$).

For the normal group (Tab. IIIB), the paired t-test among FGF-2 measured over time were not statistically significant in different occasions.

Discussion

The periodontal regeneration has become the common and most frequently used surgical periodontal therapy in periodontics. What has been proved positive technique or material for regeneration of lost periodontal structure is either improved in their concept or may not be used as frequently as before. Though there are many changes and advances in the adapted regenerative methods, the understanding of the concept of periodontal wound healing, cells required for the regeneration and other factors behind this therapeutic model are constantly

Tab. IIIA. Paired t-test between FGF-2 measured overtime among obese group (n = 15).

FGF-2	Mean differences	Mean standard error	95% CI of the difference	P-value
Pair 1				
Day 1 vs day 7	0.387	0.211	-0.066-0.839	0.088
Pair 2				
Day 1 vs day 14	-0.074	0.374	-0.876-0.729	0.847
Pair 3				
Day 1 vs day 28	0.935	0.212	0.480-1.391	0.001 **
Pair 4				
Day 7 vs day 14	-0.461	0.372	-1.258-0.337	0.236
Pair 5				
Day 7 vs day 28	0.549	0.253	0.007-1.091	0.048 **
Pair 6				
Day 14 vs day 28	1.009	2.976	3.709-1.647	0.004 **

** Significant at p < 0.05 level.

Tab. IIIB. Paired t-test between FGF-2 measured overtime among non-obese group (n = 8).

FGF-2	Mean differences	Mean standard error	95% CI of the difference	P-value
Pair 1				
Day 1 vs day 7	-0.038	0.027	-0.102-0.028	0.216
Pair 2				
Day 1 vs day 14	-0.117	0.207	-0.606-0.371	0.588
Pair 3				
Day 1 vs day 28	-0.192	0.259	-0.806-0.421	0.483
Pair 4				
Day 7 vs day 14	-0.079	0.196	-0.543-0.384	0.696
Pair 5				
Day 7 vs day 28	-0.155	0.241	-0.726-0.416	0.541
Pair 6				
Day 14 vs day 28	-0.075	0.162	-0.459-0.309	0.657

being updated and utilized for the clinical periodontal regenerative aspects [11].

Platelet-rich fibrin (PRF) first described by Choukroun et al. [12] is a new second generation of platelet concentrate. PRF provides a scaffold for cell migration and growth factors for promoting wound healing, bone regeneration, graft stabilization, wound sealing and hemostasis. Because the fibrin matrix is better organized, it is able to more efficiently direct stem cell migration and the healing program [13].

The concept of "natural bone regeneration" was proposed by Simonpieri et al. [14], which includes regeneration of gingival tissue and bone volume through PRF membrane. Yuchao et al. [15], showed that the use of PRF as the sole grafting material seems to be an effective modality of regenerative treatment for periodontal bone defects.

In the present study we have taken into consideration that, obesity may have a role to play on the PRF. As of our knowledge and review of literature till today, it is assumed that, this is the first study to be conducted to evaluate the relation between the obesity and Fibroblast growth factor (FGF) in PRF of obese patients. In consideration of the effect of obesity on inflammatory cascade and cells, this type of study is well justified [16-18].

The traditional BMI classification underestimates risk in Asian and South Asian people. A separate guideline for this population classifies overweight as a BMI between 23 and 24.9 kg/m² and obesity as a BMI ≥ 25 kg/m² [19]. In the present study we have taken into consideration universally adapted definition for the obese and overweight patients. If the BMI is 25.0 to < 30, it falls within the overweight range and If the BMI is 30.0 or higher, it falls within the obese range. Adapting the universally acceptable guideline for the obese it helps to compare the previous and future studies on same platform. Patient for the present study were recruited randomly from the outpatient department. Random selection of the patient helps in avoiding the sample bias which is helpful in the better interpretation of the results [20].

The sample size for the present study estimated as a total of 23 patients with 15 patients in the test group (obese) and 8 patients (healthy) group. Since it is the kind of first study to be conducted, for the sample size estimation, other studies done with almost similar background was chosen and minimal sample size required interpreting the acceptable results was taken into consideration.

Age group chosen for the study was between 25 to 50 years of age. Range of the age was acceptably wide to include as much as possible aged individuals, with caution taken to avoid the impact of aging on the growth factors. Age range was suitable to interpret the results with both the control and test group were in the same age range with equal inclusion of age range. Thus, the probable worsening effect of aging in one group or better effect of aging in the younger group was avoided [21].

It is to be noted that, the blood sample for the measurement of FGF-2 was done on four intervals across a month. The assessment of growth factor over this defined period and intervals helps to overcome the one-time changes

seen in FGF-2 level. It also helps to assess the true value and to avoid the one-time impact / on that one day impact of cellular changes affected by obesity on PRF growth factor. There is possibility of changing the inflammatory cascade, cytokines level and growth factor level depending upon the metabolic changes induced in the obesity. This four-time assessment will overcome all these barriers [16, 18, 22].

In the obese group of patients in the present study there was lower value of FGF-2 was seen over a month. There was significantly low level of FGF-2 was observed at first week and comparatively higher level observed at the end of the study period. The low level of FGF-2 in obese patients can be explained on the basis of impact of obesity on the other inflammatory cells. It is to be remembered that, there is always a viscous cycle between the inflammatory cell products like cytokine and growth factor which balances the formation and resorption of the periodontal tissue. When this balance is tilted towards inflammatory side, it predominates the destruction over the formation. Viceversa is seen when the growth factor dominates the cycle with formation of tissue is common. Present study results with low FGF-2 level in obese patient is justifiable, because its well-known that, in obesity adipocytes secrete pro-inflammatory cytokines such as TNF- α and IL-6 [12] which stimulates the hepatic production of acute phase proteins such as C-reactive protein (CRP) and cause alteration in host's immune response. Further it is also shown that, serum adiponectin which exerts the anti-inflammatory effect are reduced and the resisting which exerts inflammatory effect are increased [22]. Over and above with all these, excessive ROS level and a decrease in antioxidant substances also has been reported. All this negative alteration in the immune response will shift the balance towards destruction and ability of cells like platelets to produce lesser growth factors. Thus, one of the possible reasons hypothesized for the lower level of FGF-2 seen in obese patient PRF is the shift in the inflammatory process towards negative balance [18].

Though the results can be taken into consideration to explain the relation between obese and normal patients PRF response, results can be improved in the future studies. Obese patient can be further classified according to BMI and comparison of the levels of growth factors helps us to determine the severity of obesity on level of growth factors. This further establishes and explains the role of obesity on FGF-2 level. Secondly, though the sample size chosen according to available previous almost similar observations studies, the sample size increased will help to establish the relation far better than this initial study. In the present study the gender demarcation was not done. Such gender differences if at all any seen if reported in terms of growth factor release will help to achieve better treatment strategy in obese male and obese female patient separately [23].

When obese patient PRF related growth factor compared to the non-obese or healthy patients it is observed that, there is study increase in FGF-2 in the stipulated study period. Absence of inflammatory triggers, positive cycle

of productivity is expected to release a better growth factor release in healthy non obese patients. Repair or regeneration overrides the destructive inflammatory process and balances the equation with the normal production of growth factor required for the normal turnover of a cell and tissue [24, 25].

Panahi et al. [26], conducted a cross-sectional study in patients with type 2 diabetes. Of the evaluated 141 subjects, 49 (34.8%) were categorized as having well-controlled diabetes, 66 (46.8%) had poorly controlled diabetes, and there were 26 subjects in the normal control group. Serum FGF21 concentrations were determined in all subjects using ELISA. Serum FGF21 level in the poorly controlled diabetic group was significantly higher than that in the well-controlled diabetic and the healthy control groups ($p = 0.02$) but there was no significant difference between the well-controlled and healthy groups. There was no significant association between serum FGF21 levels with lipid levels, presence of diabetic complications and BMI ($p > 0.05$).

In another study by Mashili et al. [27], levels of circulating FGF-21 in 207 overweight and obese Tanzanian males with or without type 2 diabetes mellitus (T2DM) were measured. They found higher levels of FGF-21 in people with T2DM compared to those without the disease. Based on statistical models, measures of adiposity explained up to 59% of the variability in FGF-21 levels in the circulation.

Conclusions

Within the limitation of the study the following conclusion can be drawn:

- FGF-2 measurement is lower in obese patients.
- It was registered a FGF-2 level increase in normal healthy or non-obese patients.
- When FGF-2 levels are compared between the intervals of one week, the FGF-2 level showed significant difference in obese patients.
- Study finding may be utilized in the treatment of periodontal regeneration in obese patients.
- The combination of PRF with regenerative therapy has been shown to be most promising for periodontal repair of bone and furcation defects, as well as soft tissue root coverage of gingival recession. However, the effect of PRF on pure bone regeneration remains questionable as many clinicians are unfamiliar with its use and thus requires more validating studies.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors contributed equally to this work.

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RESEARCH ARTICLE

Prediction of Multiple sclerosis disease using machine learning classifiers: a comparative study

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Keywords

Classification • Machine learning • Multiple sclerosis

Summary

Introduction. Hamedan Province is one of Iran's high-risk regions for Multiple Sclerosis (MS). Early diagnosis of MS based on an accurate system can control the disease. The aim of this study was to compare the performance of four machine learning techniques with traditional methods for predicting MS patients.

Methods. The study used information regarding 200 patients through a case-control study conducted in Hamadan, Western Iran, from 2013 to 2015. The performance of six classifiers was used to compare their performance in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-) and total accuracy.

Results. Random Forest (RF) model illustrated better performance among other models in both scenarios. It had greater specificity (0.67), PPV (0.68) and total accuracy (0.68). The most influential diagnostic factors for MS were age, birth season and gender.

Conclusions. Our findings showed that despite all the six methods performed almost similarly, the RF model performed slightly better in terms of different criteria in prediction accuracy. Accordingly, this approach is an effective classifier for predicting MS in the early stage and control the disease.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease related to the central nervous system (the brain and spinal cord) without clear etiology. Focal lymphocytic infiltration in MS leads to the destruction of myelin and axons [1]. The onset of the disease happens in young adults with the most susceptibility is related to people who are in their 20s and 30s [2, 3]. Approximately 2.5 million people are affected by MS worldwide annually [4]. The prevalence of MS varies geographically between 5.3 and 74.28 per 100,000 in Iran [2]. It has been shown by epidemiological studies that the trend of MS, especially in women, is increasing [2, 5, 6]. Hamadan Province, located in western Iran, is among the most high-risk regions in Iran with the prevalence of 62.5/100,000 [2].

The burden of MS disease for the public health systems and its prevalence during have been increased the past years [7]. Therefore, identifying the most important factors related to the MS is of great importance. Many epidemiologic studies showed that MS has a multifactorial etiology that corresponds to several environmental factors for people who have complex genetic risk profiles [8]. These factors include both genetic and non-genetic exposure to dietary patterns [9], infectious agents [9], familial clustering [10], season of the birth [11], age infection during childhood [11, 12],

smoking [13], environment exposures [14], and psychological stress [15].

Early detection of the disease can play a critical role in improving MS survival by increasing the proportion of patients diagnosed at early stages [16]. To do this, traditional classification techniques including logistic regression have been widely used in different medical problems to detect cases and controls. While there can obtain simple interpretations from these models, they usually cannot account for complex relationship between variables. So, the need to use newly developed models with the least prediction error is evident and a precise and reliable system is required to early diagnosis of the patients. Most of modern medical diagnosing tools are constructed based on classification and are adapted by many researchers to improve the precision.

Recently, machine learning techniques have become very popular and have been widely used in several research area including medicine especially in classification problems [17, 18]. These methods learn through experience to improve their performance and can help physicians to better diagnose new patients by increasing sensitivity and in decision-making [19]. Although the main objective of these models is to identify effective variables and their relationships, these models can be used to predict and estimate the effects [20, 21].

Various machine learning methods have been introduced in different studies [22-24]. Examples of them include Naive Bayes (NB), Decision Trees, Random Forest (RF),

Nearest Neighbor, AdaBoost, Support Vector Machine (SVM), RBF Network, and Multilayer Perceptron machine learning techniques to predict different outcomes [25-27].

Although different studies have shown that the performance of data mining techniques is better than that of the traditional techniques in terms of higher accuracy and lower error rates, this excellence does not happen in all data sets [28] and there are inconsistencies among various studies. So, investigation and comparison of the performance of different methods in different data sets is of great importance.

The present study aimed to conduct a comprehensive comparison of four machine learning techniques of NB, Least Square Support Vector Machine (LSSVM), SVM and RF and two traditional methods (Logistic Regression (LR) and Linear Discriminant Analysis [29]) in prediction of MS to distinguish people with MS from healthy people in Iran.

Methods

DATA SOURCE

This study has been approved by the Research Council of the University of Medical Sciences of Hamadan (ID: 9204181211). The data was collected through a case-control study in Hamadan Province, the west of Iran, from September 2013 to March 2014. Participants were voluntarily entered into the study. Due to the lack of intervention, merely verbal informed consent was obtained from the participants. Based on Asadollahi et al. [30], in the patients with MS 80% of the participant was female and in the control group, this percent was 60%. According to this finding, the sample size for each group was 100, the total sample size was 200, at 95% significance level and 80% statistical power. Moreover, 100 definite patients with MS invited to the study as a case group compared to 100 infectious diseases patients as control group who had not a history of neurological disorder. In order to make the study groups similar, individuals from case and control were entered at the same time and in the same hospital. Cases and controls were selected from patients who referred to Farshchian Hospital's neurology clinic and infectious diseases clinic, respectively. The Farshchian Hospital, where the study was conducted, is a referral center to which patients referred from different cities of the province. To make similar the study base of both case and control groups, we decided to select the control group from the Infectious Diseases Ward that was next to the Neurology Ward. Furthermore, the clinical and laboratory information of the control group was available and accessible from their medical records. Regardless of age, gender, and disease onset's date cases were selected. In this study, the individual case was defined as an MS patient who was diagnosed with a neurologist and a brain MRI or a total spinal MRI. The patients with the following criteria were entered to the study: 1) diagnosed during the past 10 years; 2) inhabitant of Hamedan

Province; 3) undertreatment and had a complete medical recorder in Farshchian Hospital. Satisfaction and accessibility of patients to study entry was required. The individual control was defined as an infectious disease patient without a neurological disorder seeking medical care. Patients of infectious diseases who have come from other jurisdictions have been disqualified. A standardized questionnaire, embracing of 40 items, was designed for the data collection on socio-demographic characteristics and environmental factors. It included data on gender, age at diagnosis, occupation, marital status, educational level, weight, height, history of smoking, exclusive breastfeeding, history of measles, family history of MS, birth season, history of immune system disease, blood group, and RH variable. The Body Mass Index (BMI), which is the ratio of body weight in kg to height in square meters, was classified into three categories of individuals with BMI underweight (BMI < 18.5), average individuals (BMI = 18.5-24.9), and overweight or obese individuals (BMI ≥ 25). Moreover, to assess the participants' personality type the Friedman-Rosenman standard questionnaire was used. There were 25 two-choice (yes/no) questions with a total score of 25 in the questionnaire. Patients' scores were classified to ≥ 13 and < 13 as type A and type B personality, respectively [31, 32]. The personality questionnaires reliability, used by Cronbach's alpha coefficient, was 0.77. Face-to-face interviews were carried out to collect data.

DATA MINING ALGORITHMS

Naive Bayes (NB)

This classification method is based on the theorem of Bayes, which is straightforward, simple and quick [33, 34]. Once the test and train datasets have been allocated, the prior probability of belonging to each class can be determined using the train set using the conditional probability of independent variables X_i , given the class label C of the output variable. The probability of C is computed the

$$X_1, \dots, X_n \{ P(C = c | X_1 = x_1, \dots, X_n = x_n) \}$$

using a class label product probabilities and the conditional probability of independent variables given the class label in theory and based on the Bayes theorem.

$$P(C = c | X_1 = x_1, \dots, X_n = x_n) = P(C = c) \times \prod_{x_j} P(X_j = x_j | C = c)$$

Based on the above formula, the class with the highest posterior probability is given a new event [25].

Support vector machine (SVM)

SVM is a mapping function that uses a classification or regression model that is well known as a flexible method. To perform the classification method, a nonlinear kernel function is implemented to transform independent variables into high dimensional space, in which cases can be differentiated very well. The Radial Basis Function (RBF)

kernel makes a trade-off between the misclassification of the training sample against the simplicity of the decision surface (cost parameter). The outcome variable class is best differentiated by using the maximum-margin hyperplanes in the data. A minimal generalizing error is achieved when the distance between the hyperplanes is accomplished by comparing two parallel hyperplanes on either side of the separating hyperplane [35].

Least Square Support Vector Machine (LSSVM)

The LS-SVM is a modified model with the least squares of the loss function and the equality constrain of the SVM model, in which rather than the quadratic programming problem, the dual solution could be found by solving a linear system. The LS-SVM function, also, maps the data into a high dimensional space, in case of SVM. The primal formulation of the LS-SVM classification model is minimized

$$f(\alpha, c, \varepsilon) = \frac{1}{2} \|\alpha\|^2 + \frac{1}{2} B(\|\varepsilon\|^2)$$

with the equality constraint as:

$$y_i(\alpha^T \varphi(x_i) + c) = 1 - \varepsilon_i, (\varepsilon_i \geq 0) \quad [36].$$

Random Forest (RF)

The RF method was introduced by Leo Breiman [37] where the regression trees and classification are assembled. In this method, the trees are generated by using a replacement sampling of the main dataset. Using the independent variables that evaluate the outcome and the random subset of the predictors, the nodes are built. The most effective predictors can be found using mean decrease Gini and mean decrease accuracy [37].

Logistic Regression (LR)

This method assumes that the binary outcome is distributed binomially. The model can be written as:

$$\log\left(\frac{\pi}{1-\pi}\right) = \sum_{i=1}^k \beta_i X_i$$

In this model, X 's are the covariates and β_i is the regression coefficients denoting the effect size's measure [38].

Linear Discriminant Analysis (LDA) [29]

LDA is similar to LR and refers to a linear combination of predictors that can achieve clear interpretations of the dependent variable. LDA addresses the problem with the predictor's conditional probability given the output class. This method maximizes the dispersion between the different class cases and minimizes it between the same class cases [39].

EVALUATION CRITERIA AND CROSS VALIDATION

To compare the discriminative powers of the classification methods, several criteria of sensitivity, specificity,

positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-) and total accuracy were calculated using the following formulas:

$$\text{Sensitivity} = \frac{TP}{TP+FN}, \quad \text{Specificity} = \frac{TN}{TN+FP}$$

$$\text{PPV} = \frac{TP}{TP+FP}, \quad \text{NPV} = \frac{TN}{TN+FN}$$

$$\text{LR+} = \frac{\text{Sensitivity}}{1-\text{Specificity}}, \quad \text{LR-} = \frac{1-\text{Sensitivity}}{\text{Specificity}}$$

$$\text{Total Accuracy} = \frac{TP+TN}{TP+TF+TN+FN}$$

Where FP indicates people with MS that were incorrectly identified as healthy, TP stands for patients with MS that were correctly diagnosed as MS, TN stands for healthy controls that were correctly identified as healthy people and FN stands for patients with MS who incorrectly identified as healthy.

The most important variables are chosen to demonstrate how each variable contributes to the uniformity of the nodes and leaves in the resulting RF by its greatest mean Gini decrease [37, 40]. The Gini coefficient for the child nodes is measured and compared to that of the original node each time a particular variable is used for splitting a node. Furthermore, Partial Dependence Plot demonstrates the nature of the dependence of the approximate estimation of function on each explanatory variable. The research has been conducted using RStudio software v 3.6.2.

Results

DATA DESCRIPTION

The data set included 200 patient records in which 100 definite patients with MS invited to the study as case group compared to 100 infectious disease patients as controls group who had not a history of neurological disorder.

Table I displays the demographic and clinical characteristics of the participants. Females accounted for 80% of cases and 48% of controls ($P < 0.001$). The control group's mean (SD) age was higher than the case group's; 41.2 (14.8) years vs 36.1 (11.5) years respectively. Most of the participants were married and had no academic degree. In controls group, the smoking status ratio was significantly higher than in cases (27 vs 6%; $P < 0.001$). Nevertheless, in cases, the number of widows and divorcees was lower than in controls, but there was no statistically significant difference ($P = 0.074$). Breastfeeding in cases was higher in comparison to the controls ($P < 0.01$). Moreover, in the cases, patients with a history of measles were lower than in controls ($P < 0.05$).

Tab. I. demographic and clinical characteristics of the case and control groups.

Variable	Cases (%)	Controls (%)	P-value
Gender			
Male	20 (20)	52 (52)	0.000
Female	80 (80)	48 (48)	
Marital status			
Single	25 (25)	19 (19)	0.3
Married	75 (75)	81 (81)	
Educational level			
Non-academic	63 (63)	72 (72)	0.1
Academic	37 (37)	28 (28)	
Positive family history			
No	90 (90)	94 (94)	0.2
Yes	10 (10)	6 (6)	
Smoking status			
Non-smoker	94 (94)	73 (73)	0.000
Smoker	6 (6)	27 (27)	
Exclusive breast feeding			
Non-breast feeding	22 (22)	6 (6)	0.001
Breast feeding	78 (78)	94 (94)	
History of measles			
No	64 (64)	50 (50)	0.04
Yes	36 (36)	50 (50)	
Season of birth			
Spring	23 (23)	33 (33)	0.08
Summer	27 (27)	31 (31)	
Autumn	29 (29)	15 (15)	
Winter	21 (21)	21 (21)	
Blood group			
AB	5 (5)	14 (14)	0.3
A	21 (21)	22 (22)	
B	20 (20)	24 (24)	
O	25 (25)	40 (40)	
Blood Rh			
Negative	13 (13)	24 (24)	0.2
Positive	60 (60)	73 (73)	
BMI			
Underweight	2 (2)	4 (4)	0.6
Normal weight	32 (32)	33 (33)	
Overweight & obesity	32 (32)	43 (43)	
Type of personality			
B	30 (30)	40 (40)	0.1
A	70 (70)	60 (60)	

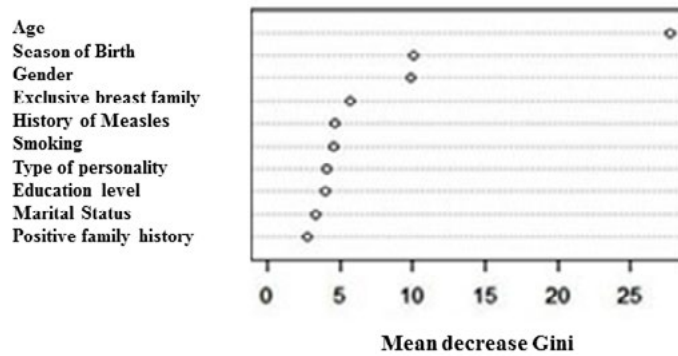
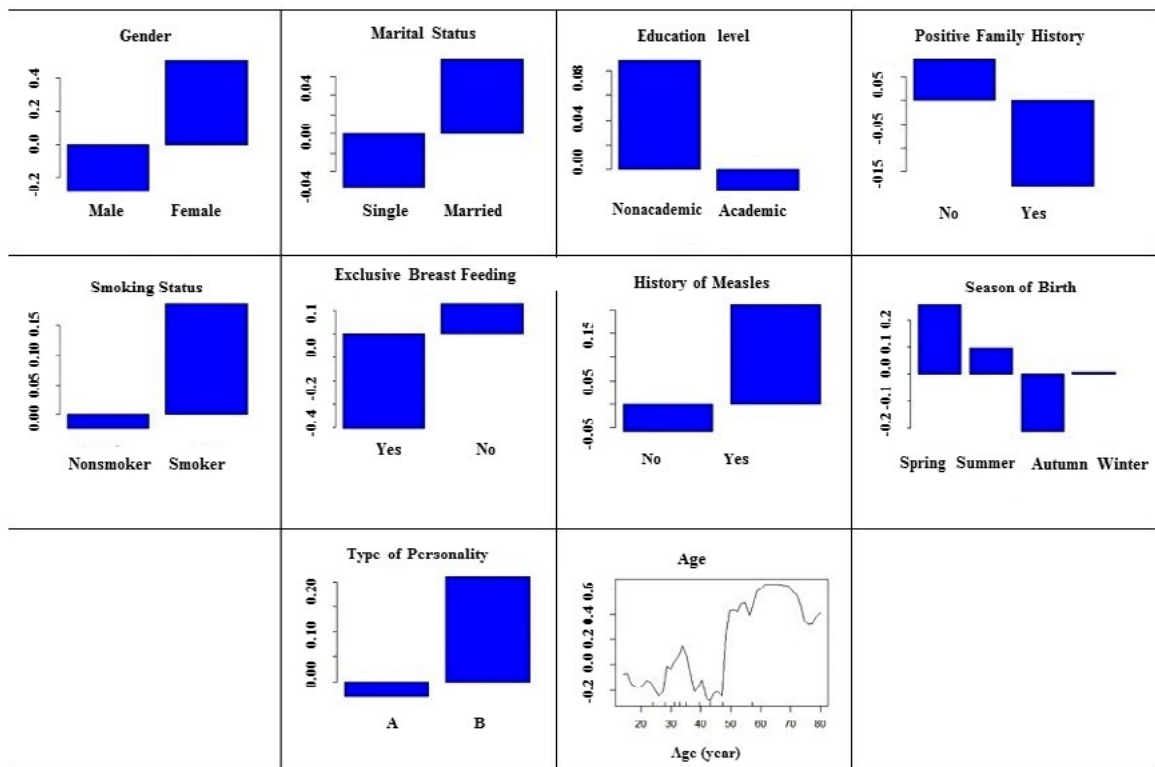
PERFORMANCE OF THE MODELS

In order to avoid overfitting, we divided the data into two sets of scenarios including training (70%) and testing set (30%) and training (50%) and testing (50%). We also repeated this process 100 times and reported the evaluation criteria as average over 100 repetitions. Table II provides a comparison of the sensitivity, specificity, PPV, NPV, total accuracy, LR+ and LR- for the classification methods training and test sets. According to the results, in both scenarios, all methods performed quite similarly in terms of LR+ and LR-. Higher accuracy was achieved by the RF in both scenarios and the SVM method in comparison to others.

As the performances of all methods in the classification of MS patients and controls were similar, we calculated the variable importance to rank the role of the variables in predicting MS. According to the results shown in Figure 1, the points represent the mean decrease Gini value, indicative of the importance of each variable in the RF plot, age was the first top rank variable in predicting MS. Also, season and sex were the second and third top rank variables in terms of the Mean decrease in the Gini index. Here, we used a threshold of 10 for Gini index, then we chose three variables as the most important variable. Moreover, the partial dependence plot (PDP) of the classes was computed and visualized the relationship

Tab. II. Mean and standard deviation of sensitivity, specificity, PPV, NPV, total accuracy, positive LR and negative LR for various models.

Scenario	Models	Sensitivity		Specificity		PPV		NPV		TA		LR+		LR-	
		Mean	Std. dv	Mean	Std. dv	Mean	Std. dv	Mean	Std. dv	Mean	Std. dv	Mean	Std. dv	Mean	Std. dv
70, 30	NB	0.79	0.10	0.55	0.13	0.64	0.08	0.74	0.10	0.67	0.05	1.92	0.54	0.35	0.14
	LSSVM	0.61	0.09	0.67	0.09	0.65	0.08	0.64	0.07	0.64	0.05	2.06	0.86	0.51	0.01
	RF	0.71	0.08	0.67	0.08	0.68	0.07	0.70	0.08	0.68	0.04	2.06	0.61	0.51	0.11
	SVM	0.72	0.89	0.64	0.1	0.67	0.08	0.70	0.09	0.68	0.05	2.06	0.65	0.51	0.13
	LR	0.67	0.08	0.65	0.1	0.66	0.08	0.66	0.09	0.66	0.06	2.06	0.64	0.51	0.15
	LDA	0.68	0.08	0.64	0.10	0.66	0.08	0.66	0.09	0.55	0.06	2.06	0.66	0.51	0.16
50, 50	NB	0.77	0.15	0.56	0.15	0.64	0.07	0.74	0.10	0.66	0.05	1.90	0.45	0.37	0.17
	LSSVM	0.62	0.10	0.63	0.10	0.63	0.07	0.63	0.06	0.63	0.04	1.90	0.46	0.51	0.13
	RF	0.71	0.09	0.57	0.09	0.68	0.07	0.70	0.07	0.68	0.04	1.90	0.43	0.51	0.11
	SVM	0.69	0.10	0.63	0.1	0.65	0.06	0.68	0.08	0.66	0.04	1.90	0.42	0.51	0.13
	LR	0.67	0.09	0.63	0.08	0.65	0.06	0.66	0.07	0.66	0.04	1.90	0.65	0.51	0.11
	LDA	0.68	0.09	0.63	0.09	0.64	0.06	0.66	0.07	0.65	0.04	1.90	0.50	0.51	0.12

Fig. 1. Variable importance in predicting MS disease using RF model.**Fig. 2.** Partial plots for variables in predicting MS using RF.

between prediction of MS on different features for the RF. Figure 2 shows that there is an MS prediction for female, married, non-academic education, history of measles, birth in spring, history of smoking and b personality type.

Discussion

The present study was aimed at a comprehensive comparison of six machine learning techniques of NB, LSSVM, SVM, RF and two traditional methods (LR and LDA) for the prediction of MS to distinguish people with MS from healthy people in Iran.

For all six methods, the performance criteria were very similar among classifiers, however, they derived from different algorithm approaches. Based on the total accuracy, it was shown that in both scenarios: 1) 70% training and 30% testing; and 2) 50% training, 50% testing), all classification methods performed almost the same for the classification of MS cases and controls (ranged: 0.54 to 0.68). Only, one of the six classifiers tested showed a total accuracy value lower than 0.6 (LDA with total accuracy of 0.55). In other words, in predicting the classes for both case and control groups, all the classification methods provided similar accuracy. However, the total accuracy of the RF model was slightly more than others in both scenarios (0.68).

In the 70, 30 scenarios, the sensitivity varied from at least 0.61 in LSSVM to at most 0.79 in the NB model. This indicator is also accurate in 50, 50 scenarios (0.77 in NB model). In the case of specificity, however, the RF model performed better than other models (0.67), the NB model was poor (0.55). This quality also remains true for PPV. In other words, RF is the best model based on the NPV and PPV criteria.

The maximum sensitivity and NPV value belonged to NB. However, the RF model outperformed other models on the basis of the other reliability indices and it is more effective than NB, LSSVM, SVM, LR and LDA. Moreover, RF and NB showed similar accuracies. Since, they were the most common algorithms used in practice [29, 30, 41, 42], RF model was used for additional analysis.

Our finding indicated age as the highest risk factor associated with MS prediction. This result is consistent with the findings [1, 7, 43]. MS is more likely to occur in the 20-40 age group [1, 7, 43]. Our analysis indicates patients in their late 20 to mid-30 were at a high risk of MS. The PDP showed that the predicted MS probability is low until 50 increases after. The result of previous studies was inconsistent with this finding [44].

According to the finding, season on birth was the second important variable in predicting MS patients, consistent with previous findings [11]. The PDP presented that the MS risk in patients who born in spring and summer was more common. Cruz et al in the United Kingdom also founded that spring-born patients are at greater risk than autumn-born patients [45]. Walleczek et al study also found a significant rise in MS births in April and a decline in November [46]. On the other hand, our

analysis opposed the results of some previous literature that reported autumn-born patients had a higher risk of MS than spring [1, 47]. In 2019, a systematic survey and multivariate meta-analysis was conducted to address this conflict and revealed that in the northern hemisphere, the impact of the birth season was related to latitude, annual dry bulb temperature and sunshine period. For populations in latitudes $> 52^\circ$ this impact was restricted to the sunshine period [48].

The third factor that influences the prediction was gender. According to a PDP, the probability of having MS is more likely to be diagnosed in females than in males. Our finding was performed the similar result of preceding research [3, 49, 50]. This can be due to the disparity between women and men in the immune state, nervous system, and lifestyle in both sexes [3]. The propensity to have fewer children and have them later in life than their grandmothers is one of the big changes in the life of the contemporary woman. Due to temporary immunosuppressant during pregnancy [51], pregnancy can have a protective impact against MS in women, and a higher age may have a share of the increased incidence of MS in women when giving birth to the first child or fewer pregnancies [51].

There were several limitations to our study. Firstly, in order to establish the models, we did not focus on quantitative MRI features. Further work plans to incorporate additional biomarker data. Second, there was some limitation in the number of samples and the matching of age and sex in both cases and control groups.

Conclusions

The aim of this research was to evaluate the performance of four machine learning and two classical techniques in predicting MS patients. Our findings suggest that in this study, RF was the best model for predicting MS in terms of multiple criteria between two group patients.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

The research topic was constructed by SD and OH, the idea was investigated, the statistical analysis

was performed and the manuscript was drafted. JP provided the data and participated in the preparation of interpretations and manuscripts. The final manuscript was read and approved by all authors.

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RESEARCH ARTICLE

Obesity: is it an additional risk factor in analyzing surgical outcomes in the South Indian population?

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Keywords

Obesity • Surgery • Postoperative pain • BMI • Duration of surgery • Risk factor

Summary

Aim. This study aims to determine whether obesity impacts surgical outcomes among patients undergoing surgery at the Surgery Unit in a tertiary care hospital.

Methods. This is a retrospective study. Data were retrieved from the medical records of patients who underwent surgery at a tertiary care hospital. Patient demographics, co-morbidities, intra-operative and postoperative pain scores and complications, if occurring, were compiled for each patient. Patients were subdivided into four subsets based on their disease profile. Each subset was divided into two groups based on their body mass index (BMI). Preoperative BMI greater than or equal to 25 kg/m² was classified as obese.

Results. The study showed that there is a considerable increase in the duration of surgery in obese when compared to non-obese. 30 days readmission rate was higher among obese in all the subsets. We find that in the subset of non-infective conditions, post operative pain mean ranking score is greater among obese (128.8 vs 109.6).

Conclusions. In conclusion, the impact of obesity resulted in increased duration of surgery and post-operative pain. The association between obesity and surgical outcome shows the importance to further research to find a way to prevention of some of the complications of surgery that could occur in patients with high BMI.

Introduction

Obesity is considered the most serious lifestyle-generated ill health of the 21st century due to its morbidity and mortality [1]. Obesity has attained “epidemic” levels worldwide, threatening healthcare systems and economies in both developed and developing countries [2]. The key reasons for overweight and obesity appear to be the modern lifestyle comprising of inactivity and malnutrition [3]. Globally, nearly 2.8 million people die from overweight or obesity each year, and about 35.8 million (2.3%) of global Disability Adjusted Life Years (DALY) are attributed to overweight or obesity [4]. In India, obesity has affected over 135 million people [5]. Further, overweight and obesity prevalence among men and women has increased to twice in the last two decades from 1998-99 to 2015-16 [6]. According to the 2016 National Family Health Survey data, the national prevalence of overweight and obesity is 14.6 and 3.4%, respectively. The highest prevalence of these conditions was seen among those aged 35-54 years, in particular women living in urban areas at the national level [5].

Obesity is linked with an elevated risk for developing severe medical conditions, particularly hypertension, diabetes, cardiovascular disease, dyslipidemia, bronchial asthma, degenerative arthritis, and cancers [3, 7]. Obesity is also associated with a higher risk of several malignancies, notably colon and esophageal cancer [8]. Obesity is a modifiable risk factor associated with an increased need for

health care resources and morbidity throughout all surgical areas [9].

Obesity is related to higher postoperative complications and increased technical difficulty in patients undergoing surgery. The excess adipose tissue hinders sufficient exposure and direct visualization, which contributes to the complexity of the procedure, resulting in prolonged operative times and technical difficulties [10].

The body mass index (BMI) is an uncomplicated measure frequently used to measure adult overweight and obesity. BMI is defined as a “person’s weight in kilograms divided by the square of his height in meters (kg/m²)”. WHO classifies BMI as underweight (< 18.4 kg/m²), normal (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²), obese class I (30-34.9 kg/m²), obese class II (35-39.9 kg/m²) and obese class III (> 40 kg/m²) [11]. The BMI offers the population-level measure of overweight and obesity, as it is similar for both the genders and for all ages of adults [4].

There is a paucity of data identifying the impact of obesity on postoperative complications. Previous studies have focused on a single surgical specialty and single disease condition. Our study centered on all the conditions in a large surgical group and divided into four subsets, namely, infectious, non-infectious, cancer, and superficial peripheral limb conditions. This study aims to determine whether obesity impacts surgical outcomes among patients undergoing surgery at the Surgery Unit in a tertiary care hospital.

Methods

This is a retrospective study. The study was conducted after attaining approval from the Institutional Ethics Committee (IEC: 113/2020). Permission was taken from the Medical Record Department (MRD) to access patient data. The physical and electronic medical records of all patients older than 18 years who underwent surgery from January 2019 to October 2019 in a single unit of the department of surgery of a medical college and a tertiary care hospital, were analyzed. Patients with missing height, weight or BMI measurement, and those who had secondary surgery at the same site were excluded from the study. A total number of 549 patients were admitted in the surgery unit during the year 2019 and complete enumeration of these patients was done. Data collected for each patient included the socio-demographic profile, (patient age, gender, place of residence and BMI), previous comorbidities (history of hypertension, diabetes, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, and hyperlipidemia), intraoperative variables (operative procedure type, duration of the procedure, anesthesia given, and analgesic given). The outcomes studied included length of hospital stay, 30-day readmission rates, and pre and postoperative pain scoring. Pain scores were documented using numerical rating scale from 0 to 10 first on the day of admission and first postoperative day. The pain score 0 suggests no pain, 1-3 mild pain, 4-6 moderate pain and 7-10 severe pain.

The surgery unit catered operative treatment to a plethora of illnesses. The pathophysiology and natural course of these diseases varied widely. It was therefore found prudent to analyze the outcome variables separately for the different types of illnesses. The patients were divided into four subsets. Patients with conditions such as abscess, gangrene, ulcer, and cellulitis were grouped into infectious diseases subset. Rectal disease, elective appendectomy, gall bladder disease, hernia and trauma were grouped as non-infectious diseases subset. All organ cancer patients were grouped together as cancer subset. Patients with superficial limb conditions which included varicose veins, skin grafting were grouped together as peripheral disease subset.

The preoperative body mass index was utilized to categorize the patients of these four subsets into two groups. For analysis, underweight and normal were considered as non-obese. These formed the control group ($\text{BMI} \leq 24.9 \text{ kg/m}^2$). Overweight and obese were classified under obese and formed the case group ($\text{BMI} \geq 25 \text{ kg/m}^2$).

STATISTICAL ANALYSIS

Descriptive statistics of categorical variables focused on frequencies and proportions. Independent samples T-test was carried out to compare mean and presented as Mean and SD. Mann Whitney U test was used to compare the continuous variable. Pearson's Chi-square test was performed to identify differences between the

two categorical variables. SPSS 20.0 software was used to carry out statistical analysis, with the significance level being $P < 0.05$.

Results

A total number of 549 patients were admitted in the surgery unit. Out of 549 patients, 37 records were incomplete and hence were excluded. Five-hundred and twelve patients' data were analyzed for this study. 248 (48.4%) were overweight or obese. 264 (51.6%) were classified as controls (Tab. I) The mean age of the patients in both the groups together was 48 ± 13 years. The mean age of the participants in non-obese and obese group is 48.6 ± 11 and 48.6 ± 12 respectively.

The mean height of participants was 159 ± 14 cm and mean weight was 69 ± 13 kg. The mean height and weight among the non-obese control group was 161.4 ± 12 cm and 55.4 ± 11 kg and that among obese was 157.1 ± 10 cm and 73.17 ± 11 kg. Among the participants 10% were underweight, 41.6% were normal, 32% of them were overweight and 16.4% were obese. Non-obese control group had a mean BMI of 20.9 kg/m^2 and it was 29.02 kg/m^2 among the obese case group. Among the total participants, 288 (56.25%) were male and 224 (43.75%) were female. A total of 125 (43.4%) were obese among males and 123 (54.9%) females were obese. Among the total participants, 257 (50.1%) had comorbidity, of which 134 (52%) were in obese group and 123 (48%) in non-obese control group. Out of 512 participants, a total of 152 (29.69%) patients had diabetes and 122 (23.83%) had hypertension. Among the 152 patients with diabetes, 74 (48.7%) were obese, and among the 122 hypertensive patients, 68 (55.7%) were obese (Tab. I).

Among the 512 patients, 95 (18.56%) had an infective condition, 236 (46.09%) were admitted with a non-infective condition, 25 (4.88%) had cancer and 156 (30.47%) had other conditions (Tab. I). Further analysis was done for these four subsets.

Independent samples T-test was carried out to compare the mean of the duration of surgery, a total length of hospital permanence, pre, and post-operative pain scores. We saw an increase in the mean duration of surgery

Tab. I. Demographic profile of the participants.

	N = 512	Non-obese (control)	Overweight & obese (cases)
Male	288	163 (56.6%)	125 (43.4%)
Female	224	101 (45.1%)	123 (54.9%)
Infective	95	49 (51.6%)	46 (48.4%)
Non infective	236	115 (49.0%)	121 (51.0%)
Cancer	25	14 (54.2%)	11 (45.8%)
Other condition	156	86 (55.1%)	70 (44.9%)
Presence of comorbidity	257	123 (48.0%)	134 (52.0%)
Presence of diabetes	152	78 (51.3%)	74 (48.7%)
Presence of hypertension	122	54 (44.3%)	68 (55.7%)
Total	512	264 (51.6%)	248 (48.4%)

Tab. II. Distribution of surgical risk among the patient with obesity and non-obese.

		Non-obese (control)	Overweight & obese (cases)	P-value
30-days readmission, n (%)	Infective	8 (17.5%)	18 (37.8%)	0.040
	Non-infective	10 (8.5%)	10 (9.8%)	0.824
	Cancer	4 (30.8%)	3 (27.3%)	1.000
	Others	4 (4.7%)	5 (7.1%)	0.516
The total length of stay at hospital, (days)		6.74 ± 6.3	7.1 ± 6.01	0.490
Duration of surgery, (hours)		1.2 ± 1.0	2.0 ± 1.6	0.027
Pre-operative pain score		1.6 ± 1.5	1.4 ± 1.5	0.136
Post-operative pain score		1.9 ± 1.4	2.2 ± 1.4	0.017

Tab. III. Comparison of obesity with the duration of surgery, the total length of hospital permanence, pre and post-operative pain scores among the different groups of condition (P-value).

Variables (in P-value)	Duration of surgery	The total length of stay at the hospital	Preoperative pain	Postoperative pain
Infective	0.049	1.000	0.631	0.203
Non-Infective	0.140	0.274	0.206	0.025
Cancer	0.796	0.561	0.149	0.336
Others	0.704	0.999	0.848	0.256

from 1.2 ± 1.0 to 2.0 ± 1.6 hours among obese with a statistically significant difference ($p = 0.017$). The mean length of hospital stay was comparable between both the groups (6.7 vs 7.1 days). There was an increase in the mean postoperative pain score among obese 1.9 ± 1.4 vs 2.2 ± 1.4 respectively, which was statistically significant ($P = 0.017$) (Tab. II).

We evaluated the relations of obesity with the duration of surgery, the total length of hospital permanence, pre and post-operative pain scores among the different subsets using the Mann Whitney U test. Both groups had a comparable level of the duration of surgery. However, for the infective subset, the duration of surgery was greater in the obese group. The result was statistically significant ($p = 0.049$) (Tab. III). The value of the mean ranking indicated that the obese group had significantly more duration of surgery (33.08 minutes) than the non-obese control group (24.53 minutes) in this subset.

The post-operative pain was greater among the obese group in the non-infective subset. The result was statistically significant $P = 0.025$ (Tab. III). The mean ranking score indicated that the obese group experienced significantly more postoperative pain (128.89) than the non-obese control group (109.63).

A Chi-square test was performed to calculate the 30 days readmission. The study showed that 30 days readmission rate among the obese in the infective condition subset was 37.8%. There was a significant difference in the parameters of 30 days readmission rate between non-obese patients and those who are obese in this subset. ($P = 0.040$) (Tab. II). The other subsets showed a difference in 30 days readmission rate among obese, but no statistically significant difference was seen between the two groups (Tab. II).

Discussion

At the outset, our study revealed that nearly half the patient population were either overweight or obese,

stressing the ever-increasing magnitude of the problem of obesity. In the female population, the obese patients were more than the non-obese individuals. More than half the obese patients suffered from comorbidities, indicating the spiraling of associated risks.

This retrospective study assessed the impact of obesity on surgical outcomes, pain scores, duration of surgery, and 30-day readmission rates between non-obese and obese patients. Our study results showed that there is a considerable increase in the duration of surgery in obese when compared to non-obese. Our results showed that the meantime of surgery in the obese group was increased by an average of 40 min compared to the non-obese group (80 vs 120 min, $P = 0.027$). Comparing the surgical procedures in different subsets, a statistically significant extension in the operating time (33.08 min in obese vs 24.53 min in non-obese, $p = 0.049$) was observed in cases with an infective condition. Similarly, a study by Kundu S et al. showed an increase in the mean of surgery time in the obese group by an average of 13 min compared to the control group. The extended operating time can be the effect of the challenging intraoperative conditions caused by internal and external obesity and the subsequent narrowing and lack of space, reduced visibility, and tiresome preparation with the need for surgical accuracy [3]. In a study by Hawn MT et al. it was seen that BMI was associated with operation time with a 7% mean increase in time for cholecystectomy, 16% for colectomy, and 20% for unilateral mastectomy procedures [12]. An increased risk of infection with longer operative times in orthopedic trauma and knee arthroplasty has been reported in a study by Colman et al. [13]. Increase in operating time affects the anesthetic drug requirement by the patient and its added complications. The drug delivery is more initially due to the higher weight of the patient and it is further increased by the prolonged time of surgery. The presence of co morbidities interferes with the pharmaco-kinetics of these intra operative

drugs too. The prolonged operative time thus has detrimental effects on the obese patient.

The mean length of stay in our study in the obese group (7.1 days) was more compared to the non-obese (6.7 days) which was not statistically significant (0.490). A previous study reported that the total hospital stay in the obese group was 9.64 days opposed to 4.93 days in the non-obese ($P = 0.001$) [3]. There has been no evidence for a prolonged length of stay for obese patients undergoing common general surgery [14, 15]. Hawn et al. do not find evidence of the prolonged length of stay for obese patients undergoing 3 common general surgery procedures (cholecystectomy, unilateral mastectomy, and colectomy) [12]. Underweight and obesity had greater lengths of stay compared to normal weight who had shorter lengths of stay [15]. Evidence from a previous study suggests that some surgeon-specific characteristics could constitute a substantial amount of variation in operating time and discharge decisions. Most of these factors are unobservable and hard to measure and could give rise to biased estimates of the impact of obesity on operating time and length of stay [12]. Comorbidities in obese patients are related with longer length of stay as observed in a study by Planchard et al. [16]. Identifying the risks may assist in changing the operating plan to reduce any postoperative complications. While each day of stay represents a measurable cost increase and increased hospital utilization, the exact effect of the increase in length of stay on surgical outcome is unknown [14]. There is a need to take special precaution both pre and post-surgery among obese, to reduce the cost and length of stay at the hospital.

Our study demonstrated that obese patients (37.8%) had higher 30 days readmission rate than the non-obese (17.5%) among those suffering from infectious conditions ($P = 0.040$). A significant difference in both groups was seen ($P = 0.040$). Other conditions had a difference in 30 days readmission between the two groups which was not statistically significant. A study on predictors of readmission with heart failures revealed that Obesity (aOR = 0.84, 95% CI = 0.82-0.86) and Morbid Obesity (aOR = 0.83, 95% CI = 0.81-0.85) were independently associated with 30-day readmission rate. Readmission at 6 months was highest among Morbid-Obese followed by Non-Obese and Obese (51.1 vs 50.2 vs 49.1%, $P < 0.01$) [17]. However, in our study, we did not follow-up for readmission in 6 months. Further study showed that predictors of higher 30-day readmission among obese patients were associated with comorbidities like diabetes mellitus, atrial fibrillation, chronic kidney disease, liver disease, and peripheral vascular disease [17]. Particular focus needs to be taken on postoperative care for obese patients admitted with infectious condition to minimize the preventable complications and promote the quality of care. Interventions such as early mobilization, precautions for pressure ulcers must be included to reduce 30 days readmission rate [17].

The study showed that post-operative pain is higher among the obese group in the non-infective subset. The mean postoperative pain score between non-obese and obese increased from 1.9 ± 1.4 to 2.2 ± 1.4 respectively, which is statistically significant ($P = 0.017$). A study by Motaghedi et al. showed that there was no association between obesity and pain scores. It showed that the mean preoperative pain scores were comparable despite weight: normal weight, 3.4 ± 3.3 ; overweight, 2.9 ± 2.9 ; and obese and 2.9 ± 3.2 . Mean postoperative pain scores at rest and activity were similar regardless of weight [18].

There were several limitations to the study. While all variables were preoperatively, perioperatively and postoperatively registered, they were retrospectively evaluated and, as such, constrained by the shortcoming in retrospective analyses. Bias in the data can occur as it was pre documented and could not be verified with any source. There were no assessments of all the risk factors that lead to surgical outcomes. Further, only the patient's BMI was considered for measuring obesity. Other measures such as weight-for-height index, BMI, waist circumference (WC), waist-hip ratio (WHR), and body fat percentage estimated by skinfold thickness (ST) could not be considered as the study had to rely on the existing data. BMI measurement is independent of age, gender, bone structure, muscle mass or fat distribution. If the outcome varied due any of these parameter differences, it might have been missed due to the BMI measurements alone. Besides these limitations, this study provides a novel perspective into considering the appropriate disease treatment in the setting of obesity. Different operation procedures were considered in the study. Each procedure poses diverse operative challenges and is expected to have different complications. Hence subset analysis was performed. This was done to determine whether obesity played an important role in changing outcomes across all kinds of operations.

Based on this study, it would be prudent to bring about the following changes while treating our patients. In elective cases, it would be beneficial for patient to undergo a weight reduction regimen before the operative procedure so as to decrease operating time and postoperative pain. In emergency patients with operative treatment for infective conditions, it would be worthwhile to stringently monitor comorbidities to reduce duration of hospital stay and the risk of readmission due to complications. Further research regarding the postoperative health of obese individuals may be brought out more beneficially by a prospective study to determine the surgical outcomes among obese patients. Further studies could use other anthropometric measurements of obesity to evaluate whether certain single parameters (waist circumference or skin fold thickness) are more predictive of worse outcomes in obese individuals than other obesity measurements.

Conclusions

In conclusion, among the obese group, the impact of obesity was seen as increased duration of surgery and post-operative pain. A slight increase in the 30 days readmission among obese was seen in the infection subset. The differences in 30 days readmission, duration of surgery, and length of stay arise due to different complex conditions among the patients. This study concludes that we should have a higher sensitivity towards the pain management and towards the parameters monitoring the possibility of complications in obese individuals. It is necessary to take early decisions and actions to prevent further complications of surgery that could occur in obese patients. In this way, readmissions due to ensuing complications can be prevented. It is also necessary for the high-risk patients to receive an overview of their overall preoperative condition to ensure effective post-operative treatment and control of complications. As obesity rates increase worldwide and as comorbidities in them increase, the negative impact in postoperative outcomes may spiral in the ensuing years. It is of utmost importance therefore to establish safe, alternate and minimally invasive surgical techniques for operations associated with increased adiposity. In addition, it is not only important to establish protocols for postoperative pain alleviation in the obese but also to establish postoperative monitoring guidelines to detect post-operative complications in its very early stages thus preventing readmissions.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

DK and VLK conceived the study, performed a search of the literature and, were responsible for data analysis and data acquisition; DK contributed to the preparation of the manuscript; DK and VLK revised critically and editing the manuscript; all authors read and approved the last version of the manuscript.

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RESEARCH ARTICLE

Financial incentive strategy for weight loss and maintenance of weight loss

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Keywords

Obesity • Weight Loss • Intervention • Financial incentive

Summary

Introduction. The aim of this study was to investigate the effect of financial incentives on weight loss, maintain in obese women and biochemical factors.

Methods. This quasi-experimental study was conducted on 103 women with body mass index (BMI) ≥ 30 kg/m². The participants were assessed over a 12-month follow-up in eight phases. Money payment for losing weight was incentive intervention in this study. The participants were given diet and physical activity.

Results. Mean of BMI was 34.78 ± 4.29 kg/m² in baseline, that reduced to 32.41 ± 3.51 kg/m² in the sixth phase, and 31.64 ± 3.71 kg/m² in the final phase ($P < 0.001$). At baseline, mean of percentage of body fat (PBF) was 40.77 ± 2.81 that reduced to 37.34 ± 4.02 at the end of the study ($P < 0.001$). Waist to hip ratio (WHR) and lean body mass (LBM) decreased signifi-

cantly over the 12-month ($P < 0.001$). At the end of each phase, the mean of BMI reduction of 0.39 units was observed in the subjects, and 9 units of change were achieved by the end of the study compared to the baseline. The mean of triglyceride in the first, fourth and seventh phases were 128.57 ± 13.33 , 101.43 ± 57.99 and 87.40 ± 57.59 mg/dl, respectively ($P = 0.003$). The mean of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamate-pyruvate transaminase (SGPT) decreased significantly over the 12-month, $P = 0.052$ and $P = 0.005$, respectively.

Conclusions. Financial incentives can effectively help to weight loss and maintenance of weight, and improve lipid profiles; blood sugar and liver enzymes. The use of motivational factors with proper training (diet and physical activity) will have a better result.

Introduction

Obesity is one of the known factors associated with an increased risk of non-communicable diseases and mortality [1]. According to the World Health Organization (WHO), obesity and overweight are the fifth leading cause of death worldwide, and a major risk factor for diabetes, cardiovascular disease, cancer, sleep apnea and poor physical health. Approximately, 44% of diabetes, 23% of ischemic heart disease, 7 to 41% of all types of cancers are related to obesity and overweight [2-5]. The prevalence of obesity and overweight in developed and developing countries is increasing and is reported more in developed countries, compared to the developing countries [6]. In 2010 estimated, obesity and overweight cause of 3.4 million deaths, 4% of years of life lost (YLL) and 4% of disability-adjusted life years (DALYs) in the world [7]. Given its ascending trend, obesity can be considered a syndrome of the modern world [8]. The financial burden imposed by obese people on the community and the health system is very high. The studies conducted in developed countries show that the annual medical cost imposed by an obese person is USD \$ 1,400 higher on average compared to the cost imposed by a normal-weighting person. The results of a study by

Wang Y et al. (2011) in the US and UK on the financial burden of obesity and the treatment of the diseases caused by obesity showed that the combined medical costs of treating diseases such as diabetes, stroke and heart disease are much higher than the costs of treating obesity, which happens to be the underlying factor of these diseases [6].

The use of financial incentives incorporating insights from behavioral economics has become more common in promoting healthy lifestyles in recent years [9-11]. Therefore, an external motivational source such as monetary incentives can be effective in inducing initial weight loss [12]. Nutritionists and diet therapists also recommended financial incentives to lose weight, along with diet [13, 14]. Previous studies have shown that variable reinforcement using money payments may be more effective over time than a fixed incentive, and frequent incentives are more effective than infrequent incentives for behavior change [12, 15-17]. Since that weight loss maintenance is arguably considerably more difficult, therefore, it is uncertain whether financial incentives will be effective in this issue. The present study was conducted to determine the association financial incentive strategies for weight loss on obesity women and its maintenance over 12 months.

Methods

PARTICIPANTS

This quasi-experimental study was conducted on 103 women with body mass index (BMI) ≥ 30 kg/m², in Kermanshah, Iran. Kermanshah is one of the provinces of Iran with about 1,000,000 populations in the western region of Iran. The sample size was calculated as 103 based on previous studies [12]. Participants were randomly selected from two health centers based on the list of women clients. The two centers were located in slum areas of the city; and all participants had a similar socioeconomic status. Including criteria were obese women (BMI ≥ 30 kg/m²) and age over 30 years. Exclusion criteria were pregnant women, experienced unsuccessful attempt for weight reduction and serious to weight loss.

MEASUREMENTS

Demographic characteristics such as age, education, marital status were collected using questionnaire and filled by an expert interviewer. Body composition such as weight, BMI, Mass of Body Fat (MBF), Percentage of Body Fat (PBF), Soft Lean Mass (SLM), Total Body Water (TBW), Body Impedance, Body Protein, Minerals, Lean Body Mass, and Waist to Hip Ratio (WHR) were measured using Bio-Impedance Analyzer BIA (Inbody Avis 333) with precision of 100 gr. The height of the subjects was measured with BSM 370 (Biospace Co, Seoul, Korea) with precision of 1 cm. Obesity and overweightness were defined according to the WHO criteria. BMI ≥ 30 indicated an obese individual [18], with the formula; BMI = weight (kg) / height² (m).

Lipid profiles, liver enzymes and fasting blood sugar were measured 3 times during the study (phase 1, phase 4 and phase 7). For collection of the blood sample, after 8-12 hours of fasting, blood samples were collected from the ante-brachial vein. Serum and plasma samples were centrifuged and stored in aliquots in cryotubes at -80°C until analyzed.

FOLLOW-UP ASSESSMENTS, INTERVENTIONS AND PARTICIPANT'S EDUCATION

The study consisted of eight phases and participants were followed-up for 12 months. Participants were given training packages for daily physical activity and diet at baseline (Tab. I). Physical activity package included 45 minutes of walking at least three times per week. Given their physical

state and since some of them had back pain and knee pain, heavier physical exercise was not recommended. Given follow-up 12 months, a seasonal diet was developed for all the subjects for every season. Due to weight loss in the previous phase, they were given a new diet in each phase. We explained face-to-face to participants at least 30 minutes about the use of physical activity and diet packages.

INCENTIVE

Money payment for losing weight was incentive intervention in this study. The participants received local currency for each 3% of weight reduction in the first phase equal to \$ 30, in the second \$ 50, in the third \$ 70 and in the fourth, fifth and sixth phases \$ 100. After the end of sixth phase, participants had to maintain their weight constant for the next 6 months. Then in phase seven (after 12 months of follow-up included 6 months of weight loss and 6 months of maintaining weight) body composition was measured again, and people who were stable in weight were encouraged [Fig. 1].

PRIMARY OUTCOME MEASUREMENTS

Primary outcome measurements weight and loss BMI will be the primary outcome measure. This will be assessed using the Bio-Impedance Analyzer BIA (Inbody Avis 333).

SECONDARY OUTCOMES

Secondary outcomes included weight maintenance, decreased lipid profile, fasting blood glucose, and improving liver enzymes after the intervention.

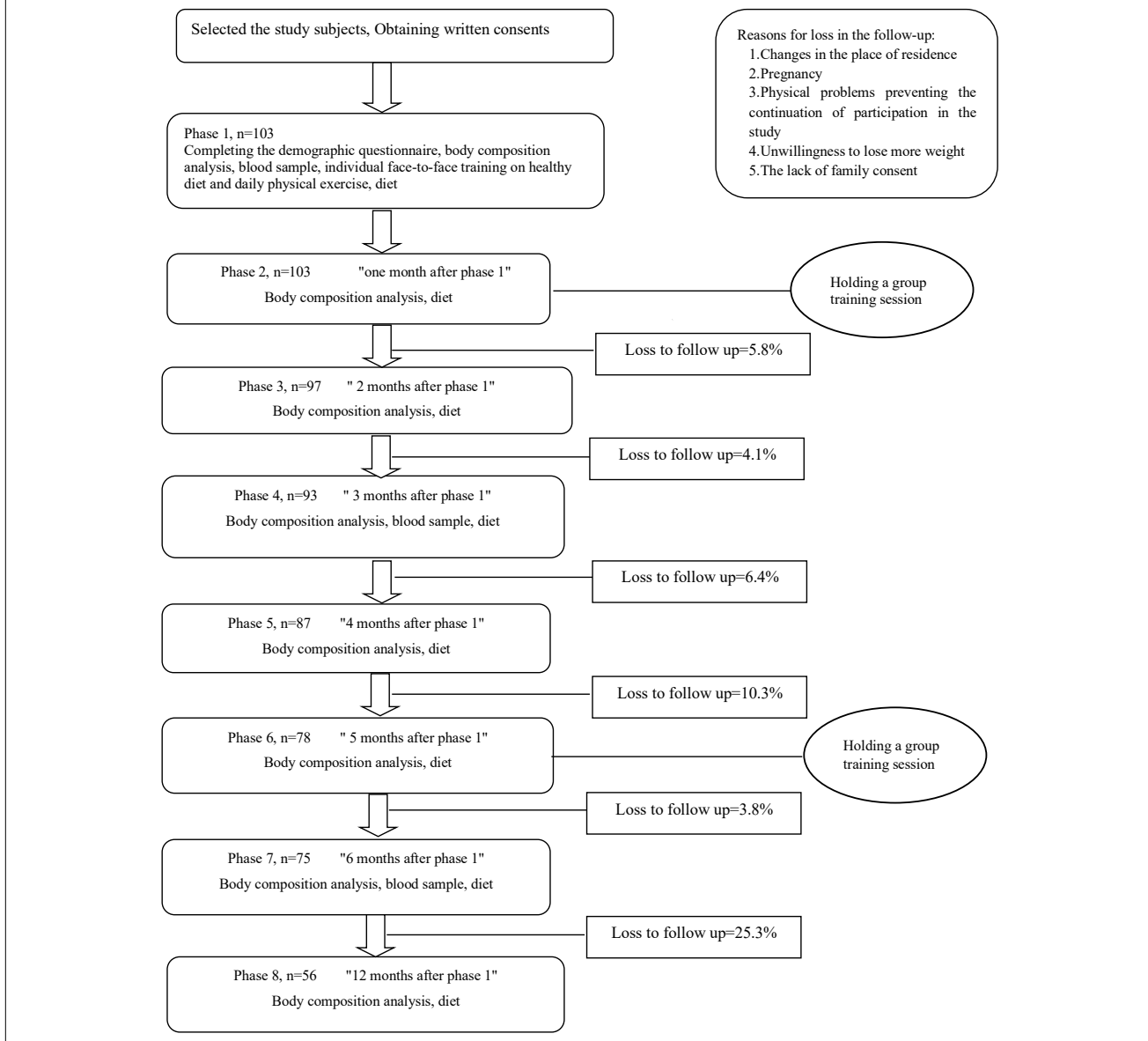
STATISTICAL ANALYSIS

The descriptive data (mean and standard deviation for the quantitative variables and frequency and percentage for the qualitative variables) pertaining to each phase of the study were analyzed in SPSS-21 at a confidence interval of 95%. The generalized estimating equation (GEE) model was used to determine the changes in the variables over time, since the changes in each phase were dependent on the previous phase. In other words, there is a correlation between the measurements during the follow-up [19]. The following equation was used to measure the changes in the variables over the 12 months of the follow-up; for example, the changes in BMI were calculated as:

$$\% \text{ changes in BMI} = [(BMI \text{ at phase 8} - BMI \text{ at phase 1}) / BMI \text{ at phase 1}] \times 100$$

Tab. I. The types of interventions and training packages in this study.

Intervention	Procedure
Nutritional education	Providing nutritional information by booklet or monthly interval lecture on food groups, nutritional value, healthy cook, having regular meals, avoiding unhealthy eating
Low-calorie diet	At the beginning of the study, a low calorie diet (1500 calories) was given to the participants who were gradually reduced to 1200 calories at the end of the study. The designed diet consists of 3 main meals: breakfast, lunch, dinner and two snacks of morning and evening. Diet was planned by an expert nutritionist. Since the study lasted one year, availability of foods in different seasons, fruits, vegetables and foods of each season were considered in the provided diet.
Physical activity	Daily or three days a week physical activity was recommended (total 180 minutes/week)

Fig. 1. The stages of the study and the training provided in each phase.

Results

Overall, 103 women were evaluated in the base line stage, with an average age of 39.74 ± 5.70 years (min = 30 year, max = 53 year). About 97 (94.2%) women were married and the rest were single or divorced. 30 (29.13%) people were illiterate, 59 (57.28%) of participants less than diploma and 14 (13.59%) persons were diploma, 96.3% were housewives. All participants were from the suburbs of the city and therefore, they were similar in terms of socio-economic status. They had a low income level. In the women studied, the average number of children was 2.86 ± 1.49 (min = 0 year, max = 6). 37.6% of women had chronic diseases including type 2 diabetes, cardiovascular disease, hyperlipidemia or hypertension. The average physical activity (walking) was 140 ± 60 minutes per week.

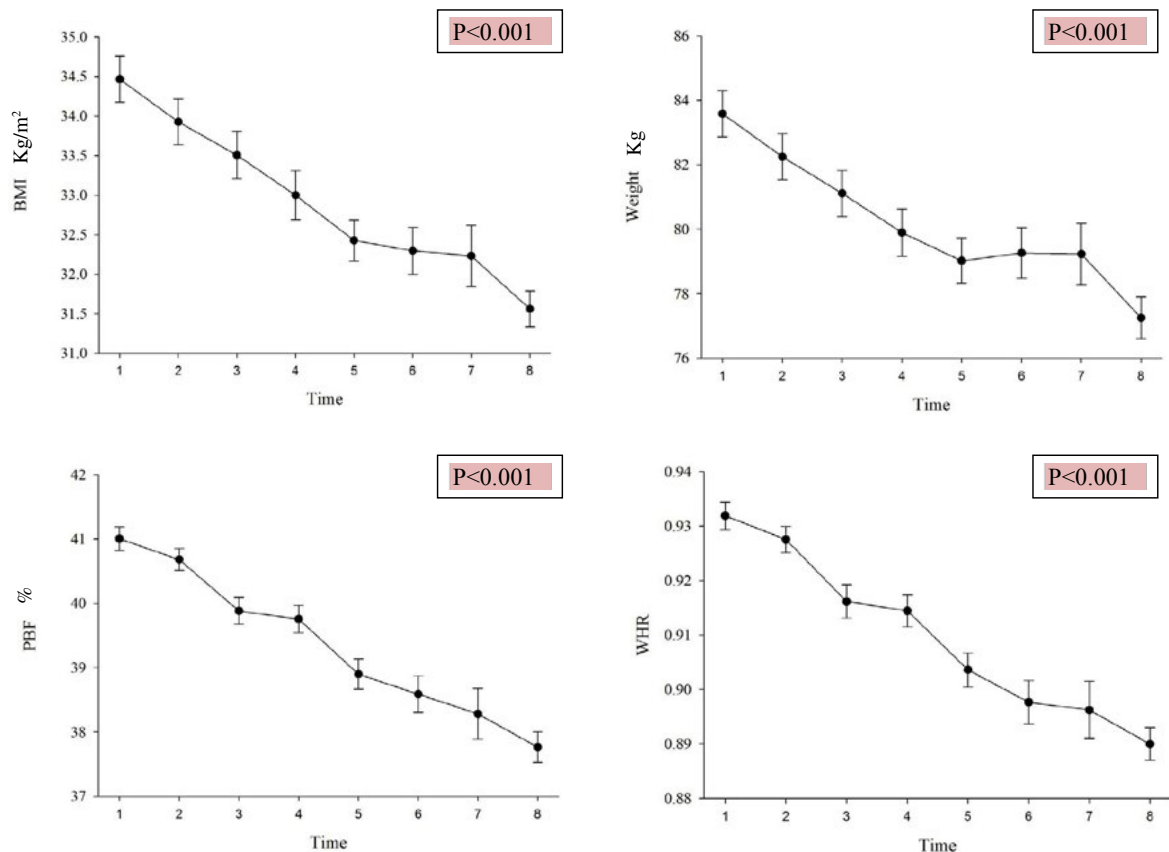
Participants lost to follow-up during the 12 months of study for the participants differed in each phase. In the first phase, participants' mean BMI was 34.78 ± 4.29 kg/m² that reduced to 32.41 ± 3.51 kg/m² in the sixth phase, and reduced to 31.64 ± 3.71 kg/m² in the final phase and after 12 months of follow-up. The mean of weight was 85.86 ± 11.36 kg in the first phase and 78.23 ± 10.83 kg in the final phase. The mean WHR in the first and final phase was 0.92 ± 0.04 and 0.88 ± 0.04 , respectively. The mean of SLM reduced by about 1 kg during the follow-up, but the mean of MBF reduced by more than 6 kg (Tab. II). Figure 2 shows the descending trend of weight, BMI, PBF and WHR during the one-year follow-up.

Average Triglyceride in the first, fourth and seventh phases were 128.57 ± 13.33 , 101.43 ± 57.99 and 87.40 ± 57.59 mg/dl, respectively, which shows a decreasing trend ($P = 0.003$). Also, LDL-C ($P = 0.006$)

Tab. II. Comparison of anthropometrics indices and body composition in the participants during the twelve months.

Variable	Phase 1 baseline (n = 103)	Phase 2 (n = 103)	Phase 3 (n = 97) Losses: 5.8%	Phase 4 (n = 93) Losses: 4.1%	Phase 5 (n = 87) Losses: 6.4%	Phase 6 (n = 78) Losses: 10.3%	Phase 7 (n = 75) Losses: 3.8%	Phase 8 (n = 56) Losses: 25.3%
Weight (kg)	85.86 ± 11.36	84.61 ± 11.09	83.15 ± 11.08	82.13 ± 11.24	80.98 ± 10.06	80.26 ± 9.95	79.69 ± 10.48	78.23 ± 10.83
BMI (kg/m ²)	34.78 ± 4.29	34.29 ± 4.23	33.70 ± 4.37	33.29 ± 4.37	32.66 ± 3.39	32.41 ± 3.51	32.13 ± 3.77	31.64 ± 3.71
WHR	0.92 ± 0.04	0.91 ± 0.40	0.90 ± 0.04	0.90 ± 0.04	0.89 ± 0.04	0.88 ± 0.04	0.88 ± 0.04	0.88 ± 0.04
PBF	40.77 ± 2.81	40.42 ± 2.69	39.69 ± 3.00	39.61 ± 2.78	38.75 ± 2.85	38.3 ± 3.20	37.65 ± 3.66	37.34 ± 4.02
MBF (kg)	35.20 ± 6.61	34.37 ± 6.36	33.21 ± 6.50	32.73 ± 6.43	31.57 ± 5.87	30.96 ± 6.12	30.27 ± 6.51	29.46 ± 6.20
LBM (kg)	50.66 ± 5.42	50.23 ± 5.36	49.94 ± 5.28	49.40 ± 5.38	49.41 ± 4.82	49.29 ± 4.45	49.42 ± 4.81	48.77 ± 5.64
SLM (kg)	45.86 ± 4.85	45.50 ± 4.72	45.29 ± 36.9	44.79 ± 4.80	44.87 ± 4.31	44.79 ± 3.95	44.92 ± 4.29	44.37 ± 5.11
TBW(kg)	36.48 ± 3.91	36.17 ± 3.86	35.96 ± 3.80	35.56 ± 3.87	35.57 ± 3.47	35.49 ± 3.20	35.57 ± 3.46	35.12 ± 4.07
BMR (kcal)	1,258.74 ± 70.82	1,254.22 ± 70.50	1,249.88 ± 68.65	1,239.46 ± 65.95	1,241.67 ± 66.11	1,240.84 ± 60.64	1,239.74 ± 64.83	1,227.83 ± 70.79

BMI: body mass index; WHR: waist to hip ratio; PBF: percentage of body fat; MBF: mass of body fat; LBM: lean body mass; SLM: soft lean mass; TBW: total body water; BMR: basal metabolic rate.

Fig. 2. The trend of changing BMI, body weight, PBF, WHR during the follow-up period.

and TC ($P = 0.001$) decreased significantly during the follow-up. Liver enzymes (ALP, SGOT and SGPT) and FBS also had a significant decreased during the study (Tab. III).

The analysis of the GEE model after adjusting the effect of age showed significant reductions in all components of the body composition during the 12-month follow-up. The biggest share of the 9.52%

Tab. III. Comparison of lipid profiles and liver enzymes and blood sugar in the participants during the twelve months.

Biochemical factors	Phase 1 baseline (n = 103)	Phase 4 (n = 93)	Phase 7 (n = 75)	P-value
Triglyceride	128.57 ± 13.33	101.43 ± 57.99	87.40 ± 57.59	0.003
LDL-C	92.27 ± 90.93	99.28 ± 40.76	84.20 ± 67.00	0.006
HDL-C	37.50 ± 35.60	39.72 ± 30.07	29.73 ± 30.79	0.014
TC	196.32 ± 38.58	158.49 ± 130.12	130.12 ± 35.34	0.001
FBS	97.28 ± 37.05	92.52 ± 10.14	90.32 ± 11.21	0.022
ALP	175.46 ± 54.56	171.71 ± 53.57	137.97 ± 46.32	0.034
SGOT	21.72 ± 8.54	18.95 ± 6.94	15.28 ± 6.04	0.052
SGPT	19.75 ± 9.45	17.32 ± 7.94	11.81 ± 5.60	0.005

LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; TC: total cholesterol; FBS: fasting blood sugar; ALP: alkaline phosphatase; SGOT: serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase.

Tab. IV. Change of body composition after financial incentives over time using generalized estimating equations adjusted for age and physical activity.

Variable	B	95% CI	P-value	% change from baseline
BMI (kg/m ²)	-0.395	-0.432, -0.357	< 0.001	-9.52
Obesity I ^a	-0.327	-0.432, -0.220	< 0.001	-6.61
Obesity II	-0.210	-0.245, -0.173	< 0.001	-1.23
Obesity III	-0.278	-0.350, -0.206	< 0.001	-1.22
Weight (kg)	-0.972	-1.066, -0.878	< 0.001	-8.52
Obesity I	-0.876	-1.141, -0.612	< 0.001	- 6.45
Obesity II	-0.550	-0.634, -0.461	< 0.001	-3.00
Obesity III	-0.700	-0.883, -0.516	< 0.001	-0.16
WHR	-0.006	-0.66, -0.005	< 0.001	-4.37
PBF	-0.494	-0.542, -0.446	< 0.001	-8.41
MBF (kg)	-0.769	-0.836, -0.703	< 0.001	-16.30
LBM (kg)	-0.202	-0.246, -0.159	< 0.001	-3.73
TBW (kg)	-0.146	-0.177, -0.114	< 0.001	-3.72
SLM (kg)	-0.152	-0.192, -0.112	< 0.001	-3.24
BMR (kcal)	-3.103	-3.550, -2.657	< 0.001	-2.45

^a Based on body mass index; first degree obesity, second degree obesity, third degree obesity (obesity I, obesity II, obesity III).

reduction in BMI and 8.52% reduction in weight over time belonged to the first degree obesity (obesity I), which showed reductions of 6.61 and 6.45%. In fact, after each phase, a significant mean reduction of 0.395 units in the BMI was observed during the follow-up, making for a total of 9.05 units of change from the start to the end of the study. The reduction in MBF was more significant than the reduction in the other components (Tab. IV).

Discussion

This study showed the positive effect of financial incentives on weight loss and maintenance of weight in obese women. The average BMI decreased by almost 3 units using monetary incentives over the 12-month follow-up of obese women. The average weight of the participants decreased about 8 kg over the 12-month. The other components of body composition, including WHR, PBF, MBF and LBM, also showed a descending trend in the follow-up period.

A study in the United States (2012) reported that in obese individuals \$ 5 per 1% weight loss has been rewarded, at the end of the study, the group that received the financial incentives had more weight loss, but weight loss was not significantly different between the two groups [15]. In a randomized controlled trial study in the United States, subjects with BMI > 30 were divided into three groups and followed for 16 months. They had a control group and in exchange for weight loss, financial incentives were given to two groups, Lottery cash was given to a group and the other group received investment savings accounts. The results showed that in the two groups that received encouragement, weight loss was higher compared to the control group [12].

A study in Finland examining the effect of different levels of financial incentives on weight loss, one group had control and gave the other two groups \$ seven and \$ 14 for weight loss, respectively. Individuals in the seven-dollar group lost 1.35 kg of weight, the 14-dollar group had a 2.11 kg weight loss and the control group (without financial incentives) had a 0.9 kg weight loss [20]. Webber et al. (2010) reported that there was no association

between motivational intervention and weight loss [14]. Other studies with different designs have shown the positive effect of financial incentives on weight loss [21-23]. The differences between the results of the studies can be due to the duration of the incentives, the financial value of the incentives, the level of economic-social status of participants and the sample size.

In addition to losing weight, another goal of the present study was to maintain weight, which was evaluated in the second six months of the follow-up and showed a positive result. After six months (24 weeks) of weight loss, participants were able to maintain their weight constant in the second 6 months of the study that was a very valuable finding. The study by Yancy et al. (2018) showed lottery-based and direct monetary incentives provided no additional benefit for weight loss maintenance [24]. The result of this goal can be relevant to the duration of the follow-up. Therefore, further studies need to be done to show how long a follow-up is appropriate for the optimal outcome of a motivational intervention for weight loss.

Although the present study and similar studies have confirmed financial incentives as an appropriate motivational strategy for weight loss, but this strategy can only have a considerable effect on low-income people and those who do not have a source of personal income, especially housewives [16].

During the 12-month follow-up, MBF decreased by 6 kg and SLM by 1 kg. Lipid profiles, Liver enzymes and FBS also showed a significant decrease during the study. This finding demonstrates the positive impact of training packages on physical activity and diet. Therefore, the use of motivational factors along with appropriate training will produce better results.

Loss to follow-up was one of the limitations of this study. Maybe, if participants received more encouragement, they were more likely to lose weight and stay in the study. Having no control group was another limitation. The strength of this study was a relatively long follow-up period.

Conclusions

Finding of this study showed the positive impact of financial incentives on weight loss and maintenance of weight in obese women. The average BMI decreased by almost 3 units using monetary incentives over the 12-month follow-up of obese women. The average weight of the participants decreased about 8 kg over the 12-month. The other components of body composition, including WHR, PBF, MBF and LBM, also showed a descending trend in the follow-up period. This study showed the positive effect of physical activity training regimens on weight loss. Because, the most weight loss was due to fat mass and the least to SLM. Therefore, using motivational factors along with appropriate training will produce better results.

Performing similar interventions on a larger scale can help reduce the burden of chronic disease. More money as a financial incentive may increase people's motivation to lose weight and make intervention more effective.

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The research was approved by the Ethics Committee of Kermanshah University of Medical Sciences under the code (KUMS.REC. 1394.484). All the participants were provided oral and written informed consent. The study protocol was registered in the Iranian Registry of Clinical Trials (IRCT) with the registration number of IRCT20120525009856N8 at 2020-02-25. We wish to thank all of the women who participated in this study.

Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: YP and MD; methodology: SHR and FN; acquisition of data: PN and MD; formal analysis: SHR and MD; interpretation of data: FN; writing - original draft: MD and YP; writing - review and editing: YP, FN, BH, MD, SHR and PN; supervision: YP; project administration: MD. All authors have read and agreed to the submitted version of the manuscript.

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RESEARCH ARTICLE

Determinants of cervical cancer screening uptake among female undergraduates in a tertiary institution in south eastern Nigeria: a cross sectional study

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Keywords

Determinants • Cervical cancer • Screening uptake • Human Papillomavirus

Summary

Introduction. Cancer of the cervix is the second most common cancer among women worldwide and is the major cause of cancer deaths in developing countries. Screening is among the common cost-effective control methods for the disease. This study ascertained the determinants of cervical cancer screening uptake among female undergraduates in a tertiary institution in south eastern Nigeria.

Methods. This cross-sectional study was conducted using a stratified sampling technique among 375 respondents. A pretested semi structured questionnaire was used for data collection and SPSS version 21 was used in data analysis in which the association between qualitative variables was ascertained using Chi-square test at $P < 0.05$ probability level.

Results. The result revealed that majority of 321 (85.6%) were aware of CC as a disease and 202 (53.9%) of the respondents were aware of cervical cancer screening test. The study revealed that the uptake of cervical cancer screening was low among the female undergraduates. Only few 27 (7.2%) of the respondents have been previously screened for cervical cancer. High cost of screening 128 (31.2%) was the major reason for not undergo-

ing screening. Significant association existed between socio-demographic variables (age, level of study, marital status and monthly allowance) and uptake of cervical cancer. Most of the respondents 10 (17.2%) that had been screened for cervical cancer were within the age bracket of 25-29 years and were in 500 level 21 (19.4%). Cervical cancer uptake was higher 9 (29%) in married females compared to single females 18 (5.2%). It was also indicated that all the participants who have been screened were screened at a cost of ₦ 1,001 - ₦ 2,000. Majority of them 11 (25.6%) earned monthly allowance of ₦ 23,001 - ₦ 30,000. Strong association were also found between awareness of cervical cancer ($X^2 = 4.89$, $P = 0.027$), availability of screening center ($X^2 = 37.433$, $P \leq 0.001$), cost of screening ($X^2 = 100.793$, $P \leq 0.001$) and uptake of screening.

Conclusions. The study revealed that the uptake of cervical cancer screening was low among the female undergraduates. In order to enhance screening uptake among female undergraduates, there is an urgent need to review the cost of screening especially in the school's health center and other hospitals/clinics within the school environment.

Introduction

Worldwide, cancer of the cervix is the second most popular cancer among women and is the main cause of cancer deaths in developing nations [1]. In sub-Saharan Africa region, 34.8 new cases of cervical cancer are diagnosed per 100,000 women per annum and 22.5 per 100,000 women die from the disease [2]. Globally, more than 530,000 new cases of cervical cancer and subsequent 275,000 deaths were documented in 2008 alone. Incidence of cervical cancer related death is usually highest among middle age women (between 30-40 years) and 90% of these deaths were observed in the developing countries [3]. This indicated that cancer is a universal health issue whose burden is more acutely felt in developing countries characterized by limited resources prevention, diagnosis, and treatment of the disease. This is actually the case in Nigeria, where estimated five-year prevalence of 21.6% for the disease was postulated in 2012 fact sheets of GLOBOCAN (2012) [4] and an estimated 10,000 new cases of the

disease and 8,000 deaths caused by cervical cancer are reported among women annually. It was also reported by Oguntayo et al. (2011) [5] that about 65.7% gynecological cancers in Northern part of Nigeria were caused by this disease. Cervical cancer disease is preventable and the disease can be detected at early stage when appropriate steps can be taken to avert progression to life-threatening advanced level of it [6]. Ingwu (2016) stressed that this disease is causing untold havoc and control measures are seriously needed [7].

Papanicolaou (Pap) smear cytology screening technique used in identifying precancerous lesions has assisted in achieving massive decrease in the burden of cervical cancer particularly in the developed countries. There are other less invasive methods that were produced for rapid screening of the disease such as Visual Inspection with Lugol's Iodine (VILI) and Visual Inspection with Acetic Acid (VIA). Even though these techniques are less cumbersome and faster, they have been found to be less sensitive when compared to cytologic screening through Pap smear. Visual Inspection with Acetic Acid

specifically has been linked with high false positive outcomes giving rise to enormous psychological issues and wrong treatment of the patient involved [3].

The great differences in morbidity and mortality in developed and developing countries occur as a result of the fact that developed countries have executed effective program over the last few decades. Such programs include screening for the prevention of cancer of the cervix, in many countries decreasing the incidence and mortality by up to 80%. But then, the incidence of women suffering from the disease continues to be high in developing countries characterized by limited access to screening services for the disease [8]. Hyacinth et al. [9] noted that although a single visit for cervical cancer screening may save above 6,000 Nigerian women yearly, but its uptake is still low. There is dearth of information on factors that influence cervical screening especially in university female students. According to previous study conducted by Ezem (2007) in mixed population in Owerri, Imo State, the reason for not undergoing cervical cancer screening test were lack of awareness (46.1%), no need for it (12.5%) and fear of bad result (11.6%) [10]. This study showed that the level of awareness of cervical cancer screening is poor and worse still is the level of uptake. The present study therefore, ascertained the determinants of cervical cancer screening uptake among female undergraduate in a tertiary institution in south eastern Nigeria.

OBJECTIVES

The present study ascertained the determinants of cervical cancer screening uptake among female undergraduates in a tertiary institution in south eastern Nigeria

Materials and method

STUDY PARTICIPANTS

The study employed a cross sectional study design to assess the factors influencing cervical cancer screening knowledge and participation among female undergraduates in Federal University of Technology, Owerri. The design was considered appropriately in carrying out this study because it will facilitate the collection of data systematically from a sample of the population and at a defined time.

AREA OF THE STUDY

This study was conducted in Federal University of Technology, Owerri, Imo State, and southeastern Nigeria. It is located in Owerri West Local Government Area and bounded by the communities of Umuchima, Ihiagwa, Eziobodo, and Obinze in Imo State. The school has eight faculties namely: School of Health Technology (SOHT), School of Engineering and Engineering Technology (SEET), School of Management Technology (SMAT), School of Environmental Sciences (SOES), School of Biological Sciences (SOBS), School of Physical Sciences (SOPS), School of Agriculture and

Agricultural Technology (SAAT) and School of Basic Medical Sciences (SBMS).

STUDY POPULATION

The target population for the female undergraduate is 5,500 students (FUTO registry, 2018).

SAMPLE SIZE AND SAMPLING TECHNIQUE

Sample size

The sample size is 373. The sample size was determined using Taro Yamane's (1967) [11] formula: $n = \frac{N}{1 + N e^2}$, where:

N = population size;

n = sample size;

e = coefficient of margin which is 0.05;

$$n = \frac{5,550}{1 + 5,550 (0.0025)}$$

$$n = 373.$$

Therefore 373 female students were used for the study.

Sampling technique

Stratified sampling combined with simple random sampling technique was used on the different categories of the study population. This was necessary as a result of discrepancy in gender distribution within the study population. Using the formula below, the ratio of participants was randomly selected.

$$\text{Ratio of participants} = \frac{n \times N_1}{N}$$

Where:

n = sample size;

N₁ = stratum size;

N = total population.

$$\text{SOHT female students} = \frac{373 \times 1,450}{5,550} = 96.8 = 97$$

$$\text{SEET female students} = \frac{373 \times 310}{5,550} = 20.8 = 21$$

$$\text{SMAT female students} = \frac{373 \times 573}{5,550} = 38.5 = 39$$

$$\text{SOBS female students} = \frac{373 \times 1,290}{5,550} = 86.7 = 87$$

$$\text{SOPS female students} = \frac{373 \times 523}{5,550} = 35.1 = 35$$

$$\text{SOES female students} = \frac{373 \times 400}{5,550} = 26.9 = 27$$

$$\text{SAAT female students} = \frac{373 \times 934}{5,550} = 62.8 = 63$$

$$\text{SBMS female students} = \frac{373 \times 70}{5,550} = 4.7 = 5$$

POPULATION DISTRIBUTION OF THE PARTICIPANTS

S/N	Stratum; Schools	Population
1	SOHT	1,450
2	SEET	310
3	SMAT	573
4	SOBS	1,290
5	SOPS	523
6	SOES	400
7	SAAT	934
8	SBMS	70
	TOTAL	5,550

DATA COLLECTION

The instrument for data collection consists of a semi-structured self-administered questionnaire which was administered on the 375 respondents. The structured questionnaire was validated using face-validity. Pre-testing was carried out on a 40 respondents in different location as a trial run for the main research intended. Cronbach's Alpha was used to determine the internal consistency and degree of relationship of the test item. Prior to administration of the questionnaire to the respondent, an informed consent was obtained. Data collection involved recruitment of participants in open spaces such as lecture halls and this done over a period of four days. Ethical clearance was obtained from the ethical review committee of Department of Public Health. Verbal informed consent was obtained from all the participants before being allowed to participate in the study. Objective of the study was explained to the respondents before the commencement of the interview. Each of the respondents was assured of confidentiality of the information she may volunteer. Each questionnaire took about 5-10 minutes to be completed.

ETHICAL ISSUES

The research followed the tenets of the Declaration of Helsinki. Ethical approval was given by the Ethical Committee of the School of Health Technology, Federal University of Technology Owerri, Nigeria. Informed verbal consent was sought and obtained from all the participants before they could take part in the study.

METHOD OF DATA ANALYSIS

Data collected were subjected to statistical analysis using Statistical Package for Social Sciences (SPSS) version 21 in which Chi-square test at $P < 0.05$ was used in ascertaining the degree of relationship between qualitative variables and screening.

Results**SOCIO-DEMOGRAPHIC CHARACTERISTICS OF RESPONDENTS**

Table I showed the socio-demographic characteristics of the respondents. The respondents that were within the age

Tab. I. Socio-demographic characteristics of respondents.

Variables	Frequency (n = 375)	Percentage (%)
Age (years)		
16-19	117	31.2
20-24	200	53.3
25-29	58	15.5
Level of study		
100 L	60	16
200 L	74	19.7
300 L	96	25.6
400 L	37	9.9
500 L	108	28.8
Marital status		
Single	344	91.7
Married	31	8.3
Monthly allowance		
1,000-8,000	131	34.9
8,001-15,000	121	32.3
15,001-23,000	53	14.1
23,001-30,000	43	11.5
Above 30,000	27	7.2

bracket of 16-19 years were 117 (31.2%), 200 (53.3%) were within the age range of 20-24 years and 58 (15.5%) were within the age range of 25-29 years. Out of the 375 students, 60 (16.0%) were in 100 L, 74 (19.7%) were in 200L, 96 (25.6%) were in 300 L, 37 (9.9%) were in 400 L and 108 (28.8%) were in 500 L. Majority of them were single 344 (91.7%), while 31 (8.3%) were married. Average monthly allowance of respondents shows that 131 (34.9%) earned ₦ 1,000 - ₦ 8,000, 121 (32.3%) earned ₦ 8,001 - ₦ 15,000, 53 (14.1%) earned ₦ 15,001 - ₦ 23,000, 43 (11.5%) earned ₦ 23,001 - ₦ 30,000 and 27 (7.2%) earned above ₦30,000.

AWARENESS AND KNOWLEDGE OF CERVICAL CANCER

Table II showed the respondents' awareness and knowledge of cervical cancer. Three hundred and twenty-one (85.6%) of respondents reported that they have heard of cervical cancer while 54 (14.4%) have not heard of cervical cancer. Among the 321 (85.6%) respondents who have heard of cervical cancer more than large proportions of them 110 (34%) reported that they heard it from the mass media. Most of the respondents 223 (59.5%) were aware that human papillomavirus is the major cause of the disease. As indicated in the Table, majority 202 (53.9%) reported that the signs and symptoms of the disease is blood stained discharge from the vagina. In response to awareness of prevention of cervical cancer, majority of them 345 (92.0%) believed that cervical cancer can be prevented while 30 (8.0%) of them disbelieved. Most of the respondents 202 (53.9%) revealed that they have heard of pap test for cervical cancer screening.

SOURCE OF INFORMATION ON CERVICAL CANCER AND PAP TEST

Figure 1 indicated the source of information on cervical cancer and pap test. A higher proportion of the respondents

Tab. II. Awareness and knowledge of cervical cancer.

Variables	Frequency (n = 375)	Percentage (%)
Heard of cervical cancer		
Yes	321	85.6
No	54	14.4
Heard of pap test		
Yes	202	53.9
No	173	46.1
Source of information		
Parents/family	63	20
Friends	50	16
Medical practitioners	82	26
Mass media	110	34
Others	16	5
Causes or risk factors for cervical cancer		
Human Papillomavirus	223	59.5
Late onset of sexual activity	27	7.2
Diabetes	8	2.1
Single sexual partner	3	0.8
All of the above	3	0.8
I don't know	111	29.6
Signs and symptoms of cervical cancer		
Regular menstrual bleeding	6	2
Blood stained discharge from vagina	202	54
High blood pressure	15	4
All the above	10	3
I don't know	142	38
Can cervical cancer be prevented		
Yes	345	92
No	30	8

110 (29.2%) reported mass media as the major source of information on cervical cancer and pap test.

PERCEPTION AND ATTITUDE TOWARDS CERVICAL CANCER SCREENING

Presented in Figure 2 are the responses to perception and attitude of respondents towards cervical cancer screening. The respondents gave their responses on people they thought should be tested for cervical cancer. Most of them 185 (49.3%) believed women above the age of 21 years should go for the test (Fig. 3). In response to the willingness of respondents to do the pap test (Fig. 4), almost all of them 349 (93.1%) admitted that they will be willing to do so.

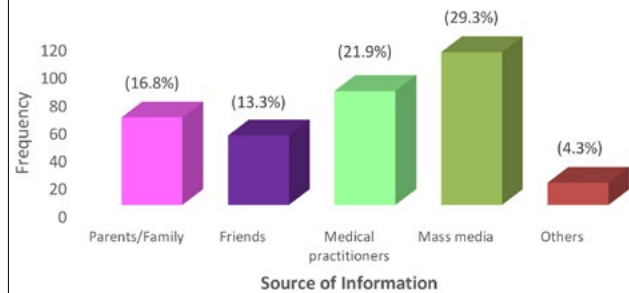
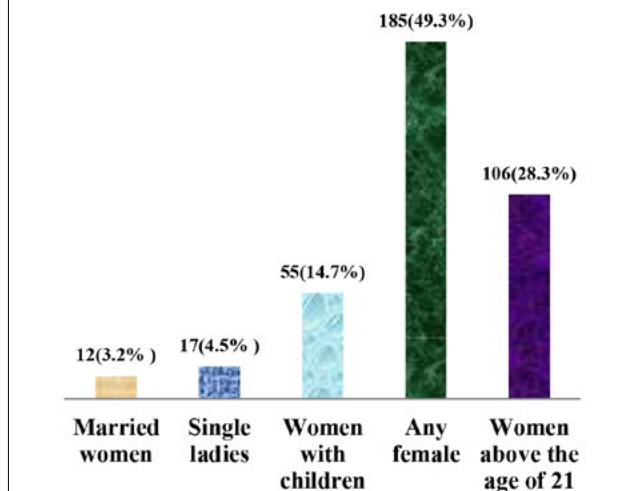
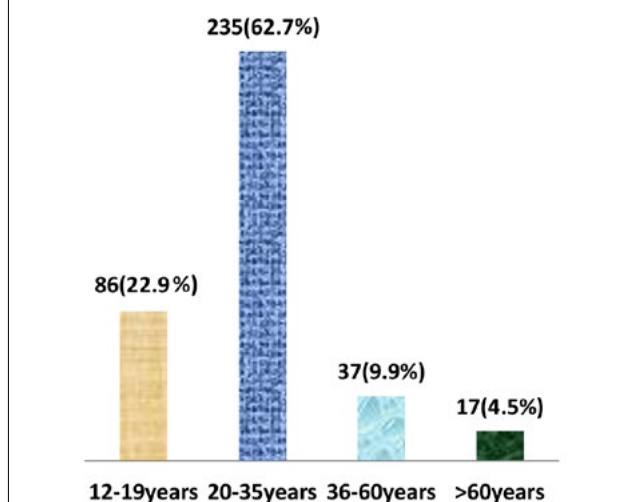
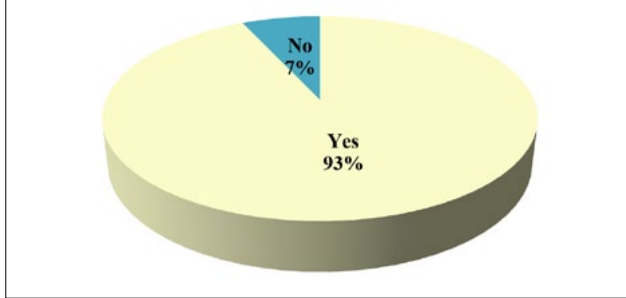
Fig. 1. Source of information on cervical cancer and pap test.**Fig. 2.** People to be tested for cervical cancer.**Fig. 3.** Age to get tested.

Figure 4 showed the willingness of respondents to utilize cervical cancer screening. Majority of them 349 (93.1%) said yes while 26 (6.9%) said no.

Fig. 4. Willingness to do the pap smear test.



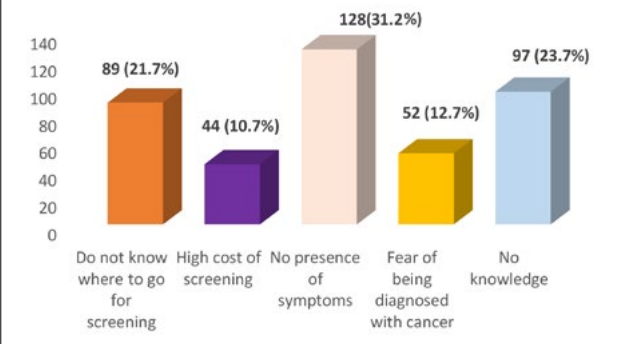
CERVICAL CANCER SCREENING UPTAKE

Table III below showed the cervical cancer screening uptake among the Respondents. Those that have been screened for cervical cancer are 27 (7.2%) while those that have not been screened are 348 (92.8%). The Table also shows that all of the 27 (7.2%) who have been screened have done the screening once. The result revealed that on the participants' response to the interval of pap test, majority 171 (45.6%) reported they had no idea of the appropriate interval. All the 27 (7.2%) respondents who have been screened for cervical cancer reported cost of screening was ₦ 1,001 - ₦ 2,000. Majority of the participants were aware of screening centers within their locality. The respondents gave their reasons for not being

Tab. III. Cervical cancer screening uptake.

Variables	Frequency (n = 375)	Percentage (%)
Previously screened for cervical cancer		
Yes	27	7.2
No	348	92.8
Number of times screened		
Once	27	100
2-3 times	0	0
> 3 times	0	0
Interval of pap test		
6-monthly	33	8.8
1-yearly	63	16.8
3-yearly	108	28.8
I don't know	171	45.6
Cost of screening in Naira		
500-1,000	27	7.2
1,001-2,000	84	22.4
2,001-3,000	63	16.8
No idea	201	53.6
Availability of screening center in the locality		
Yes	164	43.7
No	211	56.3

Fig. 5. Reasons the respondents have not been screened for cervical cancer.



screened, 89 (21.7%) respondents reported they do not know where to go for screening, 44 (10.7%) stated due to high cost of screening, 128 (31.2%) revealed no presence of symptoms, 52 (12.7%) stated they had the fear of being diagnosed with cancer and 97 (23.7%) reported they have no knowledge of cervical cancer (Fig. 5).

INFLUENCE OF CERVICAL CANCER AWARENESS, AVAILABILITY OF SCREENING CENTER AND COST OF CERVICAL CANCER SCREENING ON UPTAKE OF THE CERVICAL CANCER SCREENING AMONG UNDERGRADUATE FEMALES

Presented in Table IV is the influence of major determinant factors of cervical cancer screening uptake (cervical cancer awareness and knowledge, availability of screening center and cost of screening) on uptake of the cervical cancer screening among undergraduate females. It was showed that a significant statistical association existed between all the major determinant factors of cervical cancer and uptake of cervical cancer screening among undergraduate females ($P < 0.05$). Out of the 164 respondents who have cervical cancer screening centers in their locality only few of them 27 (16.5%) have gone for screening. All the 211 (100%) respondents who do not have screening centers in their locality have not been screened for cervical cancer. It was also shown that all the 27 (100%) respondents who said the cost of screening is between 500-1,000 did not uptake screening for cervical cancer. Of the 84 (100%) respondents who reported that the cost of screening is between 1,001-2,000, 27 (32.1%) have been screened whereas greater proportions 57 (67.8%) have not been screened. 63 (100%) respondents who reported the cost of screening is between 2,001-3,000 have not been screened for cervical cancer. All the 201 (100%) respondents who have no idea of the cost of screening have not been screened for cervical cancer with significant association ($\chi^2 = 100.793$, $P \leq 0.001$).

INFLUENCE OF SOCIO-DEMOGRAPHIC VARIABLES ON THE UPTAKE OF CERVICAL CANCER SCREENING AMONG UNDERGRADUATE FEMALES

Results of Table V showed the socio-demographic factors influencing the uptake of cervical cancer screening among female undergraduates where all the

Tab. IV. Influence of cervical cancer awareness, availability of screening center and cost of cervical cancer screening on uptake of the cervical cancer screening.

	Previously screened for cervical cancer				
Determinants	Yes (%)	No (%)	Total (%)	Chi-square	P-value
Heard of cervical cancer					
Yes	27 (8.4)	294 (91.6)	321 (100.0)	4.894	0.027
No	0	54 (100.0)	54 (100.0)		
Availability of screening center					
Yes	27 (16.5)	137 (83.5)	164 (100.0)	37.433	< 0.001
No	0	211 (100.0)	211 (100.0)		
Cost of screening in Naira					
500-1,000	0	27 (100.0)	27 (100.0)	100.793	< 0.001
1,001-2,000	27 (32.1)	57 (67.9)	84 (100.0)		
2,001-3,000	0	63 (100.0)	63 (100.0)		
No idea	0	201 (100.0)	201 (100.0)		

Tab. V. Influence of Socio- Demographic characteristics on the uptake of cervical cancer screening among undergraduate females.

	Previously screened for cervical cancer				
Socio-demographic determinants	Yes (%)	No (%)	Total (%)	Chi-square	P-value
Age					
16-19	0	117 (100.0)	117 (100.0)	18.336	< 0.001
20-24	17 (8.5)	183 (91.5)	200 (100.0)		
25-29	10 (17.2)	48 (82.8)	58 (100.0)		
Level of study					
100 L	0	60 (100.0)	60 (100.0)	37.631	< 0.001
200 L	0	74 (100.0)	74 (100.0)		
300 L	6 (6.3)	90 (93.8)	96 (100.0)		
400 L	0	37 (100.0)	37 (100.0)		
500 L	21 (19.4)	87 (80.6)	108 (100.0)		
Marital status					
Single	18 (5.2)	326 (94.8)	344 (100.0)	24.107	< 0.001
Married	9 (29.0)	22 (71.0)	31 (100.0)		
Average monthly allowance (#)					
1,000-8,000	0	131 (100.0)	131 (100.0)	45.12	< 0.001
8,001-15,000	4 (3.3)	117 (96.7)	121 (100.0)		
15,001-23,000	6 (11.3)	47 (88.7)	53 (100.0)		
23,001-30,000	11 (25.6)	32 (74.4)	43 (100.0)		
> 30,000	6 (22.2)	21 (77.8)	27 (100.0)		

socio-demographic variables had strong association with the uptake of cervical cancer screening ($P < 0.05$). It was indicated that across the age categories, uptake of screening was highest 10 (17.2%) amongst participants within the age bracket of 25-29 years compared to 20-24 years 17 (8.5%). All the respondents in 100L, 200L and 400 L have not done screening for cervical cancer. Of the 96 respondents in 300L, 6 (6.3%) have been screened while 90 (93.7%) have not been screened. Among the 108 respondents in 500 L, 21 (19.4%) have been screened while 87 (80.6%) have not undergo screening for cervical cancer. Out of 344 respondents that were single, only 18 (5.2%) have been screened. Out of the 31 respondents that are married, only 9 (29.0%) have been screened. Considering income categories, uptake of cervical cancer screening was highest among

respondents 11 (25.6%) who earned 23,001-30,000 ₦ followed by participants that earn > 30,000 ₦ 6 (22.2%), 15,001-23,000 ₦ 6 (11.3%) and 8,001-15,000 ₦ 4 (3.3%).

Discussion

SOCIO-DEMOGRAPHIC CHARACTERISTICS OF FEMALE UNDERGRADUATES

Majority of the students 200 (53.3%) were between the age group of 20-24 years. This is like the findings of Dozie et al. (2020) [12] who reported that the majority (81.7%) of the female undergraduate students selected from Imo State University were in their sexually active ages. There was strong association between uptake

of cervical cancer screening and age of participants. Screening was higher among participants aged 25-29 years (17.2%) compared to those other age groups indicating that uptake increased with increasing age. This is in agreement with the study of Nthiga (2004) [13] which found higher rates of screening within women between 25-34 years but was in contrast with other study that found screening rates to be higher among women aged 23 years [14]. Strong association was also recorded between level of study of the undergraduate females and cervical cancer screening uptake. Screening was seen to increase with level of study giving rise to majority of those screened 21 (19.4%) to belong to 500 level. This is in congruent to other study which found 300 L female students as majority of those who have taken part in the screening [14]. Majority of the respondents 344 (91.7%) were single. However, strong association between uptake of screening and marital status was showed by chi-square result where most of them who had been screened 9 (29.0%) were married. This suggested that married women are more likely to be screened than the unmarried ones. Considering marital status, previous studies also found that compared to married women, unmarried and widowed women are less willing to undergo [13]. These findings are in disagreement with the studies of Gimba (2014) [14] and Owoeye & Ibrahim (2013) [15] that showed single women to be more likely to undergo screening compared to married women. Of all the 375 students, majority 131 (34.9%) received an average monthly allowance of ₦ 1,000 - ₦ 8,000. Association between income and uptake of screening significantly showed that uptake of screening is higher among those who earn ₦ 23,001 - ₦ 30,000 as an average monthly income 11 (25.6%). This indicates that female students with higher allowance are more likely to undergo screening. In the study of Owoeye and Ibrahim (2013) [15] at Niger Delta Nigeria, it was revealed that the commonest reasons for undergoing screening was when it was free or subsidized or as part of a general screening exercise.

CERVICAL CANCER KNOWLEDGE AND AWARENESS AMONG FEMALE UNDERGRADUATES

Interestingly, high level of knowledge and awareness of the causes and risk factors of cervical cancer was recorded in the study where majority of the respondents 223 (59.5%) attributed the cause of cervical cancer to Human papillomavirus. In similar study conducted in Ghana, 140 college students only 11 (7.9%) identified HPV as a risk factor of cervical cancer [16]. Study of Nthiga (2014) [13] in Kenya identified that only 23.5% were aware that Human Papillomavirus (HPV) is a risk factor for the development of the disease. Another study [17] found that majority of the respondents (40%) identified early onset of sexual activity as a risk factor for the development of cervical cancer. There was poor knowledge on the signs and symptoms of cervical cancer in the present study since majority of respondents 202 (53.9%) attributed the signs and symptoms of cancer of the cervix to blood stained discharge from vagina.

Majority of the respondents 321 (85.6%) have heard of cervical cancer, this is similar to the study of Owoeye and Ibrahim (2013) [15] on cervical cancer screening among staff and students in the Niger Delta where 80% of the participants have heard of cervical cancer. The finding is also in line with the report of Nthiga (2014) [13] where 82.2% of respondents were aware of cervical cancer in Kenya. However, Akujobi et al. (2008) [17] in their study recorded a lower awareness (60.9%) among female students in south eastern Nigeria. Ezem (2007) [10] also reported lower (52.8%) cervical screening awareness in Owerri. Higher level of awareness in the present study could presumable be as a result of the many health related Departments in the school.

Knowledge of pap smear test was found to be 202 (53.9%) in this study. This is in agreement with Nthiga (2014) [13] and Owoeye & Ibrahim (2013) [15] studies which found the knowledge of pap test to be 75 and 56.2% respectively. However, other studies indicated low knowledge and awareness of cervical cancer screening by its respondents. A study in Onitsha, Anambra State and another study in Jos, Plateau State found awareness of pap test to be 35.56 and 33.04% respectively [8,14]. Majority of the respondents in this study 171 (45.6%) do not know the interval of pap test. this is not in agreement with a study in which 52.63% did not know the interval of pap test [14].

The major source of information for those who have heard of cervical cancer and pap test in this study was the mass media 110 (29.3%). This is in contrast with other studies which found the major source of information of cervical cancer and pap test to be from a medical practitioner or health worker. Studies of Nwozor (2013), Akujobi et al. (2008) and Gimba et al. (2014) [8, 14, 17] also found medical practitioner or health worker as the major source of information for the respondents to be 64.44, 35.8 and 37.5% respectively. Interestingly, this study revealed that there was strong association between the level of knowledge and awareness of cervical cancer and cervical cancer screening and undergraduate female's uptake of screening. This implies that female students who are aware of cancer of the cervix and screening are more likely to go for screening.

CERVICAL CANCER SCREENING UPTAKE

Findings from this study indicated that only few 27 (7.2%) of the respondents had ever been screened. The uptake of 27 (7.2%) of cervical cancer screening as found in this study is in agreement with the 7.1% reported by Ezem (2007) in Owerri, Imo state capital [10]. Other studies done among women revealed similar low uptake of screening among women. Lower rate (1.78% of 450 women and 13.91% of 120 female students) was reported in a study done in Onitsha, Anambra State Nwozor & Oragudosi (2013) and Oluwole, et al. (2017) Lagos State respectively [8, 18].

BARRIERS TO CERVICAL CANCER SCREENING

In this study, a majority of the female undergraduates 128 (31.2%) were of the opinion that screening is not necessary

since they do not feel any presence of symptoms. Studies across Nigeria have reported different reasons for not doing the test. A study in Owerri reported that the most common reasons given for not doing the test were lack of awareness (46.1%), no need for it (12.5%) and fear of a bad result (11.6%) of the 846 respondents [10]. Another study reports that majority (60%) of the participants have not heard of cervical cancer screening, 15.5% do not know where to go for screening, 2.7% have concern about embarrassment of cancer being discovered and 13.6% have no reason [17]. A study in Kenya reported that drawbacks to cervical cancer screening was that most of the women lacked information about it (77%) and had low level of understanding about the disease (85.9%) [13]. In other study Nwozor & Oragudosi (2013) [8], lack of awareness 228 (51.58%), lack of facility 70 (15.84%), cost 70 (15.84%), don't think it is necessary 52 (11.76%), distance 13 (2.94%) were reported as reasons for not undergoing screening. However, in the study of Owioye and Ibrahim [15] the barriers were that majority of the respondents (40.2%) feel they are healthy and so no need for it. At the same time, knowledge of cervical cancer, cost of screening, availability of screening and socio-demographic factors were found to be critical in determining cervical cancer screening uptake among female undergraduates. This is in line with the study of Nwobodo & Ba-Break [19] which found that low level of knowledge of cervical cancer and cervical cancer screening, unavailability, inaccessibility, unaffordability and unacceptability of cervical-cancer screening were the determinants of poor cervical cancer screening among typical Nigerian population.

Conclusions

The study clearly showed that there was high level of awareness of cervical cancer screening as well as knowledge of the signs and symptoms and risk factors associated with it. However, uptake of screening was very low. Utmost barrier to screening by the respondents was the absence of symptoms. There was strong association between socio-demographic characteristics (age, level of study, marital status, monthly allowance), awareness of cervical cancer and screening (pap test), availability of cervical cancer screening centres, cost of screening and uptake of cervical cancer screening. Therefore, to enhance screening uptake among the female undergraduates, there is urgent need to reduce the cost of screening especially in the school's health centre and other hospitals/clinics within the school environment.

LIMITATIONS OF THE STUDY

In many occasions, there was difficulty in collecting vital information as most of the students were busy with school activities. As a result of time constraints, much time was not spent every session of questionnaire filling and the included respondents were interviewed and

questionnaire filled but there may be female students who have higher level of awareness and knowledge on issues of cancer of the cervix are high but were unavailable during the period of the study.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Availability of data and materials

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

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

UWD: conceived the study, supervised the study and drafted the manuscript, CICE: study design, data analysis, revisited the manuscript, CRD: data analysis and data collection, INSD, SNOI and OCA, revisited the manuscript and critically evaluated the intellectual contents. All authors read and signed the final version of paper.

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RESEARCH ARTICLE

Construction data mining methods in the prediction of death in hemodialysis patients using support vector machine, neural network, logistic regression and decision tree

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Keywords

Hemodialysis, • Kidney failure • Survival • Data mining • Decision tree • Neural network
• Support vector machine • Logistic regression

Summary

Objectives. Chronic kidney disease (CKD) is one of the main causes of morbidity and mortality worldwide. Detecting survival modifiable factors could help in prioritizing the clinical care and offers a treatment decision-making for hemodialysis patients. The aim of this study was to develop the best predictive model to explain the predictors of death in Hemodialysis patients by data mining techniques.

Methods. In this study, we used a dataset included records of 857 dialysis patients. Thirty-one potential risk factors, that might be associated with death in dialysis patients, were selected. The performances of four classifiers of support vector machine, neural network, logistic regression and decision tree were compared in terms of sensitivity, specificity, total

accuracy, positive likelihood ratio and negative likelihood ratio.

Results. The average total accuracy of all methods was over 61%; the greatest total accuracy belonged to logistic regression (0.71). Also, logistic regression produced the greatest specificity (0.72), sensitivity (0.69), positive likelihood ratio (2.48) and the lowest negative likelihood ratio (0.43).

Conclusions. Logistic regression had the best performance in comparison to other methods for predicting death among hemodialysis patients. According to this model female gender, increasing age at diagnosis, addiction, low Iron level, C-reactive protein positive and low urea reduction ratio (URR) were the main predictors of death in these patients.

Introduction

Chronic kidney disease (CKD) is one of the main causes of morbidity and mortality worldwide [1]. Death from CKD has increased dramatically in recent years, with a 134% increase in CKD deaths in 2013 compared to 1990 [1]. It is estimated that more than 1.5 million end-stage renal disease (ESRD) cases receive renal replacement therapy through dialysis or transplantation worldwide annually [2]. On the other hand, the increase in the number of chronic diseases, such as diabetes and hypertension, as the risk factors of CKD, enhances the prevalence of CKD among countries. Therefore, CKD should be considered as a health problem priority, especially in developing countries, and a large proportion of health resources should be devoted to this problem [3].

In Iran, hemodialysis (HD) is the main way of renal replacement therapy in ESRD patients. Accumulating evidence suggests that increasing age, malnutrition, cardiovascular disease, higher glomerular filtration rate (GFR) at the time of dialysis initiation, overhydration, use of catheter as a vascular access as well as hemoglobin, ferritin, C-reactive protein (CRP), serum albumin, and creatinine, among baseline laboratory markers, are the

potential predictors of death in hemodialysis patients [4-7]. Apart from these accepted prognostic factors, the role of some factors is controversial on morbidity and mortality in hemodialysis patients and requires more investigations. Moreover, depending on different medical facilities of the hospitals as well as the cultural factors associated with the patients, the predictors for patient's death in different communities may be different. On the other hand, because of the seriousness of CKD and its complications, early screening of high-risk patients for mortality, using an accurate and efficient model, especially based on demographic characteristics, plays an important role in the prediction of death in hemodialysis patients. To this, it is possible to identify subjects who are at risk for mortality based on common risk factors, such as age and gender, through predictive statistical models.

Construction of a predictive model and identifying important risk factors of a dichotomous variable like dead/alive status for a patient is usually conducted through classical logistic regression (LR). Recently, machine learning techniques including support vector machine (SVM), neural networks (NN), and decision tree (DT) have been shown to have promising performance in classification problems [8-14].

Ideally, it would be interesting to construct a model with an increased predictive power through machine learning techniques for classification that require no distributional assumptions. These classifiers also consider nonlinear and complex relationships between the response variable and predictors. Therefore, they can produce accurate predictions for the response variable. Nevertheless, their performance may vary in different conditions and there are inconsistencies between studies about their superiority over classical models. So, they need to be investigated over different datasets.

Improved ability to identify those patients at an increased risk of death could help in prioritizing the clinical care and offers treatment decision-making for hemodialysis patients. Several studies have investigated the prediction performance of different outcomes in CKD patients [11, 14-17]. For example, Lacson used the SVM to test the hypothesis that “appropriately transformed sequential blood pressure measurements would significantly improve the prediction of mortality in hemodialysis patients” [18]. However, to the best of our knowledge, there was found no study that compared the predictive performance of SVM, NN, DT, and logistic regression in predicting hemodialysis mortality. Moreover, in each country and even in each setting, the predictors of mortality vary according to the available treatment facilities and the conditions of the patients. Therefore, the results of studies in other countries cannot be generalized to all communities. In general, the availability of a system for predicting death in hemodialysis patients can help improve the quality of the care proportionate to the patient’s demographic and clinical features and can reduce costs. In this study, we selected the most widely used machine learning methods of the SVM, NN, and DT and compared their performance with that of the logistic regression. Therefore, the purposes of this research were to develop predictive models to explain the relationships between examined independent variables and the Hemodialysis patient’s survival/mortality and choosing the model with better performance by comparison their sensitivity, specificity, accuracy, positive and negative likelihood ratio. We also compared the performance of these models with that of the classical logistic regression. Finally, we identified important variables that were associated with the outcome of interest with the model that provides better predictive power over the dataset used here.

Methods

STUDY DESIGN

We performed a retrospective cohort study to develop predictive models to explain the relationships between examined independent variables and the Hemodialysis patient’s dead/alive status.

SETTINGS AND PATIENTS

We examined 758 patients who were undergoing hemodialysis treatment in Hamadan province from March 2007 to March 2017 to investigate predictors of mortality

among hemodialysis patients. Hamadan province, with an area of 19,493 square kilometers in extent, is located in the west of Iran and has a population of 1,738,234 people; according to the national census held in 2016 by the Statistical Center of Iran. We used information of patients from eight hospitals in the province with dialysis ward including Alimoradian, Besat, Vali-asr, Ghaem, Imam Hossein, Valiasr, Imam Reza, and Shahid-Beheshti in Nahavand, Hamadan, Tuyserkan, Asadabad, Malayer, Razan, Kabudarahang, and Hamadan city.

Patients with acute renal failure or under treatment with peritoneal dialysis, patients on transient hemodialysis, and patients with incomplete medical records were excluded from this study. This study was approved by the Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1399.029).

OUTPUT AND INPUT VARIABLES

Here, we used all the medical information of the patients, including demographic, clinical, and laboratory information, to model building. Therefore, we provided a researcher-made checklist according to the hospital records of HD patients for collecting data. The checklist included features related to demographic profiles (age at diagnosis (year), gender (male, female), marital status (married, single, divorced, widow), body mass index (BMI, kg/m²), residence area (urban, rural), educational level (illiterate, primary, guidance, high school, academic), the history of tobacco use (yes, no) and substance abuse (yes, no); and clinical information (including hemoglobin (g/dl), blood urea nitrogen (BUN) (mg/dL), creatinine (mg/dL), CRP status (positive, negative), sodium (mEq/L), calcium (mg/dL), phosphor (mg/dL), iPTH (pg/ml), albumin (g/dl) and ESRD cause (Hypertension, Diabetes, Urologic& obstructive diseases, Polycystic Kidney, Glomerulonephritis, Unknown). Clinical and laboratory data related to the time before the first dialysis session were used for each patient. To minimize measurement variability, all these clinical data were measured twice and two measures for each patient were averaged. Time since diagnosis to mortality/follow up (year) was also used as a confounder and all analyses were adjusted for it. These records were collected by reviewing patients’ medical records and, if necessary, asking patients or instructor of the sector.

DATA PRE-PROCESSING AND DEALING WITH MISSING VALUES

Before model building and any analysis, the data were checked with regard to spelling errors and other irregularities/irrelevancies. Missing values were imputed. Therefore, for the variables with missingness greater than 1%, including uric acid (3.73%), hemoglobin (1.4%), Alk (1.28%), and Iron (1.05%), we used CART regression trees for imputing missing values. For the variables with missingness less than 1%, including albumin (0.47%), Plt (0.23%), hematocrit levels (0.12%) and urea reduction ratio (0.12%), we applied simple imputation using their median. The mode was used for imputing the missing data of the blood group (0.12%) and Rh (0.12%).

Anomaly detection was used for finding the outlier records to improve the precision of modeling. This technique utilizes clustering methods to recognize anomalous data. Anomaly detection provides very significant and critical information for outlier detection in various applications [19]. One record with an anomaly index greater than 2 [20] was eliminated from further investigations. To this, data mine was attached to anomaly node in the modeler. Then, the created model was added to the project. This technique uses the clustering methods. After running the model, data were divided into four clusters and then by adjusting the model, anomalous data in the model building process were deleted.

STATISTICAL METHODS

Decision tree

Decision tree is assumed as a machine learning method that utilizes recursive partitioning of potential predictors space (each partitioning happens at a node) [21] and creates a hierarchical partitioning tree and then predicts the response variable using final nodes for both categorical and continuous responses. Optimal cut-off point for a continuous predictor is the one that produces lower prediction error. In this study we used this method in identifying individuals who experienced death through an easily interpretable rule induced by binary splitting of covariates according to the predictors. Here, we used C5.0 decision tree that can automatically inspect the variables before constructing the tree which keeps only relevant variables in the model. A rule is induced by a binary split on inputs with questions such as “Is the patient female or male?” or “Is the subject a smoker or nonsmoker?”. For continuous variables, the algorithm automatically searches for the best split, using some criteria and the data are partitioned accordingly. The procedure continues until the data set is split into a number of mutually exclusive groups.

Neural network

Neural network is of the most widely used machine learning methods that works based on the human brain structure. This method uses an input layer, a hidden layer, and an output layer connected with some associated weights. These weights are adjusted during learning process, to provide a better prediction performance for the response variable. Although there are several structures for the neural network, in this study, we used the most commonly used NN called Multilayer Perceptron (MLP). In this study, to find the best performance of the NN, complex nonlinear mapping between input and output layers is conducted using different number of nodes and the NN approach with one hidden layer, using a hyperbolic tangent activation function ($f(x) = 2 / (1 + \exp(-2x)) - 1$), was utilized (the performance of the method did not improve with a greater number of hidden layers). In the output layer, the “SoftMax” activation function

($f_i(x) = \exp(x_j) / \sum \exp(x_i)$, $j = 1, \dots, p$, with x as the input vector) was used.

Support vector machine

Support vector machine is a commonly used machine learning method that recruits a kernel function to project the predictor space into a higher dimensional space where a linear hyper plane instead of the non-linear separator in the lower dimension [22]. The linear hyperplane is fitted in such a way that the training data have the maximal distance from its margin. In this study, our binary response was the dead/alive status of the patients. Therefore, considering:

$$y_i \in \{-1, 1\}$$

as the binary response for:

$$i \in \{1, 2, \dots, n\}$$

and x_i as the input vector, the equation of the hyperplane classification takes the following form:

$$\sum_{i=1}^n \alpha_i \gamma_i(x_i) + b = 0$$

Where γ is a function of x , α the original input vector of x , is the regression coefficients vector and b is the bias term (or intercept). These coefficients are obtained through a quadratic optimization problem. For more detail see Tapak et al. 2017 [11].

Stepwise logistic regression

Logistic regression is a parametric regression model that is the most commonly used model in modeling the relationship between some inputs and a binary response/output. The model is written as follows:

$$\log(\pi / (1 - \pi)) = \alpha_0 + \sum_{i=1}^p \alpha_i x_i$$

In this equation, α stands for the regression coefficients vector and π is the probability of the response variable takes the value 1 for the event of interest. Stepwise logistic regression is a method of fitting logistic regression model in which the choice of predictive variables is carried out automatically and in each step, a variable is considered for including or excluding from a set of inputs based on some pre-specified criterion like Bayesian information criterion (BIC).

Model building

In all analysis, we used the variable of mortality status (dead/alive) as the output variable and all other variables in the checklist were considered as inputs. For comparing the models, we used 10-fold cross-validation: one with 90% subjects for training and the other with 10% subjects for validation. This process repeated 10 times. Then, sensitivity, specificity, total accuracy, positive likelihood ratio and negative likelihood ratio were computed to

compare the models. The calculations were based on the following formulas:

$Sensitivity = \frac{TP}{TP + FN}$
$Specificity = \frac{TN}{TN + FP}$
$Total\ Accuracy = \frac{TP + TN}{TP + FP + TN + FN}$
$Positive\ likelihood\ ratio = \frac{Sensitivity}{1 - Specificity}$
$Negative\ likelihood\ ratio = \frac{1 - Sensitivity}{Specificity}$

Where *TP*, *FP*, *TN*, and *FN* represent the number of true positives, false positives, true negatives, and false negatives, respectively. The IBM SPSS modeler 15 was applied for data analysis.

Variable importance

The importance of a variable in each input, for the classifiers that were used in this study, was calculated according to the percentage increase in the prediction error when the variable/input was removed from the analysis. So, the input that led to the most increase in the prediction error by a classifier was selected as the most important. After scoring the importance of the variables, they were ranked based on their scores.

Results

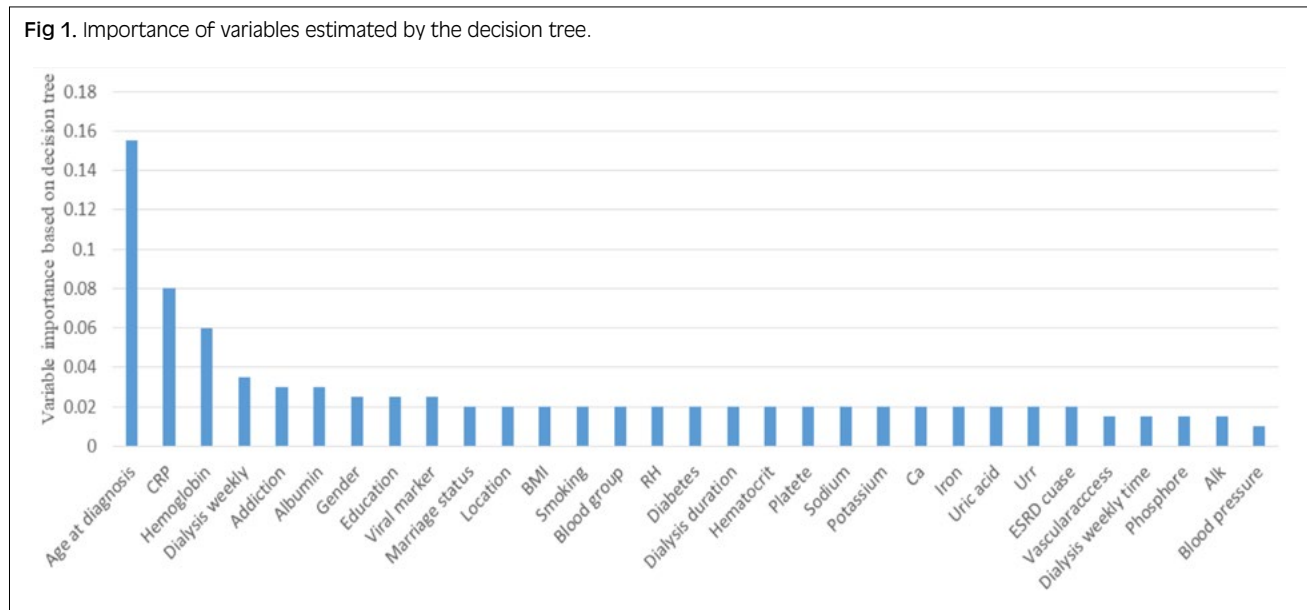
Summary statistics of the variables included in the analysis for the patients were shown in Tables I and II. According to the results, the majority of the alive patients were male (57%), married (82.0%), non-smoker (82.0%), non-substance abuser (0.89%), illiterate (43.0%) and lived in rural area (64.0%). The main causes of ESRD for 28.0% and 20.0% of them were hypertension and diabetes alone, respectively. Permanent catheter in the 48% of cases was the dominant way of vascular access. Summary statistics of continuous variables also were provided in Table II. Different settings of the parameters were tested, and the best result was obtained by expert mode with pruning severity 75 and minimum records per child branch 2. The most informative variables, according to the values of the variable importance, estimated by the DT model were shown in Figure 1. According to the results, the variables of "Age at diagnosis", "CRP" and "Hemoglobin" were

Tab. I. Descriptive statistics of discrete features related to participants.

Variables	Alive		Death	
	N	%	N	%
Gender:				
male	256	57	208	51
female	192	43	200	49
Marriage status:				
single	76	17	6	1.5
married	366	82	396	97.5
divorce	6	1	6	1
Education:				
illiterate	194	43.3	260	63.7
primary and middle	145	32.4	104	25.5
high school	87	19.3	36	8.8
university	22	5	8	2.0
Location:				
urban	287	64	248	61
rural	161	36	160	39
Smoking:				
no	366	82	296	72
yes	82	18	112	28
Addiction:				
no	399	89	331	81
yes	49	11	77	19
Blood group:				
A	153	34	126	31
B	103	23	97	24
AB	30	7	34	8
O	162	36	151	37
Rh:				
+	407	91	361	89
-	41	9	41	11
Viral marker:				
HIV	2	0.5	3	0.7
HBV	7	1.6	7	1.7
HVC	11	2.4	3	0.7
no	428	95.5	395	96.9
Diabetes:				
no	312	70	246	60
yes	136	30	162	40
Hypertension:				
no	269	60	239	59
yes	179	40	169	41
ESRD cause:				
diabetes	91	20.3	116	28.4
diabetes & bp	45	10.0	46	11.3
blood pressure	127	28.3	120	29.4
urological & obstructive	38	8.5	40	9.8
diseases	18	4.1	18	4.4
polycystic kidney	47	10.5	13	3.2
glomerulonephritis	82	18.3	55	13.5
other				
Vascular access:				
temporary catheter	69	15.4	66	16
permanent catheter	151	33.7	135	33
fistula	217	48.4	192	47
graft	11	2.5	15	4
Dialysis weekly:				
1	8	2	7	1.7
2	95	21	74	18.1
3	340	76	317	77.7
4	5	1	10	2.5
CRP:				
negative	310	69	242	59
positive	138	31	166	41

Tab. II. Summary of continues variables related to participants.

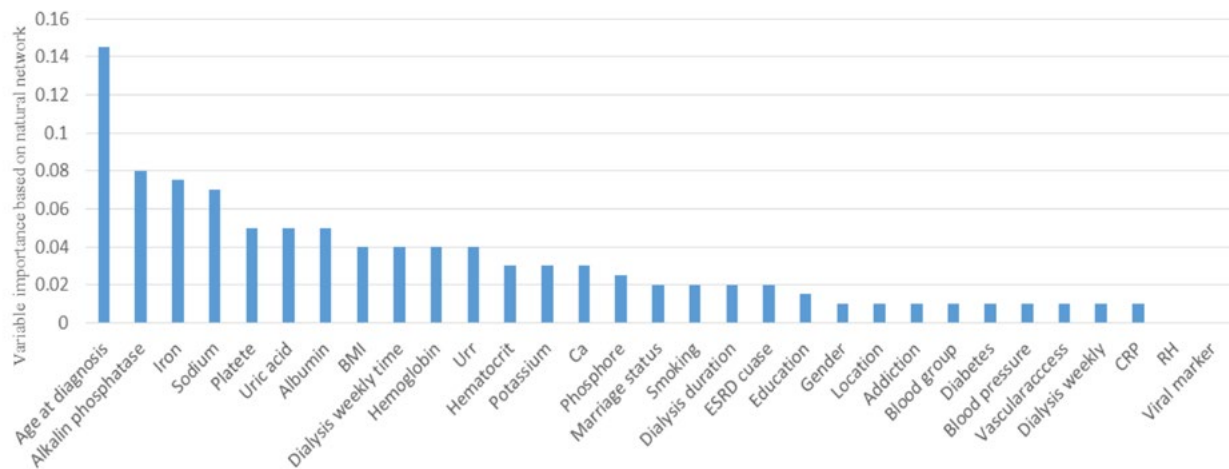
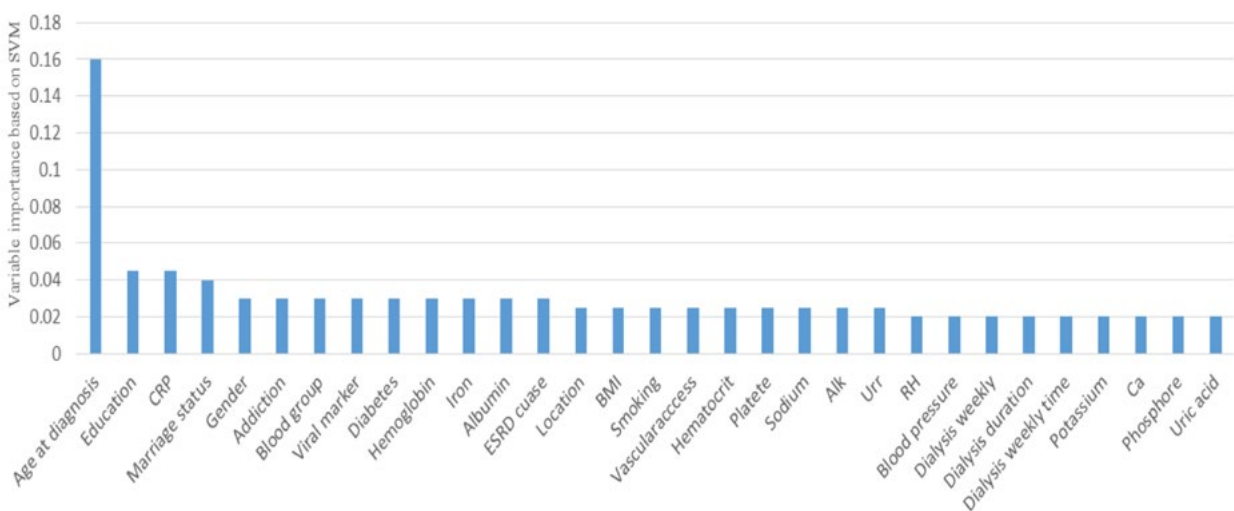
Variables	Alive					Death				
	N	Min	Max	Mean	Std. Dev	N	Min	Max	Mean	Std. Dev
Age at diagnosis (yr)	448	8	83	50.29	15.73	408	18	88	61.97	10.92
BMI (kg/m ²)	448	12.33	41.26	23.09	4.21	408	14.69	38.09	23.31	3.79
Dialysis duration (hour)	448	2	4	3.65	0.46	408	2	4	3.63	0.46
Dialysis weekly time (hour)	448	2	16	10.15	2.33	408	2	16	10.24	2.22
Hemoglobin (gr/dlit)	448	1.3	17.4	10.48	2.06	408	4	15.7	10.47	1.75
Hematocrit levels (%)	448	16.1	60	192.52	72.085	408	16.1	60	32.46	6.05
Plt (1,000/mm ³)	448	21	463	192.52	72.08	408	27	670	187.73	68.68
Sodium (mg/dlit)	448	105	198	138.78	6.8	408	106	193	138.89	7.56
Potassium (mg/dlit)	448	3	9.6	4.9	0.94	408	3	9.6	4.96	0.95
Calcium (mg/dlit)	448	5.1	12	8.9	0.90	408	5.9	11.3	8.7	0.84
Phosphor (mg/dlit)	448	2.3	12.3	5.11	1.55	408	1.7	12	5.13	1.6
Iron (ug/ dlit)	448	2	1028	111.90	115.48	408	3	520	98.3	73.49
Uric acid (mg/dlit)	448	1	14.6	6.77	1.54	408	3.2	13.7	6.70	1.42
Albumin (g/dlit)	448	1	5.6	3.74	0.73	408	1	6.4	3.59	0.72
Alk (U/L)	448	4.6	2612	316.14	262.65	408	4.2	2349	301.58	213.35
Urea reduction ratio (%)	448	1	0.96	0.643	0.124	408	0	0.89	0.62	0.13
Time to mortality/ follow-up (yr)	448	0.08	10.70	2.35	2.38	408	0.08	10.30	2.23	2.18

Fig 1. Importance of variables estimated by the decision tree.

the first topmost important variables in the prediction of death. In this study, the NN was trained with all inputs (one for each predictor) in the input layer and one hidden layer with 10 neurons. Figure 2 showed the importance of variables associated with death of dialysis patients by the NN model. According to the results, the variables of “Age at diagnosis”, “Alkaline phosphatase” and “Iron” were the three topmost important variables in the prediction of death. Since linear function had better results than other functions, it was used as kernel function for the SVM model. Regularization (C) was optimized by trying different values, and the best-obtained value was 10. We used expert mode and the stopping criterion was set 0.001. The SVM model ranked all of the variables the

final results were shown in Figure 3. According to the results, the variables of “Age at diagnosis”, “Education” and “CRP” were the three topmost important variables in the prediction of death. Based on $p < 0.05$, the stepwise LR model indicated gender, age at diagnosis, marriage status, addiction, onset year, iron, URR, and CRP as significant variables (Tab. III). For the dependent variable, we considered death as the reference group.

Table III shows the total accuracy, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio (Mean and standard deviation) estimated by the cross-validation method over the testing set for each model in 100 repetitions. According to the results shown in Table IV, LR showed a better performance compared to

Fig. 2. Importance of variables estimated by the natural network.**Fig. 3.** Importance of variables estimated by the support vector machine.

the machine learning models in terms of total accuracy (0.71), sensitivity (0.69), positive likelihood ratio (2.48), and negative likelihood ratio (0.43). The specificity of LR and logistic regression was the same (0.72) over 100 repetitions. However, among the three machine learning methods, the performance of the SVM (sensitivity compared to specificity) was closest to the LR (positive likelihood ratio (2.25) and negative likelihood ratio (0.45) with a specificity of 0.70. Therefore, the SVM and LR were compatible and showed almost similar performance in predicting death in hemodialysis patients.

Discussion

In this study, we investigated the performance of the three most widely used machine learning methods of decision

tree, neural network, and support vector machine in the prediction of death in hemodialysis patients in an Iranian population and compared it with that of the classical logistic regression. Our results showed that the prediction accuracy of the SVM was closest to the logistic regression. Our results showed that the discriminative performances of the used machine learning methods were equivalent to that of the stepwise LR method which is commonly applied for this purpose. So, these methods could be used successfully in detecting death in hemodialysis patients with clinical measurements, and laboratory tests. Other studies showed that the machine learning methods performed as good as the LR [10], which is in agreement with our results. However, other studies indicated machine learning methods of SVM, NN and DT outperformed logistic regression in terms of prediction performance [10, 11, 14, 23]. In those studies,

Tab. III. Logistic regression model.

Variables	B	OR*	Wald	P-value
Gender:				
female	-	-	-	-
male	0.428	1.534	6.459	0.011
Age at diagnosis	-0.087	0.917	135.731	0.000
Addiction:				
yes	-	-	-	-
no	0.703	2.019	8.792	0.003
Iron	0.002	1.002	7.040	0.008
Urea reduction ratio	1.562	4.767	6.120	0.013
CRP:				
yes	-	-	-	-
no	1.595	4.930	62.731	0.000

*OR: Odds Ratio which is calculated as $\text{Exp}(\beta)$.

Tab. IV. Mean and standard deviation of total accuracy, sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for DT, NN, SVM and LR.

Models	Total accuracy		Sensitivity		Specificity		Positive likelihood ratio		Negative likelihood ratio	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Decision tree	0.66	0.05	0.65	0.06	0.67	0.05	2.03	0.47	0.53	0.11
Neural network	0.61	0.05	0.58	0.09	0.72	0.07	1.7	0.38	0.65	0.17
Support vector machine	0.68	0.04	0.66	0.07	0.70	0.04	2.25	0.45	0.48	0.10
Logistic regression	0.71	0.05	0.69	0.07	0.72	0.04	2.48	0.53	0.43	0.11

there were imbalanced data such that a large proportion of the samples did not experience the event of interest. But in our study the number of observed deaths was large, and the data were almost balanced. This might indicate that machine learning methods might be more useful in the case of imbalanced data. It is also possible that the effect of the covariates on the binary outcome in this study be linear as the traditional LR assumed the linear effects of covariates and a limited number of nonlinear effects. LR also performs well in large sample sizes. However, the SVM can handle complex relationships between variables and all interactions simultaneously even with a small sample size data set.

In this study, we also investigated the predictors of death in hemodialysis patients according to the model with a better performance. Therefore, the LR with simple interpretations was used to interpret the results. In spite of the considerable improvements in medical and technical support, the rate of mortality in these patients is high. We found that female gender, addiction, increasing age at diagnosis, low iron level, CRP positive and low URR were the most important predictors of death in HD patients in the present study. These novel findings may have important clinical and public health implications since they can be used for designing preventive interventions to reduce death among these patients.

In the present study female gender was independently associated with an increase of mortality. This finding was in line with Ratna Prabha et al. [24] and in contrast to those of Depner et al. [25] and USRDS data [14]. More access of males to health resources and a lower rate of CKD risk factors including diabetes and hypertension in

males may be in connection with their better survival. Also, we found that addiction is another predictor of death in these patients. Side effects of drug addiction in different aspects of health are widely accepted [26, 27]. Increasing age at diagnosis in the present study was associated with rising odds of death in HD patients. Coric et al. [8] achieved a similar result in their study. Fatal infections are usually more common in elderly patients due to the weakness of their immune system. These patients have a higher rate of mortality due to infections and cardiovascular disease [9].

Among clinical predictors, being CRP positive was strongly associated with mortality. This positive relation has been previously identified [28, 29]. Lseki et al. in their study showed that regardless of serum albumin and other possible confounders, CRP is a significant predictor of death in HD patients [30]. Inflammation usually is in relation to insulin resistance, oxidative stress, wasting, infections, and endothelial dysfunction [25]. In the present study, the increase in iron supplement was associated with better survival. Some factors including inadequate intake of iron due to loss of appetite, continuous blood sampling for biochemical testing, and chronic iron loss through intestinal hemorrhage induced by uremic platelet dysfunction are associated with iron deficiency in the HD patients [31]. Motonishi et al. in their study showed that iron deficiency is a critical risk factor for deterioration of physical and mental conditions in maintenance HD patients [32]. However, studies in regard to the relationship between iron supplementation and death in HD patients are rare and conflicting [33, 34].

Regarding the role of adequate URR on the lower mortality rates in HD patients, consistent with our finding many studies have shown that dose of dialysis is a strong predictor of patient mortality through the highest ranges of URR recorded (i.e., URR > 75) [35, 36].

This study had several limitations. First, because of the retrospective design of the study, verifying quality control of the data was not possible. Second, the influence of risk factors on patients' death is time-varying over time, while we assessed only the influence of baseline patient features, our effect estimates may underestimate the association between mortality and investigated variables. Third, that the best performance of the LR in our study is not enough to say that LR is the best in the prediction of death among the patients with CKD, because the performance of machine learning methods of SVMs, NNs, DT, and logistic regression are bound to change depending on the situation of the dataset. Another potential limitation of the present study is that addiction and smoking status of the patients were based on their self-report and therefore, this information was prone to information bias and finally the quality of the services and technology may vary over time, and also the quality of service provision in the dialysis wards of hospitals is not the same, which could not be considered in this study.

Results of the study indicated that logistic regression had the best performance in comparison to other methods for predicting death among HD patients. According to this model female gender, increasing age at diagnosis, low iron level, CRP positive and low URR were the main predictors of death in hemodialysis patients.

Ethical statement

Ethic code: IR.UMSHA.REC.1399.029), research ID: 9911218196.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

SKH: Study conception and Design; Analysis and Interpretation of the data; Drafting of the manuscript.

SNHG: Study conception and Design; Data extraction; Drafting of the manuscript.

VRD: Study conception and Design; Interpretation of the data; Drafting of the manuscript.

All authors approved the final version of the manuscript for publication.

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RESEARCH ARTICLE

Louis Pasteur and Dom Pedro II engaged in rabies vaccine development

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Keywords

Rabies vaccine • History of medicine • Institut Pasteur

Summary

Louis Pasteur is the renowned chemist and microbiologist of the 19th century involved in the development of the rabies vaccine. He worked with a researchers team in the laboratory, mainly Pierre Paul Emile Roux, and also physicians in the clinical practice approach and the defense of Pasteur's anti-rabies technique in the Académie Nationale de Médecine, Alfred Vulpian being the most notable. Pasteur's first studies on rabies are noted in his 1881 publication. But in 1885, he revealed that he had already immunized 50 dogs against rabies. Meanwhile, he was looking for human subjects. The most polemic of this search

involves the second and last Emperor of Brazil, Dom Pedro II, who was a patron of the arts and sciences and followed and supported the work of the great scientist. During the reign of Dom Pedro II, the first Pasteur's Institute was founded in Rio de Janeiro, nine months before the Parisian, which had the financial support of Dom Pedro. This article deals with the interaction between the two outstanding characters, especially in the development of prophylactic treatment against rabies, and with the utilitarian aspects of this vaccine researches development against individual autonomy.

Introduction

In 1884, Louis Pasteur (Fig. 1), from Paris, asked the Brazilian Emperor Dom Pedro II (Fig. 2) to authorize the use of anti-rabies vaccine trials in prisoners sentenced to death in the South American country. Though the disturbing fact is that the rabies vaccine had so far only been tested on dogs by Pasteur, and the request involved imprisoned, subjugated, and vulnerable subjects, not at risk of developing rabies previously the vaccination. Rabies is a zoonotic, acute, progressive, and incurable viral infection of the central nervous system, caused

by a neurotropic RNA virus (family: *Rhabdoviridae*; genus: *Lyssavirus*). This virus infects domestic and wild animals, and the disease is transmitted to other animals and humans through close contact with saliva from the infected animals. This is an old and feared disease by humanity. However, it is still widely distributed, especially in developing countries where the burden caused by rabid dogs continues [1]. The clinical rabies mortality is virtually 100%; however, the hazard of acquiring the disease by the rabid animal bite is much less [2].

Regarding the main types of virus, there is a street virus that comes directly from the central nervous system of

Fig. 1. French scientist Louis Pasteur (1822-1895), 1878, by Paul Nadar (1856-1939). Source: Wikimedia Commons [4, 32, 33].



Louis Pasteur (*December 27, 1822, Dole, France-†September 28, 1895, Marnes-la-Coquette, France), was an outstanding French chemist and a chemist-turned-microbiologist, renowned for his discoveries of the principles of vaccination, microbial fermentation, and pasteurization. He is often called the founder of microbiology. He remained on the Faculty of Strasbourg until 1854, where he was appointed professor of chemistry in 1852. In 1873, he was elected to full membership of the Académie Nationale de Médecine. After 30 years spent at the École Normale, in 1888, Louis Pasteur moved to a specially designed apartment at his Institut. Besides, on November 1, 1894, "he had an attack of uremia, and there followed a long, slow agony, lasting for months". On June 13, 1895, he left the apartment for Marnes-la-Coquette, where he died, on September 28, at age 73. Before in 1868, he took a paralysis on his left side. Still, despite a stroke at the age of 46, he was the director of the Institut Pasteur that was established in 1888, until his death [4,32,33].

Fig. 2. Retrato de D. Pedro II of Brazil, 1885, by Marc Ferrez, Rio de Janeiro, RJ/Acervo IMS [34].



Pedro II (*December 2, 1825, Rio de Janeiro - † December 5, 1891, Paris), was the second and last Emperor of the Brazilian Empire for 58 years. A humanist and an enlightened ruler, the Emperor has established a reputation as a vigorous sponsor of knowledge, culture, and science. In recognition of his intellectual interests and achievements, scores of learned societies in many parts of the world made him a member. Williams reports that the Emperor would respect more the culture than vanities, when he astonished with the vandalisms on the ruins of Karnak and Abydos, he expressed his own concerns and priorities: "the Khedive might squander a little less on his palaces and spend a little more on the conservation of these monuments" [34].

a naturally infected host and fixed virus, been adapted through a passage in the brains of experimental animals and cell culture. The incubation period and biological behavior of the street virus are inconstant in humans, usually a long incubation period but a rapid evolution: 80% presents the classic form of the disease (furious rabies, "hydrophobic" or "spastic" form), and 20%, a paralytic form (dumb rabies, "tranquil" or "paralytic") [3]. This last one presents with an ascending paralysis of Landry type, ending in bulbar, respiratory, and encephalitic symptoms [4]. Despite the severity of the clinical symptoms, rabies caused by the street virus has relatively mild meningoencephalitis neuropathologic changes characterized by inflammatory alterations occurring predominantly in the gray matter. In the paralytic form of the disease, the most striking pathological changes are seen in the spinal cord, with neuronal degeneration in the anterior horn resembling poliomyelitis [3]. However, the pathognomonic feature of rabies is represented by the occurrence of intraneuronal protoplasmic inclusions, the Negri bodies, most frequently found in the pyramidal neurons of the hippocampus and the Purkinje cells of the cerebellum. This rabies hallmark was defined by Adelchi Negri (1903) in Golgi's laboratory [3]. This paper deals with the development of the rabies vaccine by Louis Pasteur, and the observance of it by the Brazilian Emperor, Dom Pedro II, as a savant ruler.

At Pasteur's time, he had to face opposition regarding the anti-rabies vaccine development, as he was not a physician, as well as, he suffered the resistance of the antivivisectionists because of the animal experimentation, but also of the antivaccinationists. It is still a matter of

debate on the "Trolley dilemma", which refers to the question of sacrificing some for the benefit of many – a central issue in the dilemmas of vaccination tests [5]. However, this utilitarian theory, which justifies human losses to achieve progress in science and economic gains, was widely disseminated but also criticized.

The foundations of the Institute Pasteur of Rio de Janeiro and after of Paris are presented. Besides, a letter written by Louis Pasteur to Dom Pedro II about his needs for human Guinea pigs is studied from the current bioethical point of view.

The friendship between Dom Pedro II and Pasteur

Dom Pedro II demonstrated precocious interest in Pasteur's work since the beginning of the decade of 1870. Indeed, at this time, Pedro II informed Count Gobineau, former French Minister to Brazil, of his desire to know the great scientist. This meeting was carried out in the laboratory of the École Normale when the Emperor was visiting Paris for the first time [6]. Indeed, Dom Pedro II, on several occasions, recognized the greatness of the researcher and even honored him. On 06/16/1886, Pasteur sent a letter to the Minister of the Empire, Baron de Mamoré, thanking him for the notification of his appointment as Grand Cross of the Order of the Rose. Still, he had already been appointed Commander of the same Order in 1872 [7].

The interaction between these two distinguished men was shown through their correspondence to each other [8]. The letters sent by Pasteur to D. Pedro II are collected at the Museu Imperial, and they are essential to understand the development of the rabies vaccine and Pedro II's concern about yellow fever [9-15].

On 11/15/1880, Pasteur, in his letter to Pedro II, deals with yellow fever and says that he is sending the work *Critical review of posthumous writing by Claude Seward on fermentation* [9]. On 07/07/1882, Pasteur talks about the need to study yellow fever in a country where it had its origin and regrets not being able to come to Brazil for reasons of health and age. Pasteur also addresses rabies, whose study he was currently engaged in [10]. In other letters of 6/23/1884 and 9/22/1884, Pasteur requested the collaboration of the Emperor to erect a statue in honor of Monsieur Dumas, in Alais, his hometown. In the other important letter, he addresses rabies, cholera, and the rabies vaccine. He mentions that he intended to come to Rio de Janeiro to study the subject, especially the contagion and the medicines that should be used. In the draft of the reply, the Emperor says that Pasteur's visit to Rio de Janeiro could provide an excellent service to humanity, but bringing the latest news about the studies of yellow fever [11]. In the letter of 2/23/1885, Pasteur refuses the invitation made by the Emperor to come to Brazil to study yellow fever [12]. Later, Pasteur also gives the Emperor knowledge of a note on studies of rabies presented by him in the Académie des Sciences (03/02/1886) [13]. Another presentation at the same Academy is commented on studies of rabies treatment. The scientist also talks about the purpose of establishing an anti-rabies study center in Brazil, and he considers that dr. Ferreira Santos would be perfectly capable of founding it (11/03/1886) [14].

The first Pasteur's Institutes

The first Pasteur Institute was opened on February 25, 1888, in Rio de Janeiro, nine months before the French one (Fig. 3) [15]. Its constitution was a masterly feat for having faced obstacles of the most varied natures [15].

The Journal O Brazil Médico [16] welcomed the initiative of this foundation and highlighted its dependencies with a bacteriology laboratory very well equipped with devices and instruments imported from Europe, suitable for investigations related to other diseases besides rabies. However, this Institute became restricted to the production and application of the rabies vaccine. The first director of it was the Brazilian forerunner to study with the Pasteur's group in Paris: Augusto Ferreira dos Santos. He was a professor of mineral chemistry at the Faculty of Medicine of Rio de Janeiro.

During the trip back from the "City of Light", dos Santos made the intracerebral passage of the virus from the three rabbits inoculated in Paris that fell ill on board, to normal rabbits. This was done to implement the rabies vaccination in Rio de Janeiro. The next passage of the virus took place shortly after he arrived in Rio de Janeiro, on July 23 and 24, in temporary facilities at the pharmaceutical laboratory of Santa Casa de Misericórdia [15].

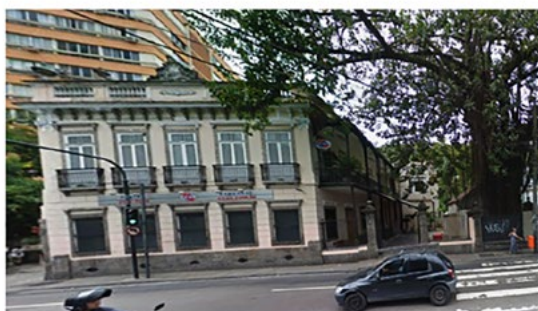
On February 9, 1888, still in Santa Casa de Misericórdia, a range of rabbit marrows subjected to desiccation was complete, when the first anti-rabies treatment in Brazil was started for a patient supposed of having been diseased with the rabies virus, a girl by the name of Isolina Torres [15]. Concerning the Pasteur's matrix Institute, D. Pedro II was one of those who contributed a large amount for its creation, as expressed at Le Figaro [17] (Fig. 4).

Pasteur, in a letter to Dom Pedro II, of 4/14/1888 and 11/28/1888, was pleased to know that the Rio de Janeiro Anti-rabies Institute was in operation. He thanked the 12 photographs of the Rio de Janeiro Anti-rabies Institute that would be displayed in one of the rooms of the Parisian Pasteur's Institute. Besides, he talked about the inauguration and news of the French Institute [18].

The rabies vaccine and human subjects

The nineteenth century was a significant landmark in the history of vaccines since it witnessed discoveries made by Louis Pasteur, the father of microbiology, and many others [19] such as Pierre-Victor Galtier and Paul

Fig. 3. Pasteur's Institute of Rio de Janeiro, responsible for preventive rabies vaccination where the first rabies inoculation was carried out in Brazil. It was the world's first Pasteur's Institute, established nine months before the Parisian one. The Institute was installed in a building previously owned by Viscondessa de Araújo, but bought by the Provider of the Santa Casa de Misericórdia [15]. Its inauguration was acclaimed and registered at the Brazil-Médico [35].



Building on Rua das Laranjeiras, 308, Rio de Janeiro-Brazil that housed the former Pasteur Institute of Rio de Janeiro, 1888-1910 [35].

Fig. 4. Inauguration of the Pasteur's Institut, on November 14, 1888. The Institute found by Pasteur also contains busts of all benefactors of the Institute at the time of its inauguration of Pasteur, Don Pedro, Alexander III, Mme. Furtado-Heine, Mme. Boucicaud, M.A. de Rothschild and the Count de Laubespain. Its inauguration was acclaimed and registered at "Le Figaro" [17].

INAUGURATION DE L'INSTITUT PASTEUR

Il y a bientôt trois ans, j'exposais de mon mieux, dans ce journal, et je défendais, avec l'ardeur d'un homme qui croit combattre le bon combat, la méthode de préservation de la rage, après morsures, quo M. Pasteur venait de faire connaître au monde savant.

Le 2 mars 1886, après avoir rendu compte de la fameuse séance de l'Académie des sciences de la veille dans laquelle fut agitée la question de la création d'un établissement vaccinal contre la rage, je terminais ainsi : « Cet établissement rappellera une conquête scientifique et humanitaire qui aura plus fait pour l'honneur de notre pays qu'une grande victoire sanglante. Quant à son nom, je n'en vois qu'un, il n'y en a qu'un. Il s'appellera : »

« INSTITUT PASTEUR »

Aussi, hier, en me rendant rue Dutot, au fin fond de Vaugirard, à l'inauguration du grand établissement scientifique dont M. Pasteur aura doté son pays, n'ai-je pu me défendre d'une certaine joie personnelle en lisant sur le frontispice de ce magnifique laboratoire le nom que la justice et la reconnaissance lui ont donné : Institut Pasteur.

Mais, j'arrive à la cérémonie.

Cérémonie n'est pas le mot. Fête vaut beaucoup mieux ; une vraie fête de l'esprit. Quelle chambre ! Environ six cents personnes dans une salle faite pour en contenir quatre cents et qui porte le nom de « salle des bustes » en souvenir des principaux donateurs de la maison : l'empereur de Russie, l'empereur du Brésil, Mme Furtado-Heine, Mme Boucicaud, M. Alphonse de Rothschild, M. le comte de Laubespain, dont le marbre rappelle ici les générosités : . . .



Speeches in honor of Louis Pasteur and his collaborators at the inauguration of the Institut Pasteur, on November 14, 1888. Drawing by Tinayre. Credit: Institut Pasteur/Musée Pasteur.

Gibier. Galtier, professor at the Lyon Veterinary School, was the precursor of rabies vaccination (1879-1881): *I inoculated, seven times rabies saliva in the sheep jugular without ever getting rabies*, apud Mérieux [20]. This was not yet a vaccination but a “variolation” [21]. Besides, Paul Gibier from the Faculty of Medicine and the Muséum d'Histoire Naturelle de Paris showed in 1883-1884 that the rabies virus lost virulence after desiccation and that this approach could be used in humans [22]. In this way, Pasteur began to work on rabies vaccine in this already vibrant and dynamic research background, as we see in the next section.

Now, we come back to the most famous letter from Pasteur to Dom Pedro II [11], presented in Figure 5, and excerpts below.

Pasteur urged to follow a next delicate step “when Guinea pigs are human” [23]: *But even though I have multiplied the examples of rabies prophylaxis in dogs, it seems to me that my hand will tremble when I have to move to the human species.*

It is clearly shown that scientific research in the biomedical field has been developed with experiments. However, at Pasteur's time, there was already an ethical limit for human experimentations, at least from the theoretical point of view. Simonds, in his book on medical deontology (1845) [2], recommends that the experiment would be allowed on limited occasions in desperate cases. Still, physicians would have to avert inhuman procedures or anything which might reduce the patient's life or impede even simple palliative resources. Besides, it is well known that there was not always a distinction between human and animal subjects. If certain classes of people were not considered socially relevant according to the moral appreciation of the time, against individual autonomy, they would be used in research, as Pasteur propose: *... If I were king or Emperor or even president of the republic, here is how I*

would exercise the right of pardon on death row inmates. I would offer to the lawyer for the convicted person, the day before the execution of the latter, to choose between imminent death and an experiment which would consist of preventive inoculations of rabies to cause the constitution of the subject to be refractory to rabies. Employing these trials, the life of the condemned man would be saved. If it were, and I have the persuasion that it would indeed be, – as a guarantee vis-à-vis the society which condemned the criminal, it would be subjected to surveillance for life.

All the condemned would accept. The death row inmate only apprehends death.

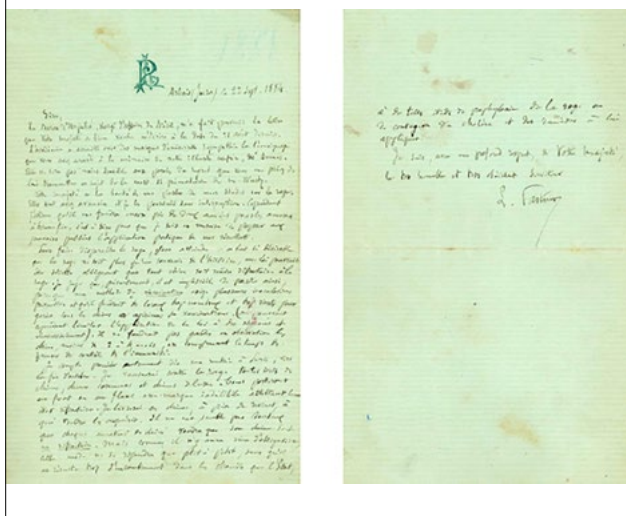
In response, Pedro II made a declined alternative suggestion to study yellow fever *in loco* because of the more significant social benefit [11].

However, Simons (1845) [2] already recommends that: *The most obscure patient, the most useless to society itself, cannot be subjected to experiments, which would obviously put his life in danger: perish science rather than such a principle!*

Indeed, the current system of human-subject-research oversight and protections has developed relatively in recent times, and their principles were first developed referring to the Nuremberg code to try Nazi war criminals [24]. At this time, the three elementary fundamentals of the Nuremberg Code (voluntary informed consent, favorable risk/benefit analysis, and right to withdraw without repercussions) turn out to be the groundwork for succeeding ethical codes and research conventions.

However, Pasteur was not isolated in this enterprise, for Pierre Paul Emile Roux, a physician at his basis, had also made crucial aids to the experiments with rabies inoculation in a variety of laboratory animals [25].

Fig. 5. Letter from Pasteur to Dom Pedro II, asking the Emperor to allow him to test the vaccine against rabies in those sentenced to death. Credit: Arquivo Histórico - Museu Imperial, Maço 192 - Doc. 8722, 23/06 e 22/09/1884 [11].



Louis Pasteur's works on rabies

Louis Pasteur wrote the first of his papers on rabies, in 1881 [26], with the collaboration of Chamberland, Roux, and Thuillier: *We have started studying rabies*.

In a publication in 1884 [27], he *Previously demonstrated that, in cases of rabies, the rabies virus had its seat in the brain and the spinal cord. We have looked for it more recently in the nerves proper and in the salivary glands*.

In other publication of the same year (1884) [28], Pasteur report: *If we go from dog to monkey and later from monkey to monkey, the virulence of the rabies virus weakens with each pass*. Consequently, Pasteur created an attenuated vaccine, and efficaciously immunized inoculated dogs.

In a next report (1885) [29], Pasteur approach *Method to prevent rabies after biting*, and he says that *Out of twenty dogs treated, I could not have responded to making it refractory to rabies more than fifteen or sixteen*.

In a publication of 1886 [30], Pasteur reported the existence of many people already saved from death. Therefore, prophylaxis of rabies after the bite was well founded, according to him.

Finally, a first real opportunity for Pasteur to apply in human his novel vaccine involved 9-year-old Joseph Meister, from Alsace, who had received numerous, severe bites from a rabid dog, on July 4, 1885, but had not yet developed symptoms of rabies. It occurred ten months after the Pasteur's letter to Dom Pedro about the human guinea pig search. Using the knowledge he had previously with the 50 dogs, the vaccine inoculations were lead in Pasteur's facilities. His most respected medical supporters were Alfred Vulpian, a member of the Académie Nationale de Médecine and Académie des Sciences, and Jacques-Joseph Grancher, head of the Paris Children's Hospital's pediatric clinic [25, 31]. Vulpian and Grancher persuaded Pasteur to give them

the material from a rabid rabbit spinal cord that had been dehydrated for 15 days [4, 31].

Afterward, Grancher administered subcutaneously the first doses of live attenuated rabies vaccine on July 6, 1885, at 8:00 PM in the presence of Pasteur and Vulpian [1, 4, 22, 25, 31]. Afterward, they were administered 12 supplementary doses, over the 10 subsequent days [22]. This vaccination was reported in the session of the French Academy of Sciences on October 26, 1885 [31].

Nevertheless, the death of 12-year-old Édouard-Jules Rouyer following Pasteur's vaccination was a scandal at the time, and the "Rouyer affair" was a court inquiry opened to determine the cause of this death.

Paul Camille Hippolyte Brouardel's medicolegal report on the boy's death was officially listed as kidney failure [23]. However, the inner circle of Pasteur's group knew for sure from laboratory testing that the boy died from rabies, "street rabies" or "laboratory rabies" [21, 25].

Grancher assumed the rabies vaccine defense team and its methods against Michel Peter's accusations that they would be dangerous. Still, on the contrary, he cited its successful survival rate. This was carried out at the Académie Nationale de Médecine, on January 11, 1887 [25].

Conclusions

In the aim to empower his country, inside also his admiration for distinguished intellectuals, Pedro II contacted prominent researchers from many countries, mainly France, such as Pasteur. This interchange constituted a feedback association, as the Ruler tried to support the effort of skilled avant-gardists, with benefits on both sides. An example is the scientific repercussion of the friendship between Pedro II and Pasteur, regarding anti-rabies vaccination development and respect for individual autonomy in addition to the priorities of Brazilian interests.

In the inner of the rabies vaccination achievements, there are two arms, at one side, the stronger one, which was led by Pasteur and Roux, and the other one contributory by clinical medicine. This was represented by Alfred Vulpian and Grancher. Besides, there are supporters of the trials, mainly the pathologist Brouardel regarding dubious vaccination results.

These achievements are in the scenario of human researcher subjects. In this way, Pasteur, in his urge to discover rabies prophylaxis by using human subjects from the researcher's point of view, became an example of a utilitarian dilemma, in the face of a fatal disease, but against individual autonomy.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

The only author did the work conception, literature review, and manuscript writing.

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REVIEW

Epstein-Barr Virus (EBV) acute acalculous cholecystitis in an immunocompromised adult patient: a case report and a literature review of a neglected clinical presentation

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Keywords

EBV • Acute acalculous cholecystitis • Immunosuppressed patient • Cholecystitis • Hepatitis

Summary

Primary Epstein-Barr virus (EBV) infection may present with self-limiting abdominal involvement, characterized by hepatitis with mild elevation of aminotransferases, splenomegaly, and rarely with acute acalculous cholecystitis (AAC). Usually, treatment of EBV related AAC is symptomatic, without the need for

surgery. Here, we describe a severe case of AAC occurring as the first manifestation of infectious mononucleosis in a young adult woman, receiving treatment with interleukin 6 receptor (IL-6r) inhibitor for rheumatoid arthritis (RA); moreover, we have performed a review of the literature on EBV-related AAC.

Introduction

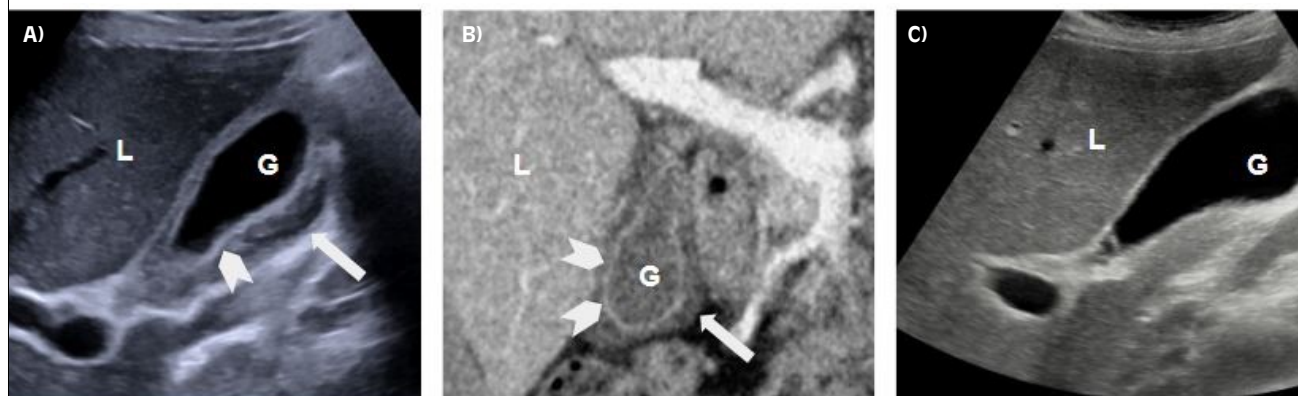
Epstein-Barr virus (EBV), a double-stranded DNA virus with a genome of about 172 kilobases, belonging to the Herpesviridae family, is one of the most common life-long viral infection, with almost 95% of the human population being infected [1]. In particular, EBV is classified within the gamma-herpesviruses subfamily, and is the prototype of the Lymphocryptovirus genus, with its formal designation of human herpesvirus 4 (HHV-4) [1]. EBV was the first isolated human tumour virus, identified in 1964 in a cell line derived from Burkitt lymphoma [1]. After infection, EBV resides persistently in memory B-cells and is usually transmitted through saliva to and between young children, often from asymptomatic individuals [1, 2]. EBV displays a broad range of clinical pictures, from asymptomatic infection (especially during childhood) to benign infectious mononucleosis, to EBV-related lymphoma, EBV-related epithelial cancers, and post-transplant lymphoproliferative disease (PTLD) due to virus-induced persistent cell activation [1-3]. Infectious mononucleosis, when symptomatic, is a self-limiting disease occurring after an incubation period of four to seven weeks [3, 4]. Clinical manifestations may include fever, pharyngitis, malaise or fatigue, and diffuse lymphadenopathy. The most common presenting symptoms are the

triad of subacute pharyngitis, high-grade fever and lymphadenopathy [4]. Self-limiting abdominal involvement, characterized by hepatitis with mild elevation of aminotransferases and splenomegaly, is also frequently reported [4, 5]. Acute acalculous cholecystitis (AAC), defined as the inflammation of the gallbladder in the absence of gallstones, is usually described in critically ill patients due to major trauma and/or infections [5]. In a few cases reported in the literature, AAC has been associated with primary EBV infection in both children and adults [6]. Here, we describe a severe case of AAC occurring as the first manifestation of infectious mononucleosis in a young woman receiving treatment with interleukin 6 receptor (IL-6r) inhibitor for rheumatoid arthritis (RA); moreover, we performed a review of the literature on EBV-related AAC.

Case report

A 24-years-old woman presented to the Emergency Department of IRCCS Sacro Cuore Don Calabria Hospital, Verona, Italy, in August 2020 complaining of low-grade fever, abdominal pain, nausea, and jaundice. She suffered from juvenile rheumatoid arthritis (diagnosed at the age of 8 months) in treatment since 2013 with tocilizumab 162 mg subcutaneously once a week (last administration one week before

Fig. 1. Ultrasound and CT scan images of EBV-related AAC. **A)** US b-mode, day 1: gallbladder distention and thickened wall > 3 mm (arrow-head), pericholecystic fluid (arrow); **B)** Contrast Enhanced CT, venous phase, day 2, mucosal hyperenhancement (arrowheads), pericholecystic fluid and inflammatory fat stranding (arrow); **C)** A) US b-mode, day 7, after therapy: gallbladder with regular wall, no more pericholecystic fluid visible (G: gallbladder lumen; L: liver).



admission), without any hepatic side-effects reported, and methotrexate, since 2010, 10 mg once a week (discontinued 6 weeks before admission). In July 2020 she underwent right hip arthroplasty due to arthritis. On admission to our hospital, an abdominal ultrasonography showed diffuse, severe thickening of the gallbladder's walls with multi-layered appearance, associated with pericholecystic fluid, suggesting AAC (Fig. 1A). Splenomegaly (bipolar diameter 15 cm; normal value < 13 cm) was also reported.

Blood examination showed lymphocytosis (70% of the total white blood cell count) with activated lymphocytes, hypertransaminasemia (AST 919 U/L and ALT 914 U/L; normal values < 50 U/L), and hyperbilirubinemia (total bilirubin 4.4 mg/dL, normal values 0.3-1 mg/dl; direct bilirubin 3 mg/dL, normal values 0-0.3 mg/dl). C-reactive protein was slightly increased (42 mg/dL; normal value < 5 mg/dL), while procalcitonin was negative. Major hepatitis virus tests (HAV, HBV, HCV) as well as serum B-D-glucan, to exclude opportunistic fungal infection, were negative. Stool culture, to investigate for salmonellosis, was also negative.

To cover empirically for bacterial cholecystitis, antibiotic therapy with piperacillin/tazobactam 4/0.5 g every 8 hours was started.

In the following three days, symptoms persisted despite fasting, antibiotic therapy and intravenous hydration. A computed tomography (CT) scan of the abdomen confirmed the ultrasound picture: a distended gallbladder with wall thickening, increased enhancement following administration of iodinated contrast medium, and no visible gallstones (Fig. 1B). The need for urgent cholecystectomy was discarded after surgical consultation, which suggested elective surgery depending on the clinical development.

Testing for minor hepatitis viruses revealed a negative serology for cytomegalovirus but positive serology for EBV, with an immunological profile characterized by positive anti-VCA IgM and anti-VCA IgG, negative anti-EBNA IgG, indicating acute infection.

Upon diagnosis of EBV infection, antibiotic therapy was discontinued. After 72 hours from admission, the patient improved spontaneously, with resolution of abdominal pain, normalization of liver function tests, and progressively resumed feeding.

Abdominal ultrasound before discharge showed resolution of the gallbladder walls' thickening (Fig. 1C). The patient was discharged after 7 days from admission in good clinical condition and with no symptoms left.

Literature review

On 30 September 2020 we performed a MEDLINE/PubMed search using the following query ((EBV) OR(Epstein-Barr)OR(infective mononucleosis)) AND (((Cholecystitis)OR(gallbladder)))". No restrictions were applied regarding publication date or language; only original papers describing cases of human AAC caused by serology-confirmed EBV were included. Data regarding the number of patients, age (children or adults aged older than 18), immune status (immunocompetent or immunocompromised), and treatment were recorded.

Out of the 100 papers retrieved, 45 were excluded by title/abstract screening. The full-text of the remaining 55 papers was retrieved, the content examined for eligibility, and the references lists examined to individuate further potentially eligible papers. Eventually, data were extracted from the finally eligible 57 papers.

Details of the eligible papers are shown in Table I (review containing multiple case reports were reported excluding papers with the single case). Since 1987, the first reported case in an adult immunocompetent female patient by Hammond [7], 70 cases were retrieved, of whom 52 (74,2%) in females and 18 (25,8%) in males. Forty-four (62.8%) patients were children (3-18 years old), while 26 (37.2%) patients were adults. Immune status was available in 55 cases (78.5%), of which

Tab. I. Review of the published EBV case report.

Author (year)	Number of patient	Immunocompromised/immunocompetent	Adult/child	Sex	Surgical treatment
Langenohl et al. (2020) [8]	1	Immunocompetent	Child	M	No
Guri et al. (2020) [9]	1	Immunocompetent	Child	F	No
Ntelis et al. (2020) [10]	1	Immunocompetent	Child	F	No
Lamprianidis et al. (2020) [11]	1	Immunocompetent	Adult	F	No
Young et al. (2019) [12]	1	Immunocompetent	Child	F	No
Mazur-Melewska et al. (2019) [13]	15	Not available	Child	9 M/ 6 F	No
Rezkallah et al. (2018) [14]	1	Immunocompetent	Adult	F	Laparoscopic cholecystectomy
Höhn et al. (2018) [15]	1	Previous major surgery	Adult	M	No
Cameron et al. (2018) [16]	1	Immunocompetent	Adult	F	No
Yesilbag et al. (2017) [17]	1	Immunocompetent	Adult	F	No
Rodà et al. (2017) [18]	1	Immunocompetent	Child	M	No
Khouri et al. (2017) [19]	1	Immunocompetent	Adult	M	No
Sheybani et al. (2016) [20]	1	Seronegative spondyloarthritis	Adult	F	No
Ono et al. (2016) [21]	1	Immunocompetent	Adult	F	No
Majdalani et al. (2016) [22]	1	Immunocompetent	Child	F	No
Koufakis et al. (2016) [23]	1	Immunocompetent	Adult	M	No
Branco et al. (2015) [24]	1	Immunocompetent	Child	F	No
Hernández-Rodríguez J et al. (2014) [25]	1	Immunocompetent	Child	F	No
Pawłowska-Kamieniak et al. (2015) [26]	1	Immunocompetent	Child	F	No
Alkhouri et al. (2015) [27]	1	Immunocompetent	Child	F	No
Agergaard et al. (2015) [28]	1	Immunocompetent	Adult	F	No
Suga et al. (2014) [29]	1	Immunocompetent	Child	F	No
Gagneux-Brunon et al. (2014) [30]	2	Immunocompetent	Adult	2F	No
Celik et al. (2014) [31]	1	Immunocompetent	Adult	F	No
Fretzayas et al. (2014) [32]	2	Immunocompetent	Child	2F	No
Strehle et al. (2014) [33]	1	Immunocompetent	Child	F	No
Kim et al. (2014) [34]	1	Immunocompetent	Child	F	No
Hamdy et al. (2014) [35]	1	Immunocompetent	Child	F	No
Poddighe et al. (2014) [36]	1	Immunocompetent	Child	F	No
Teke et al. (2013) [37]	1	Immunocompetent	Child	F	No
Beltrame et al. (2012) [38]	1	Immunocompetent	Adult	F	No
Dylewski et al. (2012) [39]	1	Immunocompetent	Adult	F	No
Carrascosa et al. (2012) [40]	1	Immunocompetent	Adult	F	No
Nagdev and Ward (2011) [41]	1	Immunocompetent	Adult	F	No
Arya et al. (2010) [42]	1	Immunocompetent	Child	F	No
Yang et al. (2010) [43]	1	Immunocompetent	Adult	F	No
Attilakos et al. (2009) [44]	2	Immunocompetent	Child	1 F / 1 M	No
Hagel et al. (2009) [45]	1	Immunocompromised (ulcerative colitis)	Adult	F	Laparoscopic cholecystectomy
Cholongitas et al. (2009) [46]	1	Immunocompetent	Adult	F	No
Chalupa et al. (2009) [47]	1	Immunocompetent	Adult	F	No
Iaria et al. (2008) [48]	1	Immunocompetent	Adult	F	No
Pelliccia et al. (2008) [49]	1	Immunocompetent	Child	F	No
Koch et al. (2007) [50]	1	Immunocompetent	Adult	F	No
Prassouli et al. (2007) [51]	1	Immunocompetent	Child	F	No
Lagona et al. (2007) [52]	1	Immunocompetent	Child	F	No
Yoshie et al. (2004) [53]	1	Immunocompetent	Child	F	No
O'Donovan et al. (1996) [54]	2	Immunocompetent	Adult	1 F / 1 M	No
Maruyama et al. (1994) [55]	2	Immunocompetent	Child	1 F / 1 M	No
Sainsbury et al. (1994) [56]	1	Immunocompromised (end-stage renal disease)	Child	M	No
Sung et al. (1989) [57]	1	Immunocompetent	Child	F	No
Hammond et al. (1987) [7]	1	Immunocompetent	Adult	F	No

4 (7.2%) were immunocompromised: 1 patient with previous major surgery (left adrenal gland resection, distal pancreatectomy, and splenectomy due to a large pheochromocytoma), 1 with seronegative spondyloarthropathy in treatment with disease-modifying antirheumatic drugs (DMARDs), 1 with ulcerative colitis in treatment with azathioprine, and 1 patient with end-stage renal disease. Surgical management with colectomy was reported in 2 (2.8%) cases, of whom 1 was immunocompromised.

Discussion

Acute acalculous cholecystitis contributes to 5-10% of all cholecystitis in adults and it is usually observed in patients with viral hepatitis, salmonellosis, major trauma, extensive burns, long term parenteral nutrition, critically ill patients and systemic diseases such as diabetes, malignancies, abdominal vasculitis, congestive heart failure, cholesterol embolization, and shock [6, 58]. EBV is a relatively rare cause of AAC; to the best of our knowledge, 4 patients with immunocompromised conditions and EBV-related AAC have been reported in the literature (Tab. I). It should be noted that the AAC could be potentially related to the acute hepatitis induced by EBV or to immunosuppressive agents. Our patient did not need any supplementary treatment or treatment adjustment (e.g. reduction of the immunosuppressive treatment) or surgical intervention, being only supporting treatment apparently of benefit, as highlighted in previous reports [59]. Moreover, in our case report, a mild case of EBV hepatitis with transient elevation of serum aminotransferases and jaundice has been noted, while it is occasionally reported in the literature (in 5% of cases), possibly caused by cholestasis or virus-induced haemolysis [60].

EBV-related AAC should be suspected when no other cause of AAC can be identified, especially in young patients, who seem to be more prone to its development, and its diagnosis is suspectable in order to avoid unnecessary antibiotic treatment or more invasive and costly procedures [60] (Tab. I).

Likewise, if an EBV first-infection displays clinical symptoms compatible with cholecystitis, ultrasonographic examination should be performed in order to confirm or rule out the diagnosis of AAC [13, 38].

Conclusions

EBV primary infection can lead to acute acalculous cholecystitis, especially in adult immunocompromised patients: clinical suspicion, coupled with ultrasound of the gallbladder are needed for a correct and timely diagnosis. Conversely, when ultrasound of the gallbladder shows evidence of AAC, with coherent clinical presentation, EBV infection should be considered and serological test for EBV should be performed.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

SR, SS, NR, MS took care of the patient, draft and approved the final version of the manuscript. EO acquired radiological images, gave radiological consultation and approved the final version of the manuscript. FT, PB, MM and AF draft, reviewed and approved the final version of the manuscript.

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RESEARCH ARTICLE

Translation and validation of the Italian version of the user version of the Mobile Application Rating Scale (uMARS)

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Keywords

uMARS • Translation • Validation • Italian • User version mobile application rating scale

Summary

Background. Health sciences are steadily developing apps to help people to adopt correct lifestyles and to help physicians to monitor patients with chronic diseases. However, a properly validated tool that can evaluate patients' perception of apps is still lacking in many languages. In English, a validated questionnaire, called User Version of the Mobile Application Rating Scale (uMARS), is currently available. We translated the uMARS into Italian and validated our version.

Methods. The uMARS questionnaire was translated from English to Italian by an official translator, and then administered to 100 smartphone users in order to evaluate the same app at times 1 and 2 (after 2 weeks). Paired t-test, Pearson Correlation Coefficient, Intraclass Correlation Coefficient (ICCs) and Cronbach's Alpha were used to evaluate the reliability and validity of the Italian uMARS.

Results. We recruited 100 subjects, 52 males (52%) and 48 females (48%), with a mean age of 22.8 (SD: 3.4). All subjects answered all questions both at time 1 and at time 2. Paired t-test showed no statistically significant difference in each answer or group of answers between times 1 and 2 ($P > 0.05$). Cronbach's alpha was 0.945, as all subjects answered all questions. Each question was further assessed through the Pearson correlation coefficient, which demonstrated high reliability, with significant $P (< 0.05)$ and Pearson Coefficients higher than 0.7. Similarly, ICCs were always higher than 0.750.

Conclusions. Our results validated the Italian version of uMARS, which may become a reliable and useful tool for evaluating health apps.

Introduction

Mobile health (mHealth) is a continuously evolving field of healthcare, owing to its particularly attractive features, such as ubiquity and portability [1]. Indeed, the number of mobile subscriptions in Europe is over 1,300 per 1,000 inhabitants, and 76% of Europeans access the Internet daily [2]. Healthcare professionals (HCPs), patients and the general public are increasingly using mHealth for a vast range of purposes, including communication and consultation with health services, HCPs and patients, the acquisition of health information and monitoring [1, 3].

Today, health-related mobile applications (apps) constitute a cornerstone of mHealth, and their overall market in 2019 was estimated as $> 350,000$ [4]. Indeed, it is believed that more than 500 million people worldwide have downloaded at least one mHealth app to their mobile phone [5].

Despite this promising outlook, mHealth apps are often of suboptimal quality and, worryingly, have poor or no evidence base [6]. This fact may compromise users'

choices and habits, thereby affecting health-related outcomes [7]. The easiest way to assess the quality of an app is to check its "star rating", which can immediately be done in app stores. However, this quality appraisal system is highly subjective and may be significantly skewed by the phenomenon of "information asymmetry" between specialists and lay users [8, 9]. For instance, a review of urology apps available in the common app stores demonstrated that, while some apps were of moderate-high quality, the average app-store rating was 1 star only [10].

In order to address the above-described quality issues in a more objective way, the Mobile Application Rating Scale (MARS) was developed [8]. Given the frequency of its citation in published papers, MARS is probably the most popular scale worldwide. The original English language MARS scale has already been successfully validated in several languages, including Italian, Spanish, German, Dutch and Arabic [9, 11-14]. Briefly, the original MARS instrument is composed of 23 Likert scale-based items that cover the objective quality

dimensions of engagement, functionality, esthetics and information, and one subjective dimension [8].

However, the original MARS scale was developed for professional use by researchers, clinicians and other specialists, and training is required before it can be used [8]. Given that most app users have no specialist knowledge, a training-free user version of MARS (uMARS) was subsequently validated and is publicly available [15].

An Italian version of the “expert” MARS instrument was successfully validated by Domnich et al. (2016). The same research group then tried to adapt the Italian version of MARS to the user version, with regard to the assessment of the quality of an app concerning invasive pneumococcal disease; however, no formal validation was performed [16]. To address this unmet need, the present study aimed to validate the Italian version of uMARS.

Methods

THE ENGLISH VERSION OF uMARS

Like the expert version, the uMARS covers four objective dimensions (engagement, functionality, esthetics and information) and one subjective dimension. Unlike the expert version, however, it is training-free, omits three items on the information subscale and has better readability properties. Briefly, the scale consists of 20 anchored 5-point Likert-type items that are distributed as follows: engagement ($N = 5$), functionality ($N = 4$), esthetics ($N = 3$) and information ($N = 4$) and 4 items belonging to the subjective quality domain. There is also a section on perceived impact (6 items), which assesses the potential impact of a given app on users’ knowledge, behaviors, intentions, help-seeking, etc.; this is a domain that evaluates users’ perception of the usefulness of the app, thereby enabling its impact to be rated. The scoring procedure is based on the mean: (i) subscale-specific scores are obtained by averaging individual item scores on that particular subscale; (ii) an overall uMARS score is an average of the four objective dimensions [15].

During the validation process, the English version of uMARS displayed both excellent internal consistency (Cronbach’s α of 0.90) and good test-retest reliability in a period of up to three months [15].

ADAPTATION AND TRANSLATION

To meet our objective, we generally adopted the process of adaptation/translation of the Italian version of MARS [9]. Following consultations with the authors of the expert MARS version, it was deemed that the two Italian versions were fully interchangeable from the points of view of conceptual, item, semantic, operational, measurement and functional equivalence. Indeed, the uMARS has simpler wording, but at the same time shares the same topics with the expert version. The formal adaptation procedure was therefore judged redundant.

The English version of uMARS was then translated into Italian by a professional bilingual translator. The resulting output was then compared with the validated expert scale and discussed by the research group, which led to only minor changes being made. A back-translation was then performed in order to verify the compatibility and accuracy of meaning between the source and target languages. The authors of the original Italian MARS scale approved the final Italian uMARS questionnaire [9]. The final version of the questionnaire is available in Appendix A.

VALIDATION PROCEDURE

To validate the final Italian uMARS scale, we roughly followed the original methodology, as described by Stoyanov et al. (2016). We aimed to test the internal consistency and test-retest reliability of the scale.

To validate the questionnaire, we set a target of 100 individuals, a sample size in line with the original uMARS validation study [15]. Potential participants were selected from the University of Florence, Faculty of Medicine. Subjects who, on the day of enrollment, were able to navigate in the study target app from their devices were potentially eligible. Participants had to be sufficiently fluent in Italian.

The app chosen for uMARS validation was Facebook. There were several strong arguments for this choice: this app is free, popular and does not require participants to spend the time they would normally need to familiarize themselves with a new app, and Facebook contains all of the components covered by the four uMARS domains; therefore, all items could be confidently validated. The choice of Facebook was also related to the cost of downloading some health apps and the unavailability of some health apps on various mobile operating systems. Moreover, the use of certain health apps would have excluded some subjects from participating in the study.

Eligible subjects were instructed to navigate all the app functions for at least 10 min and then to rate the app by using the uMARS. In order to ascertain intra-rater reproducibility, this procedure was carried out twice: on enrollment (t1) and approximately two weeks later (t2); this time-lag was deemed an appropriate waiting period by the research team.

The study was conducted in accordance with the Declaration of Helsinki. Participation in this research was voluntary and all relevant Italian and international biomedical and privacy-related guidelines were followed. As the nature of the study was neither interventional nor biomedical, participants were not exposed to any risks. Therefore, formal ethical approval for this study was deemed unnecessary. Furthermore, all participants were enrolled on a voluntary basis, and our research group guaranteed their privacy.

STATISTICAL ANALYSIS

Internal consistency was measured by means of Cronbach’s α using the following “rule of thumb” categories: excellent (≥ 0.90), good (0.80-0.89),

acceptable (0.70-0.79), questionable (0.60-0.69), poor (0.50-0.59) and unacceptable (< 0.50) [17].

The reproducibility of the Italian uMARS questionnaire was evaluated through the second application of the questionnaire at t2, two weeks after t1. First, a paired t-test was calculated in order to observe variations

Tab. I. Characteristics of participants in the validation of the Italian version of uMARS.

Sex, n (%)	Female	48 (48.0%)
	Male	52 (52.0%)
Native Italian speaker, n (%)		100 (100%)
Education, n (%)	High school	88 (88.0%)
	University	9 (9.0%)
	Middle school	3 (3.0%)
Age, mean (SD)		22.8 (3.4)

between the two measurements, for each sub-score and total score. Moreover, for every variable, test-retest reliability was evaluated through a bivariate Pearson correlation coefficient. A Pearson correlation coefficient above 0.7 and a significance level below 0.05 were considered sufficient to assess test-retest reliability. Finally, intraclass correlation coefficients (ICCs) were computed between t1 and t2, in order to provide weighted values of rater agreement and assess proximity rather than equality of ratings. The model chosen to calculate ICCs was that of random-effects average measures with absolute agreement [18].

All statistical analyses were conducted by means of SPSS version 20.0 (SPSS Inc, Chicago, IL, USA). A P-value < 0.05 was conventionally deemed statistically significant.

Tab. II. Test-retest reliability between time 1 and time 2 in the validation of the Italian version of uMARS.

		Paired t-test			Reliability		
		Time 1	Time 2	P	Pearson correlation	P	
A - engagement	A1 - entertainment	3.8 (1.0)	3.7 (1.1)	0.235	0.826	0.001	
	A2 - interest	3.9 (1.1)	3.8 (1.1)	0.352	0.810	0.001	
	A3 - customization	4.0 (0.9)	3.8 (0.9)	0.309	0.810	0.001	
	A4 - interactivity	3.9 (0.9)	4.0 (0.9)	0.498	0.797	0.001	
	A5 - target group	3.9 (1.0)	3.8 (1.1)	0.822	0.798	0.001	
A - engagement total		19.4 (3.6)	19.1 (3.8)	0.283	0.854		
B - functionality	B6 - performance	4.0 (0.9)	4.0 (0.8)	0.750	0.828	0.001	
	B7 - ease of use	4.0 (0.9)	3.9 (0.9)	0.623	0.742	0.001	
	B8 - navigation	4.1 (0.7)	3.9 (0.8)	0.160	0.803	0.001	
	B9 - gestural design	4.2 (0.8)	4.2 (0.6)	0.660	0.843	0.001	
B - functionality total		16.3 (2.1)	16.0 (2.0)	0.214	0.790		
C - esthetics	C10 - layout	3.8 (0.8)	3.9 (0.8)	0.743	0.748	0.001	
	C11 - graphics	3.9 (0.8)	3.8 (0.9)	0.822	0.771	0.001	
	C12 - visual appeal	3.8 (0.9)	3.8 (1.0)	0.323	0.802	0.001	
C - esthetics total		11.5 (2.0)	11.4 (2.1)	0.727	0.794		
D - information	D13 - quality of information	3.7 (1.0)	3.7 (0.8)	0.643	0.753	0.001	
	D14 - quantity of information	3.9 (1.1)	3.9 (1.0)	0.599	0.850	0.001	
	D15 - visual information	4.0 (0.9)	3.9 (1.0)	0.323	0.772	0.001	
	D16 - credibility of source	3.6 (1.1)	3.6 (1.1)	1.000	0.844	0.001	
D - information total		15.1 (3.4)	15.1 (3.1)	1.000	0.874		
Quality		(A+b+c+d/4)	15.6 (2.3)	15.4 (2.3)	0.339	0.881	0.001
E - subjective quality	E17 - recommendation to others	3.7 (1.0)	3.7 (1.0)	0.700	0.868	0.001	
	E18 - use and relevance	4.1 (1.1)	3.9 (1.1)	0.167	0.792	0.001	
	E19 - payment	2.5 (1.6)	2.5 (1.5)	0.686	0.803	0.001	
	E20 - overall rating	3.7 (0.8)	3.5 (1.0)	0.127	0.792	0.001	
E - subjective quality total		14.0 (3.2)	13.6 (3.2)	0.080	0.880		
F - perceived impact	F1 - awareness	3.3 (1.2)	3.2 (1.1)	0.294	0.810	0.001	
	F2 - knowledge	3.0 (1.2)	3.1 (1.3)	0.230	0.868	0.001	
	F3 - attitudes	3.0 (1.3)	3.0 (1.2)	0.822	0.849	0.001	
	F4 - intention to change	3.3 (1.1)	3.1 (1.2)	0.128	0.813	0.001	
	F5 - help seeking	3.2 (1.2)	3.2 (1.2)	0.538	0.800	0.001	
	F6 - behavior change	3.1 (1.3)	3.2 (1.2)	0.800	0.886	0.001	
F - perceived impact total		19.0 (6.4)	18.8 (6.3)	0.488	0.950	0.001	
Total score		83.8 (15.4)	82.5 (14.8)	0.197	0.917	0.001	

icc: intraclass correlation coefficient; for single measures α = cronbach's alpha. All values are scores and are reported as mean (standard deviation). Paired t-test was done as statistical analysis between time 1 and time 2.

Results

During the study, the target population of 100 was reached in approximately three months. The mean age of participants was 22.8 years (SD = 3.4) and the male-to-female ratio was close to 1 (48 female vs 52 male). All participants were native Italian speakers, mostly university students in their 2nd, 3rd or 4th year; 22 participants (22%) were students' relatives: 9 (9%) with a degree, 10 (10%) with a high-school diploma and 3 (3%) without a high-school diploma. All participants filled in the uMARS questionnaire both at t1 and at t2 (100% compliance). Their principal characteristics are reported in Table I.

The Italian uMARS displayed high internal consistency (Cronbach's $\alpha = 0.95$), and excellent reliability (Cronbach's α based on standardized items = 0.98).

The paired t-tests demonstrated that all 20 items and all the overall (sub)scale scores were similar between t1 and t2 ($P > 0.12$) (Table II). In detail, the highest variability was observed for question E20, regarding the subjective evaluation of the app: "What is your overall (star) rating of the app?" t1 mean 3.7 (SD: 0.8) vs t2 mean 3.6 (SD: 1.0) $p = 0.089$. The lowest variability was observed in the Information Section concerning question D16 "Credibility of source: does the information within the app seem to come from a credible source?", t1 mean 3.6 (SD: 1.1) t2 mean 3.6 (SD: 1.1) $p = 1.000$. Moreover, test-retest reliability showed high consistency in each sub-score and total score, with a Pearson Correlation coefficient above 0.7 and significance below 0.05 (Tab. II). Analogously, the ICCs observed were constantly high (Tab. III), confirming excellent test-retest reliability.

Tab. III. Intraclass Correlation Coefficients between Time 1 and Time 2 in the validation of the Italian version of uMARS.

		ICC	α
A - engagement	A1 - entertainment	0.85	0.97
	A2 - interest	0.83	0.90
	A3 - customization	0.81	0.90
	A4 - interactivity	0.80	0.97
	A5 - target group	0.78	0.91
A - engagement total	0.80	0.89	
B - functionality	B6 - performance	0.82	0.97
	B7 - ease of use	0.76	0.87
	B8 - navigation	0.80	0.87
	B9 - gestural design	0.87	0.94
B - functionality total	0.79	0.88	
C - esthetics	C10 - layout	0.75	0.87
	C11 - graphics	0.77	0.90
	C12 - visual appeal	0.80	0.90
C - esthetics total	0.79	0.88	
D - information	D13 - quality of information	0.76	0.85
	D14 - quantity of information	0.85	0.92
	D15 - visual information	0.77	0.87
	D16 - credibility of source	0.84	0.95
D - information total	0.87	0.93	
Quality	(A+b+c+d/4)	0.88	0.94
E - subjective quality	E17 - recommendation to others	0.87	0.92
	E18 - use and relevance	0.79	0.86
	E19 - payment	0.80	0.85
	E20 - overall rating	0.81	0.87
E - subjective quality total	0.88	0.94	
F - perceived impact	F1 - awareness	0.81	0.87
	F2 - knowledge	0.86	0.93
	F3 - attitudes	0.85	0.92
	F4 - intention to change	0.81	0.90
	F5 - help seeking	0.80	0.89
	F6 - behavior change	0.88	0.94
F- perceived impact total		0.95	0.97
Total score		0.92	0.96

ICC: Intraclass Correlation Coefficient; for single measures α = Cronbach's Alpha. All values are scores and are reported as mean (standard deviation). Paired t-test was done as statistical analysis between time 1 and time 2.

Discussion

The uMARS scale is designed to enable the quality of health-related apps to be evaluated, both within institutional bodies (e.g. researchers, scientific societies, regulatory agencies, industry) and among end-users [15]. We translated this scale into Italian and validated our version. Together with the Italian “expert” MARS questionnaire, our newly validated Italian uMARS scale completes the set of instruments for the quality evaluation of Italian health apps. Although Italy ranks relatively highly in terms of mobile subscriptions and Internet access, the overall English language proficiency of Italians is among the lowest in Europe [9, 19-21]. Therefore, original questionnaires should be translated into Italian and validated, in order to reach the majority of the population (this is also a matter of equality of access to a new technology). Moreover, the Italian version of uMARS can now also be used for wide population-based research.

The validity and reliability of the Italian uMARS version proved similar to those of the original uMARS [15]. Specifically, we obtained a similarly high level of internal consistency ($\alpha \geq 0.90$), in line with the Italian “expert” version of MARS [10]. The test-retest reliability and ICCs were also high, being similar to those of the original scale created by Stoyanov et al. (2016). In our opinion, these optimal properties were obtained because: (i) we adopted the methodology of the original MARS and consulted the original uMARS and the Italian MARS scales, and (ii) subsequent approval of the text of the scale was obtained from the authors of the previously published “expert” scale [8, 9, 15].

Considering that the present study was based on a body of previous research, we were able to identify some limitations of our study. Indeed, the total sample size of 100 participants was not powered *a priori* [8, 9, 15]. However, in a recently published review by Bujang et al., this sample size was judged sufficient [22]. Moreover, our sample was mostly composed of young university students, who are usually very familiar with modern technology and use apps more often than older people do. Consequently, the sample might be not fully representative of the general Italian population. Finally, although the app chosen for validation had the advantage of being widely used, it was not an mHealth app; this was a potential limitation, as it might have influenced respondents’ perception of the impact of the questionnaire on health.) However, the sub- and total scores in other domains can be assumed to be reliable and correctly assessed by the questionnaire.

Conclusions

The Italian version of uMARS displayed good reliability and validity. When accompanied by the “expert” MARS version, it may be used in multipurpose research/public health projects and by developers working in the sphere of digital health intervention in Italy. Furthermore, the Italian

version of uMARS can provide more equal access to the evaluation of mHealth technologies from the point of view of different stakeholders (i.e. for-profit vs non-profit).

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

The authors contributed to this paper as follows: Conception and design: MS, GS, GM, SS; Administrative support: MS, GS, GM, SS; Provision of study materials or participants: BC, GL, LA, SP; Collection and assembly of data: BC, GL, LA, SP; Data analysis and interpretation: MS, SA, GM, SS; Manuscript writing: all authors; Final approval of manuscript: all authors

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ERRATA CORRIGE

The original version of this article unfortunately contained some mistakes. These errors were corrected.

ERRATA

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CORRIGE

J PREV MED HYG 2021; 62: E257-E268. <https://doi.org/10.15167/2421-4248/jpmh2021.62.1.1832>

REVIEW

Immunogenicity and antibody persistence of diphtheria-tetanus-acellular pertussis vaccination in adolescents and adults: a systematic review of the literature showed different responses to the available vaccines

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Keywords

Immunogenicity • Antibody persistence • Diphtheria-tetanus-acellular pertussis vaccination • Adolescents • Adults

Summary

Introduction. In industrialized countries, the routine use of *Bordetella pertussis* vaccines has shifted the burden of *Bordetella pertussis* disease from children to infants, adolescents and adults, leading to the necessity for booster doses.

Materials and methods. We prepared a review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) with the aims of: a) describing the immunogenicity of the main available vaccines for adolescents and adults; b) describing antibody persistence after immunization with the main vaccines available in childhood and adults and, also, possible co-administration; and c) identifying the gold standard for adolescent and adult immunizations.

Results. We identified 6,906 records. After removing duplicate

records, we included 12 RCT (Randomized Controlled Trial) (people aged 11-73): 7 of these studies had only 1 control group, 4 had 2 control groups and 1 had 5 control groups; moreover, of the 12 studies included, only 2 regarded co-administration, while all concerned immunogenicity. Nine of the 12 studies had a Jadad score above 3 points, and 10 out of 12 met the criteria of Cochrane Back Review Group Criteria List for Methodological Quality Assessment.

Discussion and conclusion. We found a limited number of good-quality RCTs investigating our object. The 5-component vaccines, although containing a lower dose of antigen, proved more effective than the 1-component vaccine. Evidence supports the use of 5-component vaccines for booster sessions in adolescence and adulthood.

Introduction

In industrialized countries, the routine use of *Bordetella pertussis* vaccines has shifted the burden of *Bordetella pertussis* disease from children to infants, adolescents and adults [1]. Although this disease is not generally as severe in adolescents and adults as in infants, it nevertheless has a heavy impact on morbidity

and mortality; furthermore, these older age-groups are often the reservoir of infection for infants [2]. As the incidence of *Bordetella pertussis* in adults and older individuals has been seen to be increasing, reduced-dose acellular *Bordetella pertussis* vaccines combined with diphtheria and tetanus toxoids (Tdap) safe and efficacy are required. The goals of Tdap booster doses are to

protect older vaccinees, reduce the circulation of the bacterium, and thereby protect young infants [3]. Responses to immunization vary according to the different vaccines used and the immunization and infection history of vaccinees; in the scientific literature, immunity is evaluated through the assay of IgG anti-pertussis toxin (IgG anti-PT) antibodies by means of the ELISA method [4].

The following vaccines are currently available: Tdap5 vaccine, produced by Sanofi Pasteur [5], which is an adsorbed combination vaccine containing purified diphtheria and tetanus toxoids and five purified components of *Bordetella pertussis*; Tdap3, which contains purified diphtheria and tetanus toxoids and 3 purified components of *Bordetella pertussis* and is produced by Glaxo-Smith Kline [6]; and Tdap1, which is a combined adsorbed tetanus, low-dose diphtheria and monocomponent ap vaccine produced by Statens Serum Institut [7].

The aims of the present study were: a) to describe the immunogenicity of the main available vaccines for adolescents and adults; b) to describe antibody persistence in adults after immunization with the main vaccines available and, also the possible co-administration of these vaccines; c) identifying the gold standard for adolescent and adult immunizations.

Materials and methods

In accordance with PRISMA guidelines [8], we searched the main scientific libraries (PubMed including MEDLINE, Web of Science and Embase) for randomised controlled trials, cohort studies, or longitudinal studies reporting the immunogenicity and persistence of antibodies against diphtheria tetanus pertussis, for articles indexed up to the date of the search, with no language restrictions. Table I shows the keywords search strategy for one database, Web of Science. Studies were included if they investigated vaccine-induced immunity in healthy individuals who received a DTPa and Tdap vaccine, including different dosages and time-points of vaccine administration. Studies featuring child or maternal immunity, those with only one arm, and those that were not randomized were excluded. We excluded all case studies/reports, letter to editors, review papers, personal opinions and any other type of study with inconsistent data or which did not report original data. We also conducted hand searches of the reference lists of included studies and related reviews. We exported all studies retrieved from the electronic searches for deduplication and screening. Two review authors (CG and RS) independently screened the titles and abstracts to identify potentially eligible studies, and any disagreements between the two authors were resolved by discussion and consensus. We obtained the full texts of all potentially eligible studies. Two authors (RS and CG) independently screened the full texts and identified included studies, resolving discrepancies through discussion and consensus.

DATA EXTRACTION

Two independent reviewers (CG and RS) identified potentially relevant articles and collected the following data: first author's last name; year of publication; study design; total number of participants; age range; gender; exclusion criteria and study arms with number of vaccinated participants in each arm.

EVALUATION OF STUDY QUALITY

Two reviewers (CG, RS) independently assessed the quality of individual studies included in the systematic review. The Jadad scale for reporting randomised controlled trials (RCTs) was employed [9]. This assigns an overall score of the methodological quality of a study from zero to five. We also evaluated the studies according to the Cochrane risk of bias tool for randomized controlled trials [10]. The domains assessed are: randomization method, allocation concealed, similar baseline, patient-blinded, provider-blinded, assessor-blinded, co-intervention avoided, acceptable compliance, acceptable drop-out rate, timing of outcome assessment similar and intention-to-treat analysis. The studies were included also with low quality scores, but it was taken into account when describing the results.

Results

Of 6906 records identified, after removing duplicate records, we selected 34 for full text review (Fig. 1) and, finally, 12 were discussed (Tab. II). The composition of included vaccines was reported in Table III.

Description of studies

STUDY DESIGN AND POPULATION

All the studies included were randomized trials. Their characteristics are summarized in Table II. Twelve RCT were included in our review; of these, 7 had only 1 control group, 4 had 2 control groups and 1 had 5 control groups; moreover, of the 12 studies included, only 2 regarded co-administration [12, 14], while all were about immunogenicity [11-22]. The studies were conducted among people aged 11-73 years: Tdap1 in subjects aged 14-55; Tdap3 (GSK) in subjects aged 18-73; dTap3 (BNT) in those aged 18-35; and Tdap5 in those aged 11-72. The composition of the vaccines is reported in Table I.

Four studies were conducted in Europe [11, 12, 20, 21], one in Asia [19], one in America [22], seven studies were multi-centre [13, 14, 17, 18, 20, 22], and four were conducted in more than one country [15, 17, 18, 20].

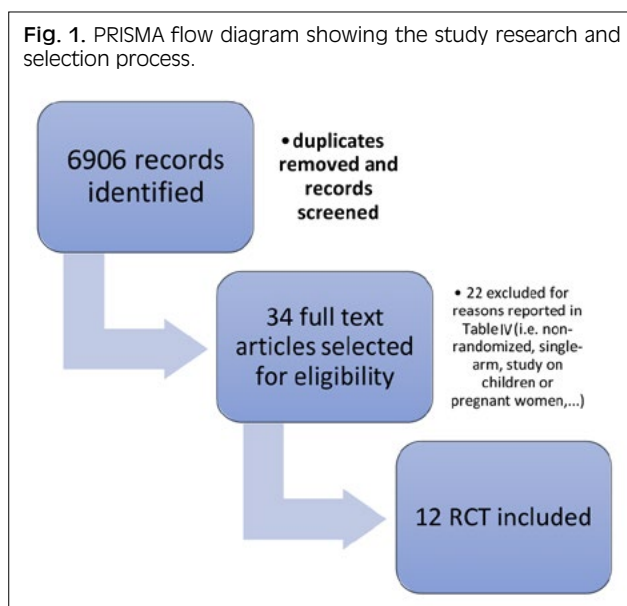
Disease background or exclusion criteria of the studies included were: a history of significant medical illness; the presence of any progressive or severe neurological disorder, seizure disorder or Guillain-Barre syndrome; immunodeficiency; administration of any diphtheria or tetanus or pertussis vaccine prior to enrolment in the study or history of allergy to any vaccine component;

Tab. I. Research strategy.

Adults [^]	TS = ((Diphtheria Tetanus Pertussis Vaccine or Vaccine, Diphtheria-Tetanus-Pertussis or DTwP Vaccine or Vaccine, DTwP or DPT Vaccine or Vaccine, DPT or DTP Vaccine or Vaccine, DTP or Di-Te-Per Vaccine or Di Te Per Vaccine or Vaccine, Di-Te-Per or Diphtheria-Pertussis-Tetanus Vaccine or Diphtheria Pertussis Tetanus Vaccine or Vaccine, Diphtheria-Pertussis-Tetanus) and (Case-Control Study or Studies, Case-Control or Study, Case-Control or Case-Comparison Studies or Case Comparison Studies or Case-Comparison Study or Studies, Case-Comparison or Study, Case-Comparison or Case-Compeer Studies or Studies, Case-Compeer or Case-Referrent Studies or Case Referrent Studies or Case-Referrent Study or Studies, Case-Referrent or Study, Case-Referrent or Case-Referrent Studies or Case Referrent Studies or Case-Referrent Study or Studies, Case-Referrent or Study, Case-Referrent or Case-Base Studies or Case Base Studies or Studies, Case-Base or Case Control Studies or Case Control Study or Studies, Case Control or Study, Case Control or Nested Case-Control Studies or Case-Control Studies, Nested or Case-Control Study, Nested or Nested Case Control Studies or Nested Case-Control Study or Studies, Nested Case-Control or Study, Nested Case-Control or Matched Case-Control Studies or Case-Control Studies, Matched or Case-Control Study, Matched or Matched Case Control Studies or Matched Case-Control Study or Studies, Matched Case-Control or Study, Matched Case-Control or Cohort Study or Studies, Cohort or Study, Cohort or Concurrent Studies or Studies, Concurrent or Concurrent Study or Study, Concurrent or Closed Cohort Studies or Cohort Studies, Closed or Closed Cohort Study or Cohort Study, Closed or Study, Closed Cohort or Studies, Closed Cohort or Analysis, Cohort or Cohort Analysis or Analyses, Cohort or Cohort Analyses or Historical Cohort Studies or Cohort Study, Historical or Historical Cohort Study or Study, Historical Cohort or Cohort Studies, Historical or Studies, Historical Cohort or Incidence Studies or Incidence Study or Studies, Incidence or Study, Incidence or Vaccinations or Immunization, Active or Active Immunization or Active Immunizations or Immunizations, Active or Intervention Study or randomized controlled trial or Clinical Trial, Phase 4) NOT ("ANIMALS" NOT "humans")
Adolescents	TS = ((Diphtheria Tetanus Pertussis Vaccine or Vaccine, Diphtheria-Tetanus-Pertussis or DTwP Vaccine or Vaccine, DTwP or DPT Vaccine or Vaccine, DPT or DTP Vaccine or Vaccine, DTP or Di-Te-Per Vaccine or Di Te Per Vaccine or Vaccine, Di-Te-Per or Diphtheria-Pertussis-Tetanus Vaccine or Diphtheria Pertussis Tetanus Vaccine or Vaccine, Diphtheria-Pertussis-Tetanus) and (Case-Control Study or Studies, Case-Control or Study, Case-Control or Case-Comparison Studies or Case Comparison Studies or Case-Comparison Study or Studies, Case-Comparison or Study, Case-Comparison or Case-Compeer Studies or Studies, Case-Compeer or Case-Referrent Studies or Case Referrent Studies or Case-Referrent Study or Studies, Case-Referrent or Study, Case-Referrent or Case-Referrent Studies or Case Referrent Studies or Case-Referrent Study or Studies, Case-Referrent or Study, Case-Referrent or Case-Base Studies or Case Base Studies or Studies, Case-Base or Case Control Studies or Case Control Study or Studies, Case Control or Study, Case Control or Nested Case-Control Studies or Case-Control Studies, Nested or Case-Control Study, Nested or Nested Case Control Studies or Nested Case-Control Study or Studies, Nested Case-Control or Study, Nested Case-Control or Matched Case-Control Studies or Case-Control Studies, Matched or Case-Control Study, Matched or Matched Case Control Studies or Matched Case-Control Study or Studies, Matched Case-Control or Study, Matched Case-Control or Cohort Study or Studies, Cohort or Study, Cohort or Concurrent Studies or Studies, Concurrent or Concurrent Study or Study, Concurrent or Closed Cohort Studies or Cohort Studies, Closed or Closed Cohort Study or Cohort Study, Closed or Study, Closed Cohort or Studies, Closed Cohort or Analysis, Cohort or Cohort Analysis or Analyses, Cohort or Cohort Analyses or Historical Cohort Studies or Cohort Study, Historical or Historical Cohort Study or Study, Historical Cohort or Cohort Studies, Historical or Studies, Historical Cohort or Incidence Studies or Incidence Study or Studies, Incidence or Study, Incidence or Vaccinations or Immunization, Active or Active Immunization or Active Immunizations or Immunizations, Active or Intervention Study or randomized controlled trial or Clinical Trial, Phase 4) NOT ("ANIMALS" NOT "humans") and (Adolescence, Adolescents, Adolescents, Female - Adolescents, Male Teenagers, Teens and Youth)

[^]In accordance with guidelines, no age restriction was used; to avoid limiting search results, we did not use the word "adult" to screen references.

Fig. 1. PRISMA flow diagram showing the study research and selection process.



pregnancy or breastfeeding. For details, see Supplementary Table I.

The risk of bias in the studies included is summarized in Table IV.

We excluded 22 studies [23-44] from our analysis because they did not meet any inclusion criteria (Supplementary Tab. I).

Seroconversion, antibody persistence and adverse events in adolescents and adults

The 12 RCT included in our analysis are described below.

Carlsson et al. [11] reported the results of a non-blind RCT (see risk of bias in Tab. III) with two vaccines, a Tdap5 and Tdap1 [5, 7]. Briefly, children born in 1994 were invited to participate in booster studies of immunogenicity and reactogenicity on two separate occasions: a

Tab. II. Studies included in systematic review.

Reference	Year of publication	Study design	Total n. of participants	Age range	Gender	Arm 1	Arm 2
Carlsson [11]	2015	RCT	230	14-15	Both	114 (Tdap5)	113 (Tdap1)
Embree [12]	2015	RCT	236	11-14	Both	144 (Tdap5 -Polio) HepB 1 month later	132 (Tdap5-Polio) HepB concurrently
Halperin [13]	2012	RCT	769	20-72	Both	407 (Naive Tdap)	362 (Repeat dose group Tdap5)
McNeil [14]	2007	RCT	720	19-64	Both	359 (Tdap5 concomitant administration with flu)	361 (Tdap5 sequential administration with flu)
Halperin [15]	2000	RCT	1,207	12-60	Both	Adolescents [^] Adults ^{^^}	Adolescents [^] Adults ^{^^}
Jahnmatz [16]	2014	RCT	230	14-15	Both	Tdap1	Tdap5
Halperin [17]	2000	RCT	749	12-55	Both	151* (Td)	449* (Tdap5)
Halperin [18]	2019	RCT	1,330	18-65	Both	1002 (Tdap5)	328 (Td)
Sirivichayakul [19]	2017	RCT	60	18-35	Both	20° (Tdap5)	20° BNA'S Tdap3
Van der Wielen [20]	2000	RCT	299	18-73	Both	96§ (Tdap3)	98§ (Td)
Thierry-Carstensen [21]	2012	RCT	802	18-55	Both	401 (Tdap1)	401 (Td)
Pichichero [22]	2005	RCT	4,480	11-64	Both	3053 (Tdap5) [§]	1427 (Td) [§]

[^] Adolescent cohort 1: Td-IPV at visit 1 and aP at visit 2; cohort 2: Tdap-IPV.

^{^^} Adults: cohort 1: Td at visit 1 and aP at visit 2; cohort 2: Tdap at visit 1 and IPV at visit 2; cohort 3: Tdap at visit 1 and aP at visit 2; cohort 4: Tdap-IPV.

* Cohort 3: n = 149 aP (5 components).

° Cohort 3: n = 20 BNA's aP (3 components).

§ cohort 3: n = 96 aP (3 components).

§ Adolescent cohort 1: n = 1,232 Tdap5; cohort 2: n = 821 Td.

Adults: cohort 1: n = 1,821 Tdap5; cohort 2: n = 606 Td.

Tab. III. Composition of dTpa vaccines analyzed.

Antigen	dTpa (1) AJ Vaccines	dTpa (3) GSK	dTpa (5) Sanofi Pasteur	dTpa (3) Bionet
Diphtheria toxoid (DT)	Not less than 2 UI	Not less than 2 UI	Not less than 2 UI	Not less than 2 UI
Tetanus toxoid (TT)	Not less than 20 UI	Not less than 20 UI	Not less than 20 UI	Not less than 20 UI
Pertussis toxoid (PT)	20 µg	8 µg	2,5 µg	5 µg
Filamentous hemagglutinin (FHA)	---	8 µg	5 µg	5 µg
Pertactin (PRN)	---	2.5 µg	3 µg	2.5 µg
Fimbriae type 2/3	---	---	5 µg	-

booster study of the DTaP5 vaccine in 1999 at age 5 years, and a second one with the same Tdap5 and a monocomponent (Tdap1) vaccine in 2009 at age 14-15 years [11]. Both studies used an open, randomized, parallel-group multicentre study design with blinded seroanalyses. The lower and upper limits of anti-PT after Tdap5 and Tdap1 were similar; regarding reactogenicity, fever, moderate or severe headache and moderate to severe swelling ≥ 2.5 at

the injection site were reported more often after Tdap1 than Tdap5 (RR 2, 1.4 and 1.5, respectively).

Embree et al. [12] evaluated serological assays (pre-vaccination, at 1 month, and 3-5-10 years after immunization) and co-administration (see co-administration section for description).

At 1-month post-vaccination, the seroprotection rates were comparable between the groups and remained

Tab. IV. Risk of bias in included studies.

First author's name and year	Jadad score	Cochrane ^a
Carlsson, 2015 [11]	3	6/10
Embree, 2015 [12]	3	7/10
Halperin, 2012 [13]	1	4/10
McNeil, 2007 [14]	3	7/10
Halperin, 2000 [15]	5	9/10
Jahnmatz, 2014 [16]	1	4/10
Halperin, 2000 [17]	5	9/10
Halperin, 2019 [18]	3	6/10
Sirivichayakul, 2017 [19]	3	9/10
Van der Wielen, 2000 [20]	5	7/10
Thierry-Carstensen, 2012 [21]	2	6/10
Pichichero, 2005 [22]	5	9/10

^a We reported the number of domains fitted by the study (ten domains were analyzed: randomization method, allocation concealed, similar baseline, patient blinded, provider blinded, assessor blinded, co-intervention avoided, acceptable compliance, acceptable drop-out rate, timing of outcome assessment similar and intention-to-treat analysis).

high for up to 10 years post-vaccination for diphtheria, tetanus and poliomyelitis, but subsequently returned to pre-vaccination levels. Anti-pertussis Geometric Mean Titers (GMTs) declined over time: anti-PT displayed the lowest percentage of participants with detectable antibodies after 10 years (74.1%) while the percentages of the other three antigens were higher. No serious adverse events were reported.

Halperin et al. [13] showed that the proportion of participants displaying a booster response to Tdap5 vaccination was similar in the naïve group and the repeat-dose group, demonstrating that a second dose of a five-pertussis-component Tdap in adults was safe and immunogenic in comparison with adults in the naïve group. A solicited adverse event was reported by just over 92% of recipients of Tdap and there were no differences in rates of any adverse events.

McNeil et al. [14] performed a study on the concomitant administration of Tdap and trivalent inactivated influenza vaccines or influenza vaccine followed (in 4-6 weeks) by Tdap. For this purpose, they enrolled 720 healthy subjects aged 19-64 years. Regarding diphtheria and tetanus, seroprotection rates and post-vaccination GMTs were non-inferior in the concomitant administration group compared with the sequential administration group. A trend towards lower antibody responses to *Bordetella pertussis* antigens PT, FHA and FIM was observed after concomitant administration, and in the case of PRN, this difference failed the non-inferiority criteria. Halperin et al. [15] performed an RCT to evaluate the safety of and antibody response to a single dose of an adult formulation of a Tdap5 and inactivated poliovirus vaccine (Tdap-IPV) in adolescents and adults, and to assess the response to a second dose of the acellular pertussis vaccine in a subset of the adults. The antibody response against *Bordetella pertussis* antigens was vigorous in all groups, although adults given the Tdap-IPV vaccine had lower antibody titers against filamentous hemagglutinin, pertactin, diphtheria and tetanus toxoids than those given Tdap vaccine. Similarly, adoles-

cents given Tdap-IPV had lower antibody titers against *Bordetella pertussis* toxin, filamentous hemagglutinin, fimbriae and agglutinins than those given Td-IPV and aP alone. A second dose of acellular *Bordetella pertussis* vaccine was not associated with increased adverse events in adults, but raised antibody titers above the level achieved by a single dose only against pertussis toxin.

Jahnmatz et al. [16] described a study on 230 adolescents (aged 14-15 years) in an open-label, randomized multicenter study without a control group and with blinded analysis. Both vaccine groups had significant increases in *Bordetella pertussis* toxin-specific serum IgG levels, and the 5-component group had significant increases in filamentous hemagglutinin- and pertactin-specific memory B-cell and serum IgG levels; these were not seen in the 1-component group, as expected.

Halperin et al. [17] measured antibody levels before and one month after immunization and investigated adverse events (at 24 h, 72 h and 8 to 10 days). They did not find statistically significant differences in tetanus and diphtheria antitoxin levels between recipients of Td and Tdap, and the antibody response against *Bordetella pertussis* antigens was vigorous in all groups. Adverse events were reported with similar frequency among the three vaccine groups. Moderate pain at the injection site was reported less frequently in the aP group than the Tdap group (RR = 0.4) and chills were reported less frequently after Td than after Tdap (RR = 0.4).

Halperin et al. [18] found a robust antibody response to each *Bordetella pertussis* antigen in the Tdap-vaccinated group, while post-vaccination geometric mean concentrations of tetanus and diphtheria antibodies were similar in the Tdap and Td groups with seroprotection rates > 99%. A solicited adverse event was reported by 87.7% of Tdap and 88.0% of Td vaccine recipients. No significant differences in the rates of local and systemic reactions between the vaccine groups were found.

Sirivichayakul et al. [19] enrolled only 60 subjects in 3 cohorts randomized to receive one of the vaccines in study, as reported in the Table II. Safety follow-up was performed for one month, while immunogenicity was assessed at the baseline and at 7 and 28 days after vaccination. One month after vaccination, seroresponse rates of anti-PT, anti-FHA and anti-PRN IgG antibodies exceeded 78% in all vaccine groups. Although the authors concluded that, in this clinical study, PTgen-based BioNet's aP and Tdap vaccines showed similar tolerability and safety profiles to those of Tdap5, the sample size was very small and moreover, follow-up was too short.

Van der Wielen et al. [20] evaluated responses to a Tdap3 vaccine. In all groups, adverse reactions were infrequent and no serious ones were reported during the study; the incidence of local and systemic reactions following the administration of Tdap or Td vaccine was comparable. One month after vaccination, a similar percentage of subjects in the Tdap and Td groups had anti-diphtheria, anti-tetanus, anti-FHA and anti-PRN antibodies, while the anti-PT vaccine response rates were 96.8 and 100.0%, respectively, for Tdap3 and aP.

Thierry-Carstensen et al. [21] showed antibody responses (anti-PT) in adults aged 18-55 years in 92% of cases. The frequencies of solicited local adverse reactions were low and comparable between Tdap and Td vaccinees. In the Tdap group, 30.7% reported pain, 4.2% swelling and 2.0% erythema at the injection site. The most frequent solicited general symptoms were headache (20.4%), fatigue (17.0%) and myalgia (10.0%).

Pichichero et al. [22] showed that Tdap5 elicited robust immune responses to *Bordetella pertussis*, tetanus, and diphtheria antigens in adolescents and adults, while exhibiting an overall safety profile similar to that of a licensed Td vaccine; these data support the potential routine use of this Tdap vaccine in adolescents and adults. Indeed, 94% of Tdap recipients had protective antibody concentrations of at least 0.1 IU/mL against diphtheria and tetanus. Geometric mean antibody titers against the five antigens of *Bordetella pertussis* used exceeded (by 2.1 to 5.4 times) levels in infants following immunization with DTaP at 2, 4 and 6 months. The safety profile was similar in the Tdap and Td groups.

Co-administration

Two studies [12, 14] evaluated the co-administration of dTdap5 with flu and with hepatitis B vaccines in adolescents and adults.

In the study by Embree et al. [12], no clinically relevant interference was observed on co-administration of Tdap5-IPV and HepB. Participants achieved seroprotective levels against tetanus (100%) and diphtheria (98.6% of group 1 and 100% of group 2). The *Bordetella pertussis* antibody seroresponses 1 month after Tdap-IPV vaccination were comparable in groups 1 and 2, as measured by 4-fold increases in PT, FHA, FIM and PRN.

McNeil [14] did not observe clinically relevant between-group differences (Tdap5 with flu or Tdap5 followed 1 month later by flu) in terms of safety; injection-site pain was the most commonly reported adverse event (66.6% concomitant administration group vs 60.8% sequential administration group), showing the possibility of concomitant administration.

In our analysis, we identified several studies on the co-administration of reduced-antigen content vaccines indicated for boosters in adults (Tdap3 and Tdap5), while no evidence emerged to support the co-administration of the Tdap1 vaccine with others one (such as HBV, flu, etc.).

Discussion and conclusion

In our systematic review, we observed that all vaccines were immunogenic but, as expected, the contents and concentrations of antigens influenced the responses.

In the study by Jahnmatz et al. [15], the authors found that the 1-component vaccine induced higher levels of PT-specific memory B cells than the 5-component vac-

cine, which could be explained by the higher concentration of antigen in the 1-component vaccine.

The 5-component vaccine, on the other hand, produced broader responses, with increases in both FHA- and PRN-specific memory B cells. Furthermore, this vaccine also elicited PT antibodies [11-18, 22, 31, 32].

It is important to establish the optimal antigen contents and concentrations to include in a booster dose, as we have shown here that these factors influence the extent of the vaccine response.

Regarding the immunogenicity and tolerability studies of Tdap vaccines, the authors of the Halperin studies [31] amply demonstrated that, on administering a booster dose of Tdap vaccine in adult subjects five years after the first vaccination, 100% and 95% of participants had protective levels of antibodies against tetanus and diphtheria, respectively). Furthermore, with regard to *Bordetella pertussis*, a post-vaccination antibody threshold of ≥ 50 IU/mL was seen in 82.1% (pertussis toxoid), 96.7% (filamentous haemagglutinin), 95.6% (pertactin) and 99.8% (fimbriae); this showed that a second dose of Tdap vaccine was immunogenic in adolescents and adults and was well tolerated (in fact, adverse events were slightly more frequent than after the initial dose) [31]. In the immunogenicity, reactogenicity and safety study by Asatryan et al. [32], one month after the administration of a single dose of Tdap vaccine all subjects (> 99.0%) enrolled were seroprotected against diphtheria and tetanus, and > 96.0% of the participants were seropositive for *Bordetella pertussis* antibodies. Furthermore, only one serious adverse event occurred, and this was not causally related to the vaccine under study.

With regard to the persistence of antibodies at 3, 5 and 10 years, there is a lack of long-term studies on the efficacy of the 1-component Tdap vaccine; such studies on the 3-component and 5-component Tdap vaccines are, however, available [11-22].

Below, we report the results of two robust follow-up studies: the first one evaluated antibody persistence after a single dose of Tdap vaccine (tetanus, diphtheria and acellular *Bordetella pertussis* 5-component vaccine) in a follow-up study of 3 RCTs [43] involving both adolescents and adults; this study amply demonstrated the presence of protective antibodies against diphtheria (99%) and tetanus antitoxin (100%). Seropositivity for one or more *Bordetella pertussis* antigens also persisted for 10 years in most of the subjects enrolled, and antibody levels remained high in nearly all adults. The second study, a follow-up study of 1 RCT, was conducted 1, 3, 5 and 10 years after immunization [44]; almost all adolescents and 91% of adults had diphtheria antibody levels > 0.01 IU/mL before receiving Tdap or Td vaccines. One month after vaccination, nearly all adolescents and 94% of adults in both study groups had diphtheria antibody levels > 0.1 IU/mL; this percentage decreased slightly to 95% at 5 and 10 years. Almost all adolescents and adults always had high levels of tetanus antibodies during the entire follow-up period. GMC antibodies against each *Bordetella pertussis* antigen contained in the Tdap vaccine decreased 1 month after vaccination but remained

higher than baseline levels at all follow-up times, with the exception of anti-PT after 5 and 10 years, which declined to near pre-vaccination levels in both adolescents and adults. The persistence of pertussis antibodies in adolescents followed a similar pattern to that observed in adults.

Therefore, the robustness of the data on antibody persistence in adults who receive vaccines with reduced antigen concentration is evident from the analysis of the present studies. This evidence is provided by RCTs and their related follow-up studies, which constitute an essential tool for monitoring the decay rate of antigens over time. However, we found a lack of follow-up studies on the persistence of antibodies against diphtheria-tetanus and *Bordetella pertussis* with regard to the 1-component Tdap vaccine.

Thus, according to the follow-up studies conducted to date on adults, it can be concluded that there are substantial differences regarding the possibility of administering booster doses in the different age-groups; this finding must guide the regulatory authorities.

On the basis of the RCTs included in our analysis and of the indications for use reported in each "Summary of Product Characteristics", we briefly analyzed the age limits at which the vaccines can be administered. Indeed, the 1-component Tdap vaccine is authorized for use in subjects aged up to 55 years (however, the short period of follow-up prevented the evaluation of long-term response) [16]. By contrast, studies on the persistence of antibodies elicited by the 3-component and 5-component Tdap vaccines [11-22] have involved subjects up to 76 and 79 years of age, respectively. Moreover, the CDC recommends these vaccines for all subjects over 65 years of age [45].

In our analysis, we identified several studies, both in children and in adults [12, 14], involving the co-administration of reduced-antigen content vaccines indicated for boosters in adults (Tdap3 and Tdap5) with other vaccines, such as hepatitis B, influenza, pneumococcal, meningococcal vaccines and HPV vaccines; however, there is a lack of evidence to support the co-administration of the Tdap1 vaccine with others one. Furthermore, vaccines with reduced antigen content display adequate immunogenicity, as demonstrated by non-inferiority studies, without yielding a clinically significant increase in reactogenicity [12, 14, 46-48].

A further problem noted in our review is the paucity of studies evaluating long-term immunogenicity and long-term persistence of antibodies elicited by the 1-component Tdap vaccine.

When a new treatment is studied, it is important to perform well-designed clinical trials; in particular, randomization, blindness, research duration and sample size calculation are key features to evaluate [49]. In our review, we noted some shortcomings in this area (as shown by bias evaluation) with regard to studies on the 1-component Tdap vaccine [11, 21].

In conclusion, we can confirm that few RCTs with a low risk of bias are currently available to guide us in choosing the best vaccine. However, the broadest antibody

response is elicited by the 3- or 5-component vaccines; the presence of antibody persistence, as demonstrated by the studies analyzed in this review, should prompt public health authorities to choose a vaccine with multiple *Bordetella pertussis* components (Tdap3 or Tdap5).

Although there is a lower content of *Bordetella pertussis* toxin in 2 out of 3 of the vaccines described, several studies support their use as vaccines during booster sessions in adolescence and/or in adults, and those with more components are generally considered more effective than a vaccine/Pa that contains only PT or even FHA [50]. Finally, as changes in circulating *Bordetella Pertussis* strains may affect vaccine efficacy, the incidence and transmission of *Bordetella pertussis* deserve to be closely monitored. In conclusion, although 3-component and 5-component vaccines contain a lower dose of antigen, they are more effective than 1-component vaccines in the prevention of diphtheria-tetanus and *Bordetella pertussis*, owing to the persistence of the antibodies elicited and the feasibility of their co-administration. The robustness of the data and the analytical tests support the use of vaccines with reduced antigen concentration for decennial booster sessions in adolescence and adulthood.

The Tdap vaccine remains of fundamental importance throughout life. Not only does it protect children through the "cocoon strategy" and immunize them in their early years, it also protects subjects who are at risk because of their working conditions or chronic diseases. Moreover, it can effectively be administered to all people every 10 years, given the demonstrated need for booster doses [51]. Finally, in order to protect infants in the post-partum period, the immunization of pregnant women is of paramount importance and is recommended in the third trimester of each gestation, regardless of the woman's vaccination history and the time that has elapsed since the previous gestation [52]. However, if women are not vaccinated during pregnancy, administration of the dTpa vaccine remains important. Indeed, the Advisory Committee on Immunization Practices recommends that all adolescents and adults who have, or who anticipate having, close contact with an infant younger than 12 months (siblings, parents, grandparents, child care providers and health care workers), and who have not previously undergone vaccination with the Tdap vaccine, should receive a single dose of Tdap at least 2 weeks before coming into close contact with an infant [53].

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Conflict of interest statement

The authors declare no conflict of interest.

Author's contribution

All authors carried out a systematic review to identify all scientific publications. Screening was carried out independently by the two authors (RS, CG). Any disagreement about eligibility between reviewers was resolved by discussion. The two authors extracted data from included papers using a data extraction form reviewed by each other. The two reviewers (CG and RS) identified potentially relevant articles, collected the data and independently assessed the quality of individual studies included.

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Supplementary Tab. I. Disease background and exclusion criteria of included study.

Reference	Disease background and exclusion criteria
Carlsson [11]	a. Serious chronic illness (cardiac or renal failure, failure to thrive, progressive neurological disease, uncontrolled epilepsy, infantile spasm) b. immunosuppression c. Previous culture-confirmed pertussis
Embree [12]	a. Any substantial underlying chronic disease (including malignancy; known impairment of neurological function or a seizure disorder of any etiology) b. Immunodeficiency, immunosuppression, or receipt of high-dose steroids c. Receipt of any pertussis-, diphtheria-, tetanus-, or poliomyelitis-containing vaccines or HBV vaccine within the previous 5 years; history of physician-diagnosed or laboratory-confirmed pertussis disease within the previous 2 years; receipt of blood products or immunoglobulins within the previous 3 months; receipt of any vaccine within 2 weeks of any study vaccine administration; or daily use of non-steroidal anti-inflammatory drugs d. Known or suspected allergy to any vaccine components in the study
Halperin [13]	a. Pregnant or nursing b. Allergic to Tdap vaccine or any of its constituents or to latex
McNeil [14]	a. Any significant underlying chronic disease (malignancy, neurological disease or seizure disorder requiring medication) b. Primary disease of the immune system or use of immunosuppressive therapy or daily non-steroidal anti-inflammatory therapy c. Received any Tdap vaccines within 5 years prior to enrolment, influenza vaccine during the current year, blood products or immunoglobulins within three months of enrolment, or if they had a history of physician-diagnosed or laboratory-confirmed pertussis disease within 2 years prior to enrolment d. Known or suspected allergy or previous adverse events to any of the vaccines or vaccine components being used in the trial e. Pregnant or breast feeding or unwilling to use effective contraception during the study
Halperin [15]	a. Significant underlying chronic illness and seizure disorder b. Known or suspected diseases of the immune system or immunosuppressive therapy, receipt of a blood product in the previous 3 months c. Receipt of any pertussis-, polio-, diphtheria- or tetanus-containing vaccine in the previous 5 year d. Allergy to a vaccine constituent, physician-diagnosed pertussis in the previous 2 years e. Pregnancy or planned pregnancy during the study period
Jahnmatz [16]	a. Clinical or bacteriological diagnosis of pertussis
Halperin [17]	a. Significant underlying chronic illness, seizure disorder b. Known or suspected diseases of the immune system or immunosuppressive therapy, receipt of a blood product in the previous 3 months c. Physician-diagnosed pertussis in the previous two years, or receipt of any pertussis-, diphtheria- or tetanus-containing vaccine in the previous 5 years d. Allergy to a vaccine constituent e. Pregnancy or planned pregnancy during the study period
Halperin [18]	a. Had a chronic illness or medical condition b. Suspected congenital or acquired immunodeficiency or had received blood or blood-derived products in the previous 3 months; had received any vaccine within 30 days before receiving study vaccine (except for flu vaccine, which was allowed up to 15 days before the study vaccine) or had plans to receive another vaccine before the second study visit; had participated in another interventional clinical trial; had reported seropositivity to HIV, HBV or HCV; thrombocytopenia or a bleeding disorder that would be a contraindication for an intramuscular injection c. Received any dtp vaccine since receipt of the qualifying dose of Tdap vaccine 8 to 12 years earlier or had physician-diagnosed or laboratory-confirmed pertussis in the previous 10 years d. Hypersensitivity or previous severe reaction to a pertussis-, tetanus-, or diphtheria-containing vaccine; Guillain-Barré syndrome; moderate or severe illness at the time of vaccination e. Pregnancy or breastfeeding
Sirivichayakul [19]	a. History of significant medical illness or individuals with any progressive or severe neurological disorder, seizure disorder or Guillain-Barré syndrome b. Immunodeficiency c. Having received any Diphtheria or Tetanus or Pertussis vaccine within 5 years prior to enrolment in the present study d. History of allergy to any vaccine component or history of serious adverse event or neurological adverse event after injection with DTP vaccine e. Pregnant or breastfeeding women f. History of alcoholism and/or intravenous drug abuse



Van der Wielen [20]	<ul style="list-style-type: none"> a. Administration of immunosuppressive/ immune-modifying drugs b. Previous vaccination against either diphtheria or tetanus within 5 years or vaccination against pertussis since childhood; a known history of diphtheria or tetanus; known exposure to diphtheria or pertussis within the previous 5 years; or a known history of non-response to diphtheria, tetanus or pertussis vaccination c. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine; or previous record, following DTP vaccination, of any serious adverse reaction or precautionary indication for DTP vaccination d. Administration of vaccines not foreseen by the protocol (one month before or after the start of the trial), of immunoglobulins and blood products (3 months prior or during the trial)
Thierry-Carstensen [21]	<ul style="list-style-type: none"> a. Progressive neurological disease, uncontrolled epilepsy, progressive encephalopathy b. Immune deficiency or administration of immune-modulating drugs ≤ 3 months before inclusion c. Tetanus, diphtheria, or pertussis vaccination or infection ≤ 5 years before inclusion d. Known hypersensitivity to any of the vaccine components e. Pregnancy f. vaccination with any vaccine ≤ 1 month before inclusion
Pichichero [22]	<ul style="list-style-type: none"> a. Malignancy, significant underlying disease, neurological impairment, acute respiratory illness b. Any immunodeficiency or daily use of oral nonsteroidal, anti-inflammatory drugs; receipt of blood products or immunoglobulins within 3 months c. Receipt of any DTP vaccine within 5 years; diagnosis of pertussis within 2 years d. Allergy or sensitivity to any vaccine component, including previous vaccine reactions e. Pregnancy

Supplementary Tab. II. Characteristics of excluded studies.

Study	Reason
Barkoff, 2012 [23]	Single-arm study evaluating the antibody response induced after booster vaccination and infection
Gustafsson, 1996 [24]	RCT evaluating serological response in child at 2, 4 and 6 months of age (range of age out of the aim of the study)
Ohfuji, 2015 [25]	Multicentre case-control study comparing the history of DTaP vaccination between 55 newly diagnosed pertussis cases and 90 age- and sex- matched controls
Keijzer-Veen, 2004 [26]	Observational study of reactivity of acellular pertussis vaccine in 4-year-olds
Hanvatananukul, 2020 [27]	Cross-sectional study to determine the seroprevalence of antibodies against DTP among Thai adolescents
Afari, 1996 [28]	RCT study of acellular DTP in southern Ghana on children under 5 years of age and women of fertile age
Halperin, 1995 [29]	RCT study of acellular pertussis vaccine as a booster dose for 17- to 19-month-old children previously immunized at 2, 4 and 6 months of age
Fortner, 2018 [30]	RCT study on pregnant and non-pregnant women
Halperin, 2011 [31]	Open-label, non-randomized, multicentre study in which participants in three previous randomized, controlled trials of Tdap received a second dose of Tdap vaccine
Asatryan, 2020 [32]	Phase III, open-label, non-randomized study
Cherry, 2010 [33]	Described other study performed in the 1980s and 1990s
Collins, 2004 [34]	RCT on immunogenicity and reactivity of two combined low-dose DTaP vaccines in children aged 3-3.5 years
Hori, 2016 [35]	RCT of two dtap vaccines in Ghana in 89 infants
Knuf, 2004 [36]	A controlled open-labelled double-blind trial with Biken acellular pertussis vaccine
Langley, 2005 [37]	RCT on children 4-6 years old
Schmitt, 1996 [38]	Blinded prospective follow-up of immunized children
Pichichero, 1996 [39]	RCT on 190 infants
Meyer, 2008 [40]	RCT on immunogenicity and reactivity in 4- to 6-year-old children
Trollfors, 2006 [41]	Open study on 502 10-year-old children
Tiru, 2000 [42]	Post hoc analysis
Tomovici, 2012 [43]	Follow-up study of 3 RCT
Pool, 2018 [44]	Follow-up of an RCT at 1, 3, 5 and 10 years post-vaccination

