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Contents

First wave of the COVID-19 pandemic in Madrid: handling the unexpected in a tertiary hospital

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Keywords

Summary

Introduction. *The COVID-19 pandemic was declared on March 11th, 2020. By the end of January, the first imported cases were detected in Spain and, by March, the number of cases was growing exponentially, causing the implementation of a national lockdown. Madrid has been one of the most affected regions in terms of both cases and deaths. The aim of this study is to describe the epidemic curve and the epidemiological features and outcomes of COVID-19 patients hospitalized in La Paz University Hospital, a tertiary hospital located in Madrid.*
Methods. *We included confirmed and probable COVID-19 cases admitted to our centre from February 26th to June 1st, 2020. We*
studied trends in hospitalization and ICU admissions using join-point regression analysis.
Results. *A sample of 2970 patients was obtained. Median age was 70 years old (IQR 55-82) and 54.8% of them were male. ICU admission rate was 8.7% with a mortality rate of 45.7%. Global CFR was 21.8%. Median time from symptom onset to death was 14 days (IQR 9-22).*
Conclusions. *We detected an admissions peak on March 21st followed by a descending trend, matching national and regional data. Age and sex distribution were comparable to further series nationally and in western countries.*

Introduction

Since a cluster of patients with pneumonia of unknown origin was detected in Wuhan, China [1], SARS-CoV-2 infections [2] have rapidly spiked around the world, with COVID-19 being declared a pandemic by WHO on March 11th 2020 [3].

On January 31st 2020, the first imported cases were detected in Spain and by February 28th, patients with no epidemic link started to be diagnosed. By March 13th, cases had been confirmed in all 50 provinces in the country and started to grow exponentially. Some non-pharmacological public health measures were implemented in order to control the epidemic, the most important being a national lockdown on March 14th. On March 26th, at the peak of the epidemic in Spain, 9181 cases were reported on a single day and up to 900 deaths were reported in one day. From April 28th on, as cases had been consistently decreasing, the country gradually started to reopen, and the state of alarm ended on June 21st.

In late February, the first series of patients with COVID-19 infection in China were published [4-6], with patients being predominantly adult males, and case fatality rates (CFR) ranging from 1.4 to 28.3% [4]. Following series in other countries present some variability in age and sex distribution and CFR, which can be explained by differences in the base populations, the burden of the epidemic and overload in healthcare facilities [7, 8].

The Community of Madrid was one of the most affected regions in Spain. It has registered the highest number of cases and deaths in the country. Healthcare facilities were overwhelmed and close to saturation, with limited capacity for testing all of the suspected cases during the peak of the epidemic. Surveillance systems were also challenged by the rapid surge in cases, with no capacity for contact tracing in mild cases.

La Paz University Hospital is a tertiary care public hospital located in Madrid, with 1300 beds and a catchment area with a population of more than 500000. In 2018, 48945 patients had been hospitalized in this centre.

The aim of this study is to describe the epidemic curve of hospitalization and the epidemiological features and outcomes of all of the patients admitted in our centre with confirmed or highly suspected infection by SARS-CoV-2 until June 1st 2020.

Methods

STUDY POPULATION

The current study included all individuals who were admitted to La Paz University Hospital from February 26th to June 1st 2020.

COVID-19 diagnosis included confirmed cases (any individual with positive reverse transcriptase

polymerase chain reaction (RT-PCR) assay) and probable cases (any individual meeting clinical criteria with an epidemiological link or radiological evidence compatible with SARS-CoV-2 infection) [9].

DATA COLLECTION

Data collection effort was conducted by the department of Preventive Medicine in La Paz University Hospital as a part of their regular activities. We registered every new patient admitted to the hospital daily on a database. The epidemiological data and outcomes (discharge, transfer or death) were obtained from electronic medical records, including clinical notes for date of symptoms onset (DXC-HCIS - Healthcare Information System). Country of origin was grouped following WHO regions. Intensive care unit (ICU) admissions were also recorded.

ETHICAL CONSIDERATIONS

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was reviewed and approved by the Research Ethics Committee of La Paz University Hospital (PI-4195).

STATISTICAL ANALYSIS

All statistical analysis was performed using R. Continuous variables were presented as means and standard deviations (SD) or medians and interquartile ranges (IQR), as appropriate. Categorical variables were summarized in terms of frequency (percentage).

Means for continuous variables were compared by independent group t-test when the data were normally distributed. The Mann-Whitney test was used when the data were non-normally distributed. Proportions in categorical variables were compared using the χ^2 test, although Fisher´s exact test was used in cases where data was limited.

Temporal trends in hospitalization and ICU admissions were evaluated using joinpoint regression analysis. This method describes changes in data trends by connecting different line segments by "joinpoints", or points where the trend significantly changes (increases or decreases). Those points are presented with a 95% confidence interval (95% CI). We also present daily percent changes (DPC) of the different trends identified. As all lines are based on the log-linear model, the joinpoint regression model is free from complex spline selections and sensitivity concerns [10]. Joinpoint analyses were performed using the Joinpoint software from the US National Cancer Institute [11].

Results

A total of 3007 COVID-19 patients were hospitalized in La Paz University Hospital before June 1st, 2020. After excluding 37 patients that were still hospitalized as of June 1st, the final analysis included 2970 individuals. Of these, 2627 were confirmed cases diagnosed by SARS-CoV-2 RNA detection while 343 were probable cases, diagnosed by clinical or radiological criteria.

Median age was 70 years (IQR 55-82) ranging from 0 to 102 years. Of all patients, 54.8% were male, while 45.2% were female. Median age in females was 71 years (IQR 55-83) while in men was 69 years (IQR 56-80), p-value = 0.01.

CFR was 21.8% and ICU admission rate was 8.7%. The ICU mortality rate was 45.7%. Patients' characteristics, sex differences and outcomes are presented in Table I.

Median age in patients with Europe as their WHO Region of birth was 74 years (IQR 61-84), whilst, in those from the Americas region, it was 52 years (IQR 40-60). ICU admission rate was 7.8% for the Europe region and 12.1% for the Americas region. Mortality rate for the Americas region was 8.1% while for the Europe region it was 24.8%.

Most patients hospitalized were males above 50 years of age. For patients admitted in the ICU, most of them were males aged between 60 and 70 years old. Age and sex distribution, and hospitalisation status are shown in Figure 1.

Tab. I. Patients' characteristics and outcomes.

	Global	Female	Male	p-value
Age *median years (IQR)*	70 (55-82)	71 (55-83)	69 (56-80)	0.01
Hospitalization				
Patients admitted	2970	1342 (45.2%)	1628 (54.8%)	
Patients who died	646 (21.8%)	232 (17.3%)	414 (25.4%)	< 0.01
ICU				
Patients admitted	258 (8.7%)	78 (5.8%)	180 (11.1%)	< 0.01
Patients who died	118 (45.7%)	29 (37.2%)	89 (49.4%)	0.06
WHO Region of birth				
Europe	2406 (81.0%)			
Americas	480 (16.2%)			
Eastern Mediterranean	25 (0.8%)			
Africa	5 (0.2%)			
South-Eastern Asia	7 (0.2%)			
Western Pacific	46 (1.6%)			

Fig. 1. COVID-19 hospitalized population pyramid. Age and gender distribution of hospitalizations are shown here. Hospitalization status is added in terms of ICU admissions and deaths, showing its age and gender distribution
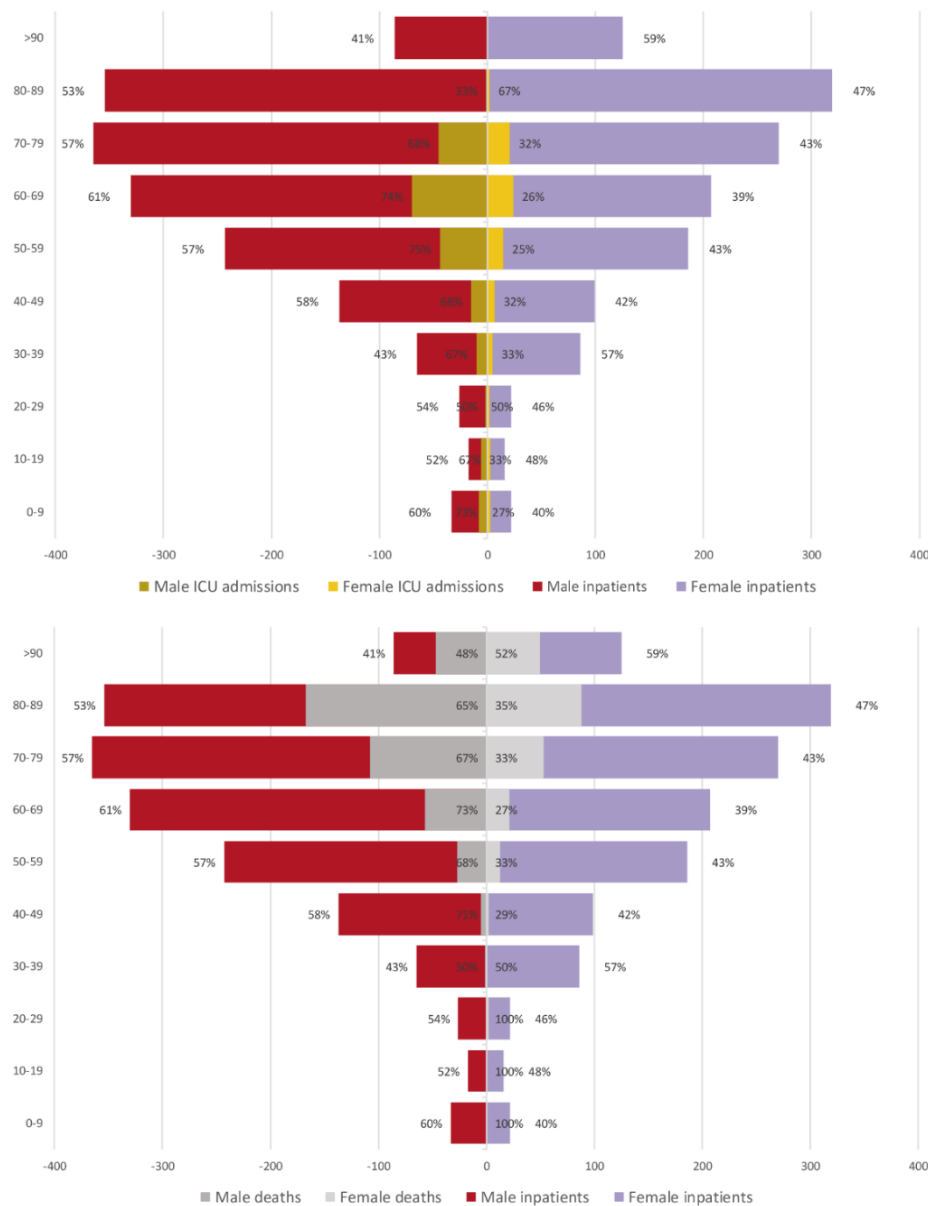
Figure 2 shows length of stay in days of hospitalization. Figure 3 shows time from symptom onset to hospital admission. Median length of hospital stay for all patients was 8 days (IQR 4-15). For critically ill patients, median length of hospital stay was 25 days (IQR 13-40). For patients who died during hospitalization, median length of hospital stay was 7 days (IQR 4-15).

Two comparisons were made regarding length of hospital stay: among patients who died and survivors, and among those who were admitted to ICU and those who weren't. Patients who died had shorter hospital stay. Patients admitted to ICU stayed longer. Differences were statistically significant.

Comparisons were made among patients who died and survivors and among those who were admitted

to ICU and those who weren't. Patients who died had less time from symptom onset to hospital admission. No significant differences were found regarding ICU admission status.

Median time from symptom onset to hospital admission was 7 days (IQR 5-10), being 7 days (IQR 5-10) for patients admitted in ICU and 6 days (IQR 3-9) for patients who ended up dying.

For patients admitted to the ICU, median stay in days of ICU was 12 (IQR 4-24), with a minimum of 0 days (less than 24 hours) and a maximum of 83. Median time, in days, from symptom onset to admission to the ICU was 10 (IQR 7-13).

Median time, in days, from symptom onset to death was 14 (IQR 9-22), with a minimum of 3 days and a

Fig. 2. Length of stay in days of hospitalization. Boxplot distribution is shown here.
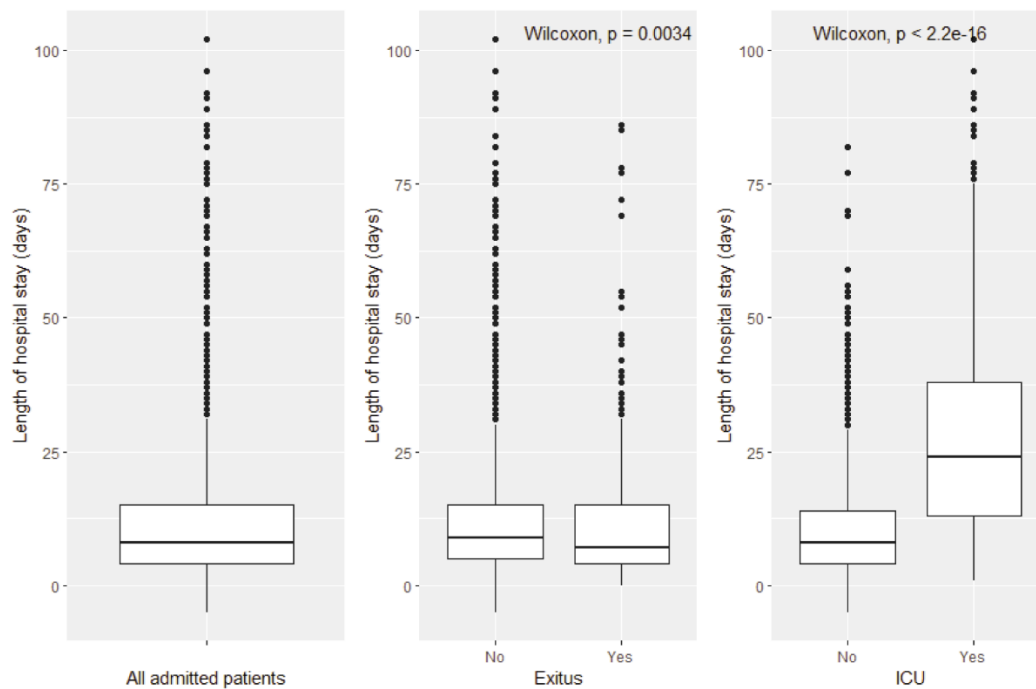
Fig. 3. Time from symptom onset to hospital admission. Boxplot distribution is shown.
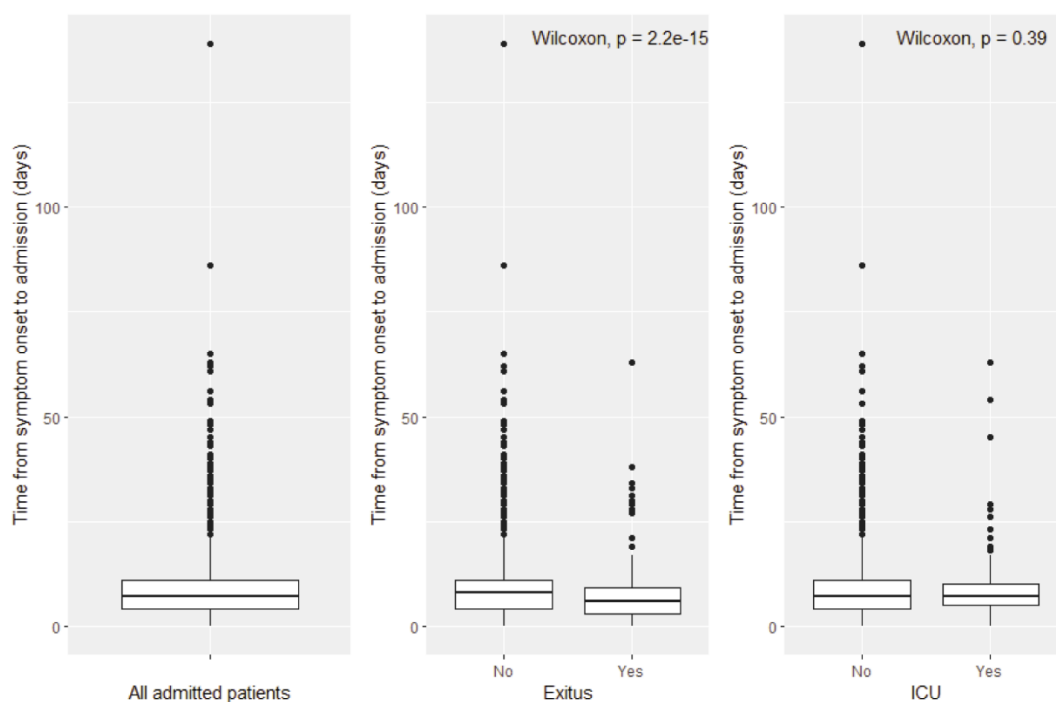
maximum of 100 days. For patients who died in the ICU, median time from symptom onset to death was 29 days (IQR 18-39).

TRENDS OF ADMISSIONS

The epidemic curve according to symptom onset date and date of diagnosis is shown in Figure 4.

On March 9th, (95% IC 6-17) a significant change in the trend of admitted patients was identified, and the joinpoint analysis revealed a significant decrease in the daily percent change (DPC) of admitted patients after that date (46.7% on the first segment versus 9.9% on the second one). An additional joinpoint was identified on March 21st (95% IC 19-28), signalling a change in

Fig. 4. Number of COVID-19 cases by date of diagnosis and date of symptom onset.
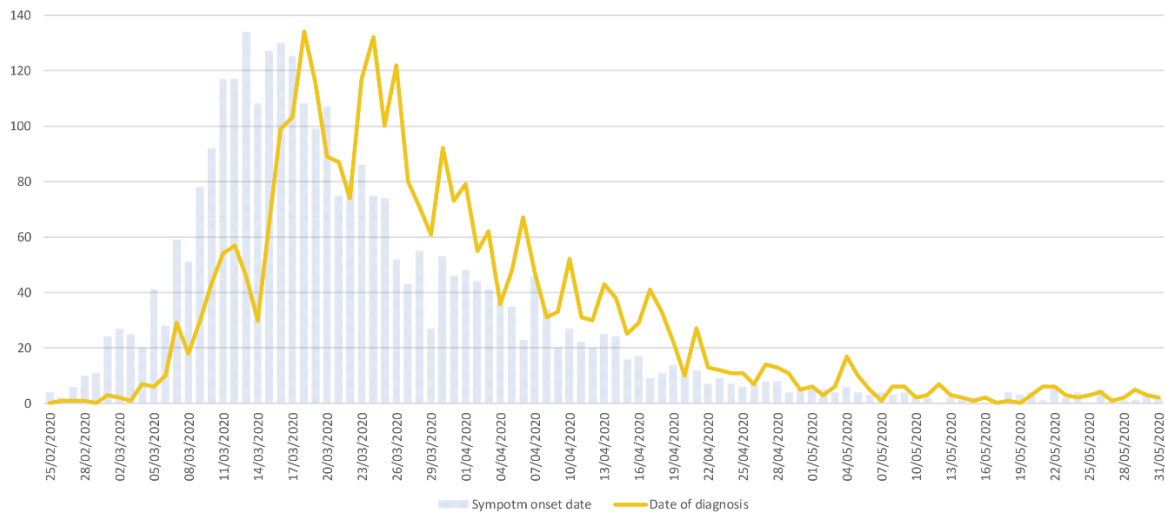
Fig. 5. Joinpoint regression model: admitted patients by date of diagnosis.
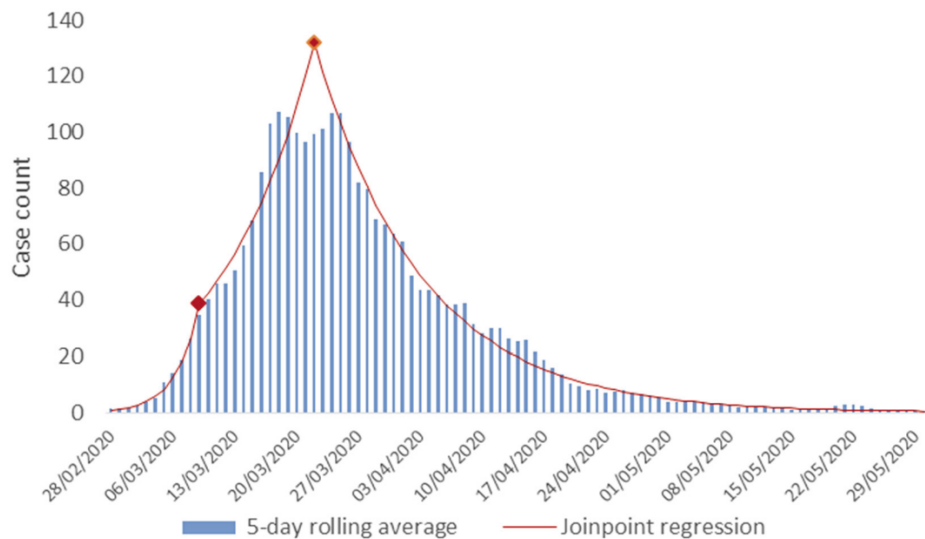
Fig. 6. Joinpoint regression model: ICU admissions.
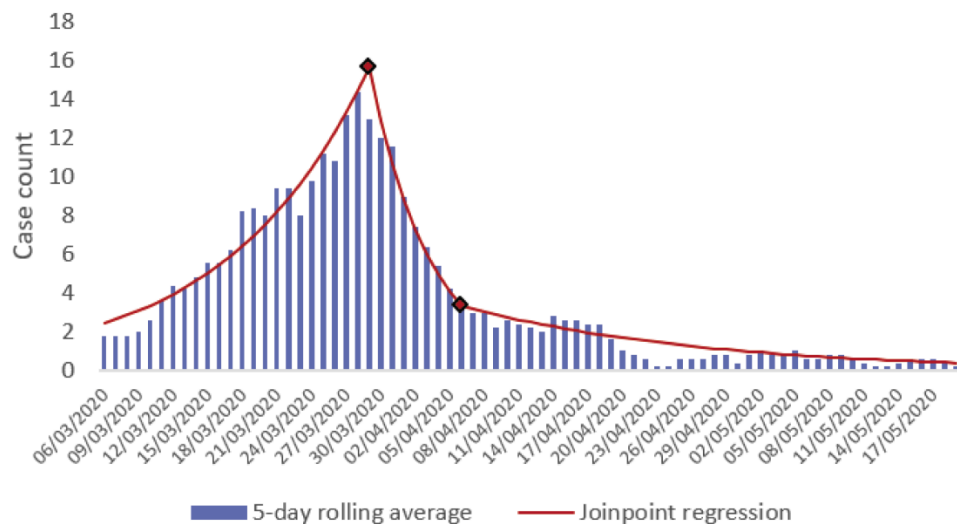
trend, with the number of admitted patients starting to decrease and the DPC going from the previous 9.9 to -7.9%.

TRENDS OF ICU ADMISSIONS

On March 22nd, (95% IC March 21st-25th) a significant trend change was detected in ICU admissions, going from a positive DPC to a negative one (8.4 vs -17.5%). On March 31st (95% IC March 29th-April 2nd) another joinpoint indicates a new change in trend, in this case not changing the direction, but slowing down the DPC from -17.5 to -4.8.

Discussion

The first confirmed COVID-19 case was admitted to our centre on February 25th, 2020. The present study describes a series of patients who were hospitalized with a COVID-19 diagnosis between that date and June 1st in La Paz University Hospital and trends of admissions over that period.

The evolution of the COVID-19 pandemic observed in our hospital was very similar to the epidemic curve observed in Spain and the whole Community of Madrid region. After some cases in February, an exponential growth was observed during the first weeks of March. Measures in response to the pandemic were taken nationally on March 14th under the state of alarm decree [12] and the epidemic curve reached its peak two weeks later, around March 26th, with 3383 new hospitalizations in the Community of Madrid region [13, 14].

In our study, a joinpoint regression detected a peak of COVID-19 hospital admissions on March 21th (95% IC 19-28) followed by a decrease, matching the observed regional and national data. The change in trend found on March 9th (95% IC 6-17) was not present in the epidemic curve of the Community of Madrid region or Spain. However, this change could be explained by the epidemic control measures adopted in Madrid on March 10th, which could have predisposed Madrid residents to move to second residencies in other regions, thus affecting the expected number of cases and hospitalizations [15].

Another aspect that affects the epidemic curve observed in our centre is hospital bed occupancy. Due to the exponential growth in cases, the hospital experienced progressive shortage of hospital beds, which influenced the number of new patients susceptible of admission.

To cope with the major pressure the pandemic put on the healthcare system, our hospital had to quickly increase the number of hospitalization and ICU beds.

Wards were organized as COVID-19 cohorts or "no COVID-19" wards. At the beginning of the pandemic there were only a few COVID-19 cohorts but, due to community transmission and the consequently rapid increase of cases, by mid-March almost every ward in the hospital was turned into a cohort. A few wards remained "no COVID-19", destined to care for vulnerable patients whose assistance could not be delayed (Haematology, Oncology, Nephrology, Stroke Unit, Coronary Unit and Emergency surgeries). To take care of critical patients, operating rooms and post-anaesthesia care units were adapted into ICU, making it possible to increase the ratio of ICU beds by 500%.

The age and sex distribution of our cohort is comparable to further series from Spain and other western countries [7,18,19]. Patients included in the first cohorts from China were younger (median age of 47 years in Guan et al. [4] and 56 in Zhou et al. series [20]), reflecting main differences in the demographic structure of the populations.

The proportion of patients admitted to an ICU was 8.7% and for most age groups, the proportion of males hospitalized and admitted to the ICU was significantly higher than females. A study in a secondary hospital in Madrid reported a lower figure (6.7%) despite having a similar distribution of sex and patients being younger [16]. This could be attributed to a difference in admission criteria in each hospital's ICU, as well as their capacity. Our centre, being a reference hospital, also received ICU patients transferred from other hospitals of the region.

CFR varies according to admission criteria (stricter admission criteria lead to higher CFR) and the distribution of sociodemographic variables in the population. It is also affected by the burden on the healthcare system, so two hospitals in a different region of the same country can show dramatic differences in the CFR, as shown in China when comparing Hubei with other regions [20]. Mortality in our cohort is similar to that observed in New York, another hotspot for COVID-19, [19] and lower than the UK multicentre cohort, which reported a 33% mortality [18]. However, it is much higher than the figure reported in Italy (7.2%), [7] likely because the work includes data from the whole country and not only the most affected regions (Lombardy and Veneto).

In our study, 16.2% of all patients were born in a country from the Americas WHO Region of birth. Approximately, 9.3% of the Community of Madrid population were born in America [21]. Most of these patients were from South and Central America and the Caribbean, only two patients of this region were North Americans. Our data showed that these patients were younger than European patients, with a difference of 20 years in median age, and had a higher ICU admission rate (12.1%), although their mortality rate was lower (8.1%). 97.8% of the Europe WHO Region of birth patients were Spanish. These findings are similar to those reported in other studies of the region [16].

Differences in age can be explained by the demographics of the Hispanic population in our country. Younger patients tend to have less comorbidities, thus having more chances to be admitted to an ICU and having a better prognosis. A systematic review and meta-analysis by Shirley Sze et al. which explored the relationship between ethnicity and clinical outcomes in COVID-19 did not find differences between Hispanic and non-Hispanic patients [22].

Despite all, our work has some limitations. First, the study included patients diagnosed by PCR (confirmed

cases) and patients diagnosed using clinical and epidemiological or radiological criteria (probable cases). Furthermore, case definition criteria changed during this period, only introducing probable case definition by the end of March 2020. Due to all of this, we cannot exclude heterogeneity among cases. Another potential bias is that we only included hospitalized patients, therefore we lack information about mild cases, which are more likely handled in Primary Health Care. In addition, due to the overload of Madrid Healthcare System, paediatric and maternal urgent care was redistributed, and our hospital was one of the few attending these patients. Because of this, our results cannot be widely generalized.

Nevertheless, the fact that our study was conducted in a tertiary hospital, including all admitted COVID-19 cases during Spain's first outbreak is proof of the relevance of this work. This allows for a big sample size which, despite the limitations, we believe is representative of the COVID-19 hospitalized Madrid population.

The use of joinpoint regression is another highlight from our study. Joinpoint regression models are useful tools to evaluate efficiently time-trend curves and to identify a phase change in the pandemic [23].

Conclusions

In summary, our hospital had to cope with a great number of COVID-19 patients and the exponential growth of admissions from the end of February until approximately a week after national lockdown (March 21st), when a peak in hospitalizations was detected. As reported in other studies, most affected patients were males over 50 years old. This group had both higher ICU admission and mortality rates.

Acknowledgements

Conflict of interest

All authors report no conflicts of interest relevant to this article.

Authors' contributions

LHR, EFB, TP, CGV, MCM and JMCE equally contributed to data collection, design of the study, performed the analysis, interpretation of results and drafting of the article.
VPB and ARR contributed to data collection, design of the study, interpretation of results, drafting of the article and revised the article critically.

Ethics approval and consent to participate

The study was approved by an ethical committee. This manuscript has been read and approved by all authors and has not been published and is not under consideration for publication elsewhere.

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COVID-19 - HEALTH CARE MANAGEMENT

Reorganization of Intensive Care Units for the COVID-19 pandemic: effects on nursing sensitive outcomes

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Keywords

COVID-19 • Hospital reorganization • Intensive care • Pandemic • Nursing outcomes • Healthcare-associated Infections

Summary

Background. *Since the first months of 2020 COVID-19 patients who were seriously ill due to the development of ARDS, required admission to the intensive care unit to ensure potentially life-saving mechanical ventilation and support for vital functions. To cope with this emergency, an extremely rapid reorganization of premises, services and staff, to dedicate an entire intensive care unit exclusively to SARS-CoV-2 patients and increasing the number of beds was essential. The aim of the study was to evaluate the effects of reorganization of the COVID-19 intensive care unit in terms of nursing sensitive outcomes.*

Methods. *a retrospective observational study was conducted to compare nursing sensitive outcomes between pre-COVID period and COVID period.*

Results. *Falls (0.0 and 0.4%, respectively), physical restraint (1.8 and 1.1%, respectively), and pressure ulcers (8.0 and 3.0%, respectively) were similar in the COVID and in the pre-COVID group. After adjusting for gender, age, BMI, and number of comorbidities, the incidence of bloodstream infections was significantly higher in the COVID group than in the pre-COVID group. There were no statistically significant differences in the incidence between the two groups regarding other evaluated outcomes.*

Conclusion. *The selected nursing sensitive outcomes maintained similar values in the pre-COVID and COVID patient groups. Healthcare-related infections rate must be considered an important alarm signal of quality of nursing care especially in conditions of excessive workload, stress and the presence of less experienced staff increase.*

Background

Coronaviruses, widely distributed among mammals and birds, constitute a heterogeneous group of large single-stranded RNA viruses. In some rare cases, the subspecies Coronavirinae, consisting of alpha and beta coronaviruses, can evolve and be transmitted from animals to humans [1]. At the end of 2019, the world witnessed the spread of a new coronavirus, named SARS-CoV-2, and taxonomically classified among the severe acute respiratory syndrome-related coronavirus (SARS-CoV) species, subgenus Sarbecovirus, genus betacoronavirus [2]. The novel coronavirus was initially referred to as novel coronavirus 2019 (2019-nCoV) and later officially renamed by the International Committee on Taxonomy of Viruses as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). With the term COVID-19, the disease caused by the virus has been called. Although the first outbreaks were identified in China in the Hubei region near the city of Wuhan [3], the rapidity with which it spread and its severe symptoms soon became a serious global public health threat. There were significant outbreaks in many regions of China, followed by a global spread in Asia, Australia and Oceania, Africa, Europe, North America, South America [4]. Uncertainty dominated the first months of 2020. Information regarding its actual transmission modes and speed was lacking [5]. Only during the following months, after the first experiences lived by the population and health personnel from all over the world, more information was available to describe the spectrum of clinical diseases associated with SARS-CoV-2, and the effectiveness of therapeutic and pharmacological treatments [6, 7].

The first cases of COVID-19 in Italy were detected in the third decade of February 2020, in the Lombardy region. Compared to the situation experienced in other countries in that period, the regions of Northern Italy were hit hard by the pandemic. At the end of March 2020, over 40% (42,161) of the total Italian cases (101,000) were in the Lombardy region. These numbers continued to rise, and by the end of June 2020 in Italy there were 237,000 positive cases and 34,400 deaths, classifying Italy as one of the most affected areas during the initial phases of the pandemic [8]. The first available studies from China described the main initial symptoms, which included fever, cough, headache, muscle pain, and fatigue. They also reported a high incidence of severe cases with acute respiratory distress syndrome (ARDS) (17-29%) and critical conditions, septic shock, metabolic acidosis, coagulopathy, and multi-organ failure (23-32%) in hospitalized patients [9, 10]. Similar incidence rates for critical conditions (16%) were also observed in Lombardy and Northern Italy [6, 11].

Following the initial scientific evidence and available guidelines, the critical clinical cases required immediate admission to intensive care units to receive life-saving treatments, such as mechanical ventilation and support for other vital functions [12].

The beds in hospitals and especially in the intensive care units (ICUs) were all occupied in a very short time. As in the rest of the world, also in Italy hospitals were equipped specifically for COVID-19 patients and the number of ICU beds was increased. The University Hospital of Pisa (in Central Italy) reorganized its spaces, services, staff and dedicated an entire intensive care unit exclusively to COVID-19 patients, and increased the number its beds to cope with the emergency caused by the pandemic. This type of reorganization, carried out in very little time, in the first week of February 2020, with new additional health personnel, was implemented to improve the quality of care for patients and the well-being of health personnel in the workplace. Higher numbers of beds in the COVID-19 intensive care unit, entailed the presence of more staff. This was possible through three main actions: (i) reduction of general ICU beds and transfer of specialized nurses to the COVID-19 ICU; (ii) selection of nurses with previous experience in critical and intensive care currently working in departments of other medical specialties to be transferred to the COVID-19 intensive care unit; (iii) the hiring of over 120 new nurses. Different nursing teams were set up by balancing the different skills of individual nurses within groups. The one-to-one ratio of experienced nurses to novice nurses was maintained [13]. To guide the members of each group and promptly identify clinical, organizational or health problems, nurse who were experts of intensive care and educational and organizational processes were selected and assigned to each group. This reorganization made it possible to admit all the COVID-19 patients who presented to the hospital. At the end of the emergency caused by the first wave of the pandemic, the authors decided to investigate – under the umbrella of a broader research project [14] that included also this study – how this rapid and thorough reorganization, together with the hiring of new staff, could affect the quality of the care provided. Even if numerically speaking, the hospital managed to admit all patients presenting with SARS-CoV-2 thanks to its reorganization, once the healthcare emergency phase was over, the researchers decided to investigate the effects produced by this reorganization in terms of nursing sensitive outcomes. In the literature there are many studies that report outcomes sensitive to nursing, and how to measure and interpret them [15-19].

The aim of this study was to evaluate the effects of staff and environment reorganization of the COVID-19 intensive care unit in the context of the pandemic and of the global health emergency in terms of nursing sensitive outcomes.

Methods

STUDY DESIGN AND DATA SOURCES

A cohort retrospective observational study was conducted to evaluate the effects of the reorganization of an intensive care unit (ICU) exclusively for COVID-19 patients in terms of nursing sensitive outcomes compared to ICU patients before the pandemic outbreak. This study followed the STROBE guidelines for observational studies [20]. This study was conducted in the ICU of a Teaching Hospital in Central Italy, between September 2019 and April 2020. The patients' data were collected in May 2020 through the hospital's database that includes data from the electronic medical records (EMRs). This database includes all the treatments provided by physicians, nurses, and various other health professionals, including patients' medical history, diagnoses, treatments, and medications.

STUDY POPULATION

The study population included all patients admitted to the study setting ICU in the period between September 2019 - February 2020 (pre-COVID period) and March 2020 - May 2020 (COVID period).

The index date was defined as the patient's date of admission to the ICU.

The follow-up period for each patient was defined as the time between the index date and the earliest of the following dates: date of transfer to a non-intensive ward, date of patient's death, or date of last data collected for this study.

Patients who stayed in the ICU for less than one day were excluded from the study.

MEASURES

The following patient characteristics were considered for our data analysis: age, sex, ethnic group, (comorbidities diagnosed before SARS-CoV-2 infection), and body mass index (BMI). In relation to the type of ventilatory therapy the patient was receiving, we considered: spontaneous breathing with oxygen, non-invasive ventilation (NIV), intubated/tracheostomized with mechanical ventilation.

In agreement with the major studies that have developed sets of indicators on the quality of nursing care in the ICU [21-24], the following were measured during this study: pressure ulcer incidence (patients who developed a pressure ulcer during stay in the ICU), incidence of falls (patients who fell with and without an injury during stay in the ICU), incidence of physical restraint (patients with physical restraint during stay in the ICU), mortality (deaths of to those in the ICU), incidence healthcare associated infections (HAIs) – cases presenting with HAIs during stay in the ICU: including urinary tract infections, bloodstream infections, local central venous catheter (CVC) associated infections, local peripheral venous catheter associated infections, and gastrointestinal tract infections.

Data analysis

Categorical variables were summarized by frequencies and percentages, and continuous variables by medians and interquartile ranges. Differences in the characteristics between the patients of the pre-COVID and COVID period were evaluated with Fisher's exact test and the Kruskal-Wallis test, for categorical and continuous variables, respectively.

Associations between the outcomes and length of stay were assessed using Poisson regression models. To obtain finite estimates for those outcomes that presented no occurrences either in the pre-COVID or COVID period, penalized Poisson regression models with Jeffreys prior were also fitted, without and with adjustment for age, sex, BMI, and number of comorbidities [25]. For all the Poisson regression models, the estimates and 95% confidence intervals for the incidence rate ratios (IRRs) of post-COVID *vs* COVID period were reported, together with the corresponding Wald tests p-values. All the statistical tests were two-sided, with a significance level of 0.05.

Statistical analyses were performed using the statistical software R v.4.0.0 [26]; the brglm2 R package was used for fitting the Poisson models.

Ethical aspects

The research protocol was approved by the Ethics Committee of the Teaching Hospital (Approval number 021.2020). The anonymity of the patients was ensured by attributing an individual code.

Results

Overall, 679 patients were observed. Of these, 7 patients were excluded from the study because they stayed in the ICU for less than one day. The data of a total of 672 patients were included for the analyses, 560 were admitted during the pre-COVID period and 112 during the COVID period. All the characteristics of the sample are shown in Table I.

Regarding the percentages of spontaneously breathing patients, these were 40.9% (n = 229) in the pre-COVID group, and 1.8% (n = 2) in the COVID group; patients undergoing non-invasive ventilation (NIV) were 21.9% (n = 123) in the pre-COVID group and 58.9% (n = 66) in the COVID group; instead the percentages of mechanically ventilated patients were similar between the two groups, 37.2% (n = 208) in the pre-COVID group and 39.3% (n = 44) in the COVID group.

The median age of the patients was 68 years (interquartile range 56-76 years) for pre-COVID patients and 69 years (interquartile range 57-76 years) for COVID patients.

Compared to the pre-COVID group, the COVID group was characterized by a higher proportion of males (329 (58.8%) and 82 (73.2%,) respectively), lower median BMI values (24 and 22, respectively), more comorbidities (2-3 comorbidities, respectively 16.6 and 26.8%), of the Sequential Organ Failure Assessment (SOFA) (1 and 2, respectively), the Simplified Acute Physiology Score (SAPS) II (20 and 26, respectively), and a worse Braden Scale score (16 and 14, respectively). Length of stay in the ICU was longer in the COVID patient group than in the pre-COVID group (median values: 1 day and 5 days, respectively).

Tab. I. Characteristics of the patients and outcomes; overall and by period of admission.

	All (n = 672)		Pre-COVID (n = 560)		COVID (n = 112)		P-value*
	n	(%)	n	(%)	n	(%)	
Sex							0.004
Female	261	(38.8)	231	(41.2)	30	(26.8)	
Male	411	(61.2)	329	(58.8)	82	(73.2)	
Ethnicity							0.13
Caucasian	664	(98.8)	555	(99.1)	109	(97.3)	
Non-Caucasian	8	(1.2)	5	(0.9)	3	(2.7)	
BMI (kg/m²)†	24	(21 to 26)	24	(22 to 27)	22	(21 to 26)	0.02
Weight (kg)†	85	(80 to 95)	90	(80 to 95)	80	(80 to 91)	0.14
Age (years)†	68	(57 to 76)	68	(56 to 76)	69	(57 to 76)	0.68
Number of comorbidities							0.02
0	192	(28.6)	159	(28.4)	33	(29.5)	
1	357	(53.1)	308	(55.0)	49	(43.8)	
2-3	123	(18.3)	93	(16.6)	30	(26.8)	
SOFA score†	1	(0 to 1)	1	(0 to 1)	2	(1 to 5)	< 0.001
SAPS II score†	21	(19 to 23)	20	(19 to 22)	26	(21 to 35)	< 0.001
Braden score†	16	(16 to 16)	16	(16 to 16)	14	(14 to 16)	< 0.001
Length of stay in ICU (days)†	1	(1 to 2)	1	(1 to 2)	5	(1 to 15)	< 0.001

* Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. † Median (interquartile range). ‡ Composite event: any of falls, physical restraint, pressure ulcers, pneumonia, bloodstream infections or gastrointestinal infections.
Pre: admission to hospital before 1st March 2020; post: admission to hospital at or after 1st March 2020.

Tab. II. Patients' outcomes; overall and by period of admission.

	All (n = 672)		Pre-COVID (n = 560)		COVID (n = 112)		Mean Difference	P-value*
	n	(%)	n	(%)	n	(%)		
Falls								
No	670	(99.7)	558	(99.6)	112	(100.0)	9.21	< 0.001
Yes	2	(0.3)	2	(0.4)	0	(0.0)		
Physical restraint								
No	664	(98.8)	554	(98.9)	110	(98.2)	15.1	0.027
Yes	8	(1.2)	6	(1.1)	2	(1.8)		
Pressure ulcers								
No	646	(96.1)	543	(97.0)	103	(92.0)	7.3	< 0.001
Yes	26	(3.9)	17	(3.0)	9	(8.0)		
Pneumonia								
No	666	(99.1)	558	(99.6)	108	(96.4)	11.4	0.018
Yes	6	(0.9)	2	(0.4)	4	(3.6)		
Bloodstream infections								
No	667	(99.3)	560	(100.0)	107	(95.5)	5.1	0.021
Yes	5	(0.7)	0	(0.0)	5	(4.5)		
Gastrointestinal infections								
No	671	(99.9)	559	(99.8)	112	(100.0)	7.2	0.012
Yes	1	(0.1)	1	(0.2)	0	(0.0)		
Composite event[‡]								
No	632	(94.0)	537	(95.9)	95	(84.8)	5.7	0.003
Yes	40	(6.0)	23	(4.1)	17	(15.2)		

* Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. [†] Median (interquartile range). [‡] Composite event: any of falls, physical restraint, pressure ulcers, pneumonia, bloodstream infections or gastrointestinal infections.
Pre: admission to hospital before 1st March 2020; post: admission to hospital at or after 1st March 2020.

Tab. III. Incidence rate ratios in COVID *vs* pre-COVID patients.

Outcome	Model 1*		Model 2[†]		Model 3[‡]	
	IRR (95% CI)	p	IRR (95% CI)	p	IRR (95% CI)	p
Falls	Not applicable		0.30 (0.01 to 6.15)	0.43	0.53 (0.05 to 5.72)	0.60
Physical restraint	0.49 (0.10 to 2.44)	0.39	0.57 (0.13 to 2.44)	0.45	0.72 (0.18 to 2.91)	0.65
Pressure ulcers	0.78 (0.35 to 1.75)	0.55	0.80 (0.36 to 1.77)	0.58	0.70 (0.32 to 1.53)	0.37
Pneumonia	2.95 (0.54 to 16.12)	0.21	2.66 (0.57 to 12.47)	0.22	1.30 (0.34 to 5.01)	0.70
Bloodstream infections	Not applicable		16.24 (0.90 to 293.71)	0.06	14.81 (1.32 to 166.08)	0.03
Gastrointestinal infections	Not applicable		0.49 (0.02 to 12.08)	0.66	0.31 (0.03 to 2.87)	0.30
Composite event[§]	1.09 (0.58 to 2.04)	0.78	1.10 (0.59 to 2.04)	0.76	1.00 (0.53 to 1.86)	0.99

* Unadjusted Poisson regression model. [†] Unadjusted penalized Poisson regression model. [‡] Penalized Poisson regression model adjusted for sex, age, BMI and number of comorbidities. [§] Composite event: any of falls, physical restraint, pressure ulcers, pneumonia, bloodstream infections or gastrointestinal infections.
Pre: admission to hospital before 1 March 2020; Post: admission to hospital on or after 1st March 2020; IRR: incidence rate ratio.

During ICU admission, 47 deaths occurred in the pre-COVID group and 32 deaths in the COVID group, respectively; the corresponding mortality rates were 6.6 (95% CI = 5.0 to 8.8) and 15.1 (95% CI = 10.7 to 21.4) per 1000 person-days, resulting in a COVID *vs.* pre-COVID incidence rate (IRR) ratio of 2.3 (95% CI = 1.5 to 3.6, p < 0.001).

The percentages of outcomes regarding falls (0.0 and 0.4%, respectively), physical restraint (1.8 and 1.1%, respectively), and pressure ulcers (8.0 and 3.0%, respectively) were similar in the COVID and in the pre-COVID group (Tab. II).

During the ICU admissions, no events were observed for urinary tract infections, local central vascular catheter associated infections, or local peripheral vascular catheter associated infections. After adjusting for gender, age, BMI, and number of comorbidities, the incidence of bloodstream infections was significantly higher in the COVID group than in the pre-COVID group (IRR = 14.81, 95% CI = 1.31 -166.08, p = 0.03). There were no statistically significant differences in the incidence between the two groups regarding other evaluated outcomes. No evidence of association with the COVID group was found for all the other outcomes (Tab. III).

Discussion

The study compared patients admitted to the ICU in the pre-COVID period with those in the COVID period to evaluate the effects of staff and environment reorganization in the ICU for COVID-19 patients in terms of nursing sensitive outcomes. Due to the unpredictability of the pandemic, it was not possible to select the participants to be included in the study, therefore the patients' characteristics were not homogeneous across the two groups.

The predominant number of males in our COVID group confirmed the 3-to-1 ration between males and females reported in the epidemiological studies conducted in Chinese ICUs [7, 27-29]. In fact, males were not at a greater risk of developing serious conditions females but were 1.55 times more likely to be admitted to an ICU than females.

Ventilatory therapy

The percentage of patients undergoing NIV was significantly higher in the COVID group confirming the data already reported in the literature [30-32]. The use of NIV – a potentially life-saving ventilatory treatment, strongly recommended by the treatment guidelines in patients with severe conditions of respiratory insufficiency due to COVID-19 [12] – was possible in our study setting, thanks to the reduced risk for health workers and the surrounding environment of being contaminated by the aerosol evacuation systems used for the COVID-19 patients, because the premises were already previously used as operating rooms, and offered negative-pressure isolation of the surrounding environment with at least 12 air changes per hour [32, 33].

Comorbidities

The higher number of comorbidities observed in our COVID group is in line with those reported in the literature. Chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD) and hypertension were the comorbidities mostly associated with ICU admission. Patients affected by dyspnoea were 6.6 times more likely to be admitted to the ICU than those without dyspnoea. Although COPD was relatively rare, in other studies it was found to be by far the strongest comorbidity for admission to the ICU. Patients affected by cardiovascular diseases and hypertension had respectively a 4.4 and 3.7-fold higher probability of being admitted to the ICU than patients without comorbidities [34].

Mortality rates

The COVID versus pre-COVID mortality rate ratio (Incidence of Relative Risk, IRR) of 2.3 (95% CI = 1.5 to 3.6, p < 0.001) was in line with the SOFA (1 pre-COVID and 2 COVID respectively) and the SAPS II (20 pre-COVID and 26 COVID respectively) predictive indices, which are commonly used for classifying disease severity, measuring risk of death, and choosing the best treatment for ICU patients.

The mortality rates observed in the COVID group were similar to those of the Spanish [35] and the northern Italian [36] studies, and to the average rate reported in the Quah review [37]. They were higher than those of the German studies [38], and lower than the US [39, 40], Chinese [10, 39, 40] and British [41] studies.

Pressure ulcers

Although the risk index for the development of pressure ulcers (Braden Scale) found in the COVID group was lower (= higher risk) than in the pre-COVID group (16 in the COVID and 14 in the pre-COVID group) and length of stay was longer in the COVID group compared to the pre-COVID group (1 day and 5 days, respectively), the IRR of the COVID versus the pre-COVID group was 0.70 (95% CI = 0.32 to 1.53) with no statistically significant difference (p = 0.37).

This could be due to the frequent mobilization of mechanically ventilated patients or patients undergoing NIV who, for therapeutic purposes, were in supine and prone positions with regular cycles and timings established according to recommendations [42]. The availability of an anti-decubitus mattress on each bed, more attention placed on the use of anti-decubitus materials and devices due to pronation-supination movements, may have contributed to preventing this phenomenon.

Bloodstream infections

The incidence of bloodstream infections was higher in the COVID group compared to the pre-COVID group (IRR = 14.81, 95% IC = 1.31-166.08, p = 0.03) thus confirming the results obtained by other similar studies both in Italy [43, 44] and in other countries [45, 46]. The risk that multidrug-resistant bacteria (MDRB) could spread during a viral pandemic had been theoretically studied and predicted, but no real data were available in relation to this phenomenon because previous pandemics had occurred before the era of antimicrobial resistance. Experts have expressed their concerns about the spread of MDRB during the COVID-19 pandemic, and preliminary studies and reports indicate an increase of such infections in COVID patients admitted to ICUs [47].

The higher incidence of bloodstream infections could be due to several factors related to the pandemic: the shortage of personal protective equipment PPE [48]; excessive emotional and physical workload of health workers in the ICU; overcrowded ICUs [49]; higher numbers of unexperienced staff leading to poorer adherence to preventive measures and infection control; and excessive use of antibiotic treatments [47, 50-52]. In addition, protective equipment used by the health workers increased the feeling of protection to and from the patients, triggering a greater risk of contamination in the event they did not change their protective equipment when caring for another patient.

LIMITS

The study has some limitations, like the differences of the patients' characteristics between the two groups, which was not possible to avoid due to the unpredictability of the pandemic. In addition, no data were available regarding observations regarding staff compliance with infection prevention measures. These data would have enabled a better understanding of the observed phenomenon.

Conclusion

The study showed how the selected nursing sensitive outcomes maintained similar values in the pre-COVID and COVID patient groups. The reorganization of the ICU for COVID-19 patients – despite it was thorough and carried out in an extremely limited amount of time – with additional health staffing, it responded effectively to the health needs generated by the pandemic.

This reorganization did not affect the quality of care, which was similar to that provided in the pre-COVID period. Healthcare-related infections, especially bloodstream infections, were comparable to those of other similar studies.

This result must be considered an important alarm signal. Conditions of excessive workload, stress and the presence of less experienced staff increase patients' risk of being contaminated by multi-resistant bacteria.

Ethics approval and consent to participate

The research protocol was approved by the Ethics Committee of Pisa Teaching Hospital (Approval number 021.2020).

Availability of data and materials

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

Competing interests

The authors of this manuscript have no competing interests as defined by the editorial policy of Journal of Preventive Medicine and Hygiene. They moreover have no other interests that may have influenced the results and discussion of this paper.

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COVID-19: yesterday, today and tomorrow. The quality of COVID-19 management and the evaluation of the "Health" chapter of the Recovery Plan

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Keywords

COVID-19 • Quality management • Local health • Digital healthcare • Recovery Plan

Summary

Introduction. *The COVID-19 pandemic represented an unprecedented challenge for the healthcare world and the introduction of a new stronger and believable project plays a fundamental role for the quality of work and the provision of qualitative care.*
Aim. *The survey provided by Italian Association for the Quality of Health and Social Care (ASIQUAS) aims to examines the impact of "Health" chapter included in the Recovery Plan, through the assessment of management quality of the COVID-19 pandemic.*
Methods. *Starting from a literature review, in September 2021, a web-based survey has been conducted and administered by e-mail. It has been taken into account measures widely used by different healthcare structures in order to analyze the projects implemented in the face of pandemic and to evaluate the new real possibility to invest funds in new healthcare structures and projects.*
Results. *The survey consists of 19 multiple choices and respondents were from different types of structures, including regional departments and regional health agencies (1.4%), universities, research centers and scientific hospitalization and treatment institutes (IRCCS) (11%), hospitals and university polyclinics (34.2%), Local Health Authorities (39.7%), socio-health organizations and Others (13.7%). The pandemic has highlighted many vulnerabilities at both hospitals and territorial level. The major weaknesses revealed by the survey are mainly due to the lack of support from new staff units and poor availability of specific training tools for COVID-19 procedures. The Recovery Plan is still unclear with a lot of concern about the implementation and many limits of diffusion.*
Conclusions. *It becomes essential to guarantee a new effective and interoperative model of integration. Today we can start more aware for the implementation of a system closer to everyone's needs, making shortcomings the new strength and starting point.*

Introduction

Coronavirus disease 2019 (COVID-19) outbreak has heavily influenced almost all the world's healthcare systems. COVID-19 is an infectious respiratory disease caused by SARS-CoV-2, a highly contagious virus that belongs to the coronavirus family, which was a stressor of the healthcare systems.

Italy was the first European country to be heavily hit by the pandemic.

In Italy, the COVID-19 pandemic has caused more than 14 million cases of infection and over 156,588 deaths to date [1]. It is meaningful to stress that the epidemic mainly affected the country's northern area during the first wave and spread more widely throughout the country in the summer months and during the next wave [2]. However, COVID-19 disease did not cause the same mortality everywhere, but it occurred with extreme variability in the Italian regions. It is difficult to establish the reasons for these differences, which should be source among a very comprehensive range of factors (such as organizational deficiencies, initial delays in understanding the seriousness of the emergency, deficits in infection tracking systems, different levels of aggressiveness of the virus, individual behavior and choices of central and local governments) [3].

To properly face this emergency, the Italian health system should have been equipped with clear guidelines and important organizational and managerial skills to react promptly.

Healthcare workers had to face challenging and unknown scenarios, not always enough supported by current management strategies and facilities. They had to withstand an enormous physical effort and, in particular, an unexpected psychological and emotional burden.

But, while, the pandemic needed a strong central intervention of coordination and impulse, given the "health decentralization" and, consequently, the greater autonomy of Italian Regions in the organization and

management of health services [4], each Italian Region has adopted its own strategies to face the pandemic. In fact, the greatest disparities have been felt in the provision of services in terms of prevention and assistance, poor integration between hospital, territorial and social services, as well as very high waiting times for many other services and pathologies [5].

It can be said that where territorial health care has been weaker, there have been more infections and higher lethality [6, 7].

The existence of a healthcare system based on the hospital as the center of every problem has proved to be totally inadequate, leading to increasingly integrative and connected solutions.

According to this scenario, the new perspective outlined by the Recovery Plan, the largest recovery reform plan ever funded in Europe, responds in a very coordinated way to the needs highlighted by the pandemic and to the need for an integrated approach between the hospital and territorial network. Developing a "close and digital" healthcare conceived by the plan passes various challenges and objectives.

The first challenge is represented by developing a model of care for prevention and management of chronic diseases oriented to health promotion (initiative healthcare), which does not wait for the patient in the hospital or another health facility. However, it takes care of him proactively in the early stages of the disease's onset or evolution [8].

The second challenge is represented by the rethinking of services, with better performing hospitals, new territorial and home care, community care, and the achievement of a critical unitary vision on E-health, care, and assistance able to operate online [8].

Last but not least, it is necessary to strengthen the sense of belonging to a single integrated system and the ability to work together as one big team [9, 10]. Being aware of the shortcomings and new opportunities is the first optimal way to heal our health system from a long-term perspective and to talk seriously about resilience.

The survey aims to understand the future needs and challenges of our healthcare system, starting with the analysis of healthcare management of the COVID-19 pandemic in Italy after 18 months from the first wave. It wants to highlight lacks and weaknesses of healthcare system, but also starting points for improvements.

In addition to this, the study investigates on the "Health" chapter of Recovery Plan, evaluating expectations and doubts of its introduction.

Methods

To better understand the major limitations and future needs that the pandemic has highlighted, a web-based survey proposed by the Italian Association for the Quality of Health and Social Care (ASIQUAS) was set up and administered in September 2021, after 18 months from the first wave of the COVID-19 pandemic [11].

At first, in order to outline the impact of COVID-19 on healthcare workers' wellness and mental health, an extensive search of the main evidence-based literature was performed.

The treated items in the survey are provided by government organizations, published literature, evidence-based practice, and Recovery Plan [8, 12-15]. Following the review results, a structured questionnaire was defined and shared within the working group for validation.

The survey consists of 19 multiple choice questions and it is composed of three sections:

- management quality of COVID-19 pandemic;
- implementation specificity for COVID-19 pandemic;
- evaluation of the healthcare chapter of the National recovery and Resilience Plan (PNRR).

The great advantage in proposing this type of study derives from the presence of different types of structures: regional departments and regional health agencies (1.4%), universities, research centers and scientific hospitalization and treatment institutes (IRCCS) (11%), hospitals and university polyclinics (34.2%), Local Health Authorities (39.7%), socio-health organizations and Others (13.7%). (Tab. I)

The questionnaire was created using Google Modules and then, spread by e-mail.

Concerning with the sample size, Local Health authorities, University Hospitals and Polyclinics, Universities/Research Centers/IRCCS and others such as Consulting and design firm in network health systems, Nurse, Provincial health authority, Scientific Association, Faculty of Medicine and Psychology/AUC Sant'Andrea, I-Tel srl, Institute of private medical analysis, Hospitaller Physiotherapy Institutes IRCCS (IRE-ISG) of Rome, Regional company, Regional health emergency company, Regional departments and regional health agencies were invited and answered to the survey. Respondents were asked to fill the form anonymously. Participation was voluntary.

The answers were collected immediately, and descriptive statistics on the frequency distributions and percentages were reported through pie and bar charts.

Data were analyzed using Microsoft® Excel (2016). We performed a descriptive analysis of collected data. Univariate and bivariate statistics were used to describe the need of future investments in the NHS by using SPSS.

Tab. I. Type of membership structure.

Type of structure	N°	%
Ministero AGENAS ISS	1	1%
Assessorati Regionali e Agenzie Sanitarie Regionali	1	1.4%
Università/Centri di Ricerca/IRCCS	8	11.0%
Azienda Ospedaliera e Policlinici Universitari	25	34.2%
Azienda Sanitaria Locale	29	39.7%
Others	9	12.3%
Total	73	

Tab. II. Future investments.

The lesson of COVID-19: looking forward 12 months (September 2022), what it would invest in and at what level of governance?	%
Technological and instrumental equipment (diagnostic equipment, PPE)	39.7%
Administrative equipment (information systems, computer systems, etc.)	52.1%
Management equipment (provision of specific guidelines, organizational tools, etc.)	39.7%
Staffing	60.3%
Logistic equipment (spaces, logistic routes, supply chain, etc.)	52.1%
Training tools	34.2%
Re-planning of hospital networks	1.4%
All of the above	1.4%

Results

The questionnaire had an high compliance rate (about 35%): 73 participants out of about 200 invited, without recall.

The survey reveals a predominance of structures belonging to Central Italy (72%), while fewer in the North (21%) and very few in Southern Italy and islands (7%).

The population interviewed is composed of a huge variety of healthcare professions (both employees in managerial or administrative field and doctors who act on the ward).

The most represented gender is female and the average age belongs to the group of over 50 years old (67%), followed by the group between 35-50 (28%) and only a few in the group of under 35 (5%). It shows a high emotional involvement in the consulted subjects; in particular it was found that they were little supported from both a logistical and a psychological side. This underlines a high emotional impact.

Furthermore, it appears that 41.4% of the respondents feel fairly prepared in teamwork, communication skills, leadership and organizational abilities. This points out how soft skills play a fundamental role in difficult situations such as the pandemic.

In addition, the questionnaire reveals a fair technical and cultural predisposition to follow specific guidelines on quality and safety, management protocols or managerial techniques; however, there is no clear position in positive terms, underlining the need for a greater support and updating network.

Concerning the major shortcomings, it emerges a serious shortage of new staff units and their support (31.4% of participants felt they were not well supported and even 27.7% not at all) and a poor availability of specific training tools for COVID-19 patient care procedures.

Hence the need and desire to invest in the logistics system and equipment (52.1%), in the implementation of new staff units (60.3%) and in the provision of effective training tools (34.2%).

Another small amount of support comes from administrative equipment, such as information and IT systems, on which most of the structures would invest more in the future (52.1%) (Tab. II).

As a statistically significance correlation was found between the need of future investments in the Italian NHS, the pre-COVID preparedness and the way how the surveyed professionals felt themselves supported by their healthcare management, respectively ($p < 0.05$), unfortunately no statistical significancy emerged from the application of an univariate analysis on the above mentioned variable on the need of future investments ($p > 0.05$) (Tab. III).

Tab. III. Binomial test on future needs.

Binomial test							
						95% Confidence Interval	
	Level	Count	Total	Proportion	p	Lower	Upper
Technological and instrumental equipment (diagnostic equipment, PPE)	y	29	73	0.397	0.101	0.28453	0.519
	n	44	73	0.603	0.101	0.48140	0.715
Administrative equipment (information systems, computer systems, etc.)	y	38	73	0.521	0.815	0.40038	0.639
	n	35	73	0.479	0.815	0.36100	0.600
Management equipment (provision of specific guidelines, organizational tools, etc.)	y	29	73	0.397	0.101	0.28453	0.519
	n	44	73	0.603	0.101	0.48140	0.715
Staffing	y	44	73	0.603	0.101	0.48140	0.715
	n	29	73	0.397	0.101	0.28453	0.519
Logistic equipment (spaces, logistic routes, supply chain, etc.)	y	38	73	0.521	0.815	0.40038	0.639
	n	35	73	0.479	0.815	0.36100	0.600
Training tools	y	25	73	0.342	0.010	0.23532	0.463
	n	48	73	0.658	0.010	0.53717	0.765
Others	y	3	73	0.041	<.001	0.00856	0.115
	n	70	73	0.959	<.001	0.88456	0.991

Nevertheless, the Recovery Plan is still unclear and most of participants are not even aware of the actions and goals expected by the "health" chapter.

Today there is still concern about the planning tools and the implementation of the plan, highlighting the limits of diffusion and the knowledge of both contents and strategies.

A problem of clarity? Lack of references? Or maybe of interest?

Furthermore, concerning with monitoring and assessment, the survey reveals many weaknesses and gaps related to the knowledge of impact assessment tools, proposing to set up independent, rigorous and intellectually honest "watchdogs networks" whose goal is to participate in the support process, including training.

ASIQUAS considers itself the promoter of this activity.

Discussion

We aimed at understanding the future needs and challenges of our healthcare system, starting with the analysis of healthcare management of the COVID-19 pandemic in Italy after 18 months from the first wave.

Our analysis also aimed at providing decision makers quantitative inputs for improvements, also by evaluating expectations and doubts of the introduction of the Italian Recovery Plan and the post-COVID healthcare planning and management.

To invest in physicians, nurses, and technological innovation to respond to population needs are the most relevant recommendations of the survey. The number of physicians in Italy [16], now similar to other EU nations, is hit by retirement (more than half of doctors are older than 55 years), limits on medical school admissions, and stringent specialisation programme requirements combine to shrink numbers. Nursing has been strained by chronic understaffing for years, with ratios of nurses and midwives to inhabitants only half those observed in Germany [17, 18].

Without providing a solution to this problem, the application of the PNRR is at risk [19].

In fact, investing 2 million in community houses and drawing up staffing plans are not enough to make this a reality; otherwise, if the shortage of personnel is not covered, the risk is to have facilities but not activities and services.

In addition to this, data from 2017 show that Italian nurses are the lowest paid among European industrialized countries.

This arises the necessity for long-term strategies, which consider future epidemiological trends and new health technologies (*e.g.* mobile health) so that health professionals are truly in step with the actual and future needs [17].

The COVID-19 pandemic highlighted many shortcomings that have long been recognized but little considered in resolutive terms.

The highly fragmented and non-homogeneous territory has caused considerable variability in terms of response and the most virtuous regions in handling the situation have been those that have implemented the assets already owned [19].

The impact of the pandemic on a weak and not fully prepared system has caused an increased workload which was difficult to manage, exacerbated by tired and psychologically unstable personnel [12, 14].

Infact, the workers involved in the pandemic were exposed to the risk of infection but also to an emotional overload associated with a reduction of useful human resources and, in some cases, organizational precariousness. The vast literature related to the stress of health workers confirms that the health sector is an area full of psycho-social risk factors, mainly linked to working aspects such as organization, safety and health [14, 20].

COVID-19 represented a clear accelerator from a managerial and cultural point of view towards the acceptance of important changes able to reduce the variability of responses and to create a transversal and concerted system of actions throughout the territory.

These changes are now proposed by the Recovery Plan [21], which has allocated $15.63 billion to health, structuring the mission in two specific components:

• proximity networks, intermediate structures and telemedicine for territorial health care;
• innovation, research and digitalization of the national health service.

The perspective becomes that of an important organizational and technological innovation capable of avoiding fragmentation and miscommunication and strengthening the building blocks of a healthcare organization [22].

The priorities of the recovery plan at the European level are different, as well as the actions on the total resources [23-25].

For example, Spain has focused more attention on health, associating it with 16.5% of the total billion, much more than 8% of Italy [26] (Fig. 1, 2).

Furthermore, Spain is very close to the Italian vision, promoting technologies capable of collecting, processing and verifying useful health information and data, the first through implementing the "Electronic Health Record" and the second through creating sanitary "data lakes."

The first identified priority in Italy consists in the passage from "taking care of the disease" to "taking care of the person" through the creation of a network on the territory able to bring the health services closer to the citizens and make the response more homogeneous [27].

One of the supporting initiatives has been undertaken by the implementation of a new home care services [28].

The second priority sees the interoperability of data as the core of all reforms, which, thanks to the exploitation of new technologies that are assuming a new role in support of prevention, quality of services and simplification of processes, would represents an

Fig. 1. Italian Recovery and Resilience Plan.

Italy

Category	Value
HEALTH	8.20%
INCLUSION AND COHESION	10.30%
EDUCATION AND RESEARCH	16.10%
INFRASTRUCTURE FOR SUSTAINABLE MOBILITY	13.30%
GREEN REVOLUTION AND ECOLOGICAL TRANSITION	31.10%
DIGITIZATION, INNOVATION, COMPETITIVENESS…	21.10%
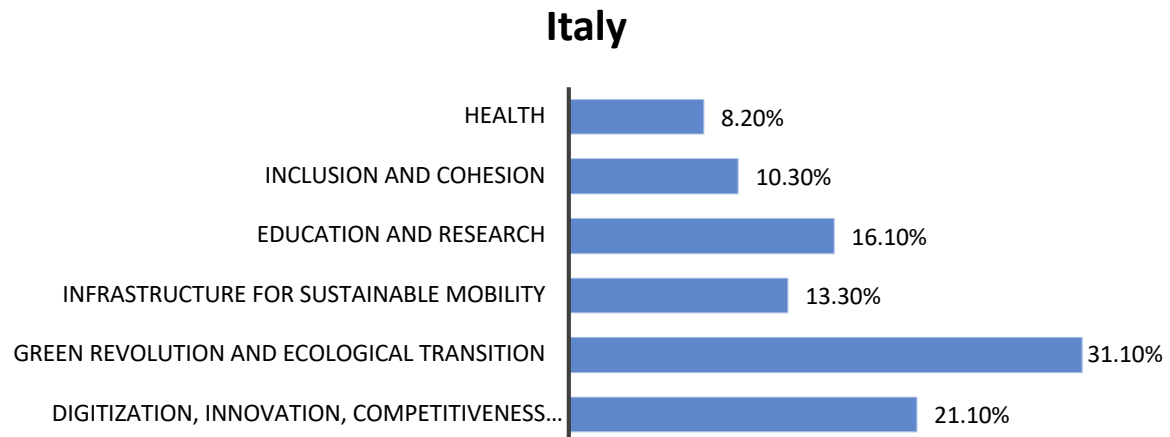
Fig. 2. Spanish Recovery and Resilience Plan.

Spain

Category	Value
CULTURE AND SPORT	1.10%
WELFARE AND EMPLOYMENT	5.70%
INSTRUCTION	17.60%
HEALTH	16.50%
DIGITIZATION, INNOVATION AND COMPETITIVENESS	17.10%
EFFICIENCY OF THE PUBLIC ADMINISTRATION	5%
ENERGY TRANSITION	8.90%
INFRASTRUCTURES AND ECOSYSTEMS	12.20%
AGRICULTURAL AND RURAL DEVELOPMENT	16%
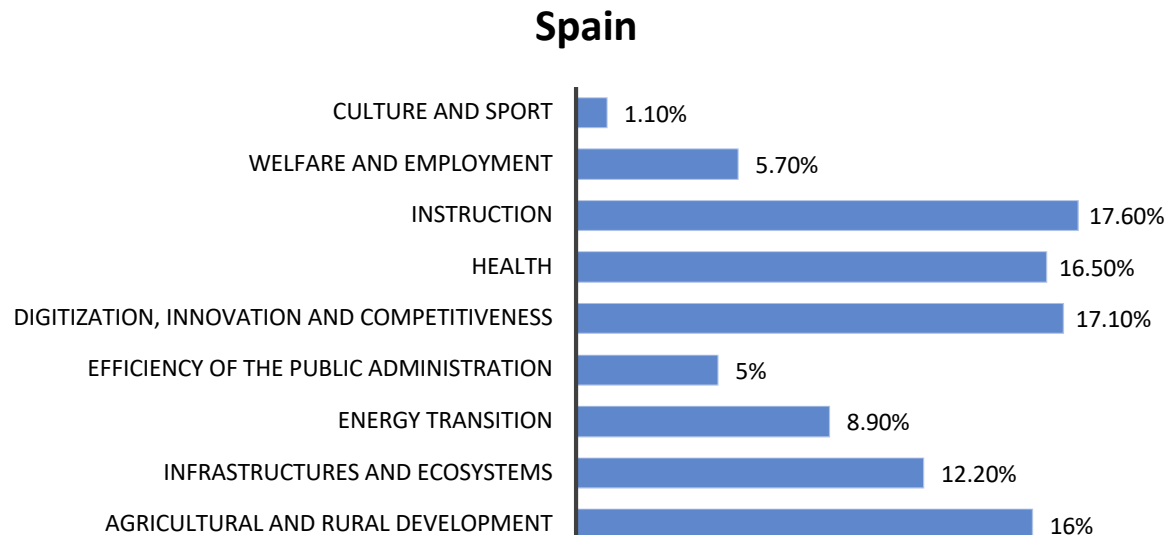
important tool for the collection, processing and sharing of data and information [29].

Both priorities attempt to address the critical aspects and territorial inequalities, although they find still obstacles and lack of awareness.

In fact, compared to other studies and starting from another survey carried out by ASIQUAS between June and November 2020 [30], the intent of this work is to identify and deepen the needs of a more resilient health system, going beyond the benefits of this ambitious reform and addressing the current skepticism and future issues to be resolved for its real and effective implementation.

Another critical point refers to the primary care, characterized by a similar phenomenon of understaffing; the pandemic highlighted the need of a strong, easily integrated and connected network of general practitioners that is lacking today, unlike what happens in some other countries like Denmark.

The Danish healthcare system is considered among the best in terms of qualitative care in Europe mainly because it is strongly based on general practitioners [31] all Danes have 6.9 contacts per year with their GP (in-person, telephone, or E-mail consultation.

Home care and support services for elderly people is highly developed, including home visiting, retirement homes and rehabilitation facilities.

Even before the pandemic, the Danish system focused on primary care and its integration, underlining the importance of a close collaboration among general practitioners in the territory and hospitals

To invest in technological innovation to respond to population needs - the second most relevant recommendations of the survey, matches with the challenge of digital health in Italy. As in many other

Fig. 3. The use of telemedicine by doctors.

	Before Covid-19	During Covid-19
Tele-consultation	21%	47%
Tele-visit	13%	39%
Tele-monitoring	13%	28%
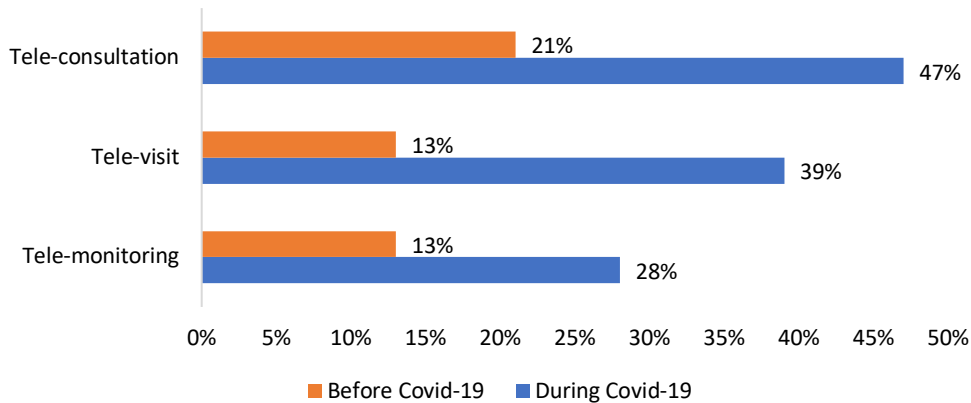
countries, telemedicine is still scarcely used, despite the rapid change of mind of many doctors and other health professionals (Fig. 3).

The use of digital health technologies, such as mobile health, telemedicine, wearable devices, artificial intelligence, and interoperable information technology, although long suggested to better manage patients with chronic diseases, increased substantially in Italy and elsewhere during the pandemic as in-person contact became inopportune or impossible [17, 32].

Digital health shows great promise as a means to better manage patients with chronic conditions and help them avoid hospital visits and admissions.

Our results confirm the increasing physicians' interest and use of telemedicine tools during the COVID pandemics [33].

These significant data show the rapid change in mindset not only by physicians and specialists, but also by patients who have become increasingly involved in digital services [34].

Although the importance of the priorities identified, there are still several issues to be addressed.

First of all, one of the biggest problems in Italy starts from the interoperability of data, actually organized in silos and dependent on a single department, isolated from others.

The Italian healthcare system, heavily penalized by strong heterogeneity and multimorbidity, requires the presence of data warehouse where data of each patient are integrated.

It seems essential to develop a network of knowledge and support and an uniform system of interoperable models and infrastructures [35].

Another critical issue is about the clinicians' skills and approach towards technological innovations, therefore specific courses are expected to take place.

Then, it has been considered patients' skills and approach to digital services, considering Italy is largely made up by over 65's, most of which cannot use technological devices.

On the other side, the benefits of using telemedicine to treat older patients included the reduction of deferred care and travel burdens, the enhancement in communication

and timely care and a general improvement of the efficiency for physicians.

Finally, an ethical element, associated with patients who are increasingly adverse and reluctant to share their data, must be considered.

Therefore, it is important to consider the educational and cultural aspects not only of healthcare professionals but also and especially of patients.

On the other hand, feasibility comes from the right ambition we will have in considering new opportunities and offering the right tools and certainty.

The overall effects would translate into a more flexible, value-based and patient-centered healthcare delivery, along with the cost savings and timeliness and appropriate support of all groups of disease.

Furthermore, we have to consider the significant downsizing and redistribution of the workload for health workers, considering that many applications have alleviated office closures and staffing shortages due to the pandemic [36].

Limitations

Some limitations should be considered when interpreting our results.

First, our research has been conducted by means of an electronic survey: the low number of respondents, their heterogeneity belonging to different types of health facilities, their different geographical distribution are limiting issues to be considered [37].

Second, we targeted to professionals joining to a quality improvement society, thus arising the risk of a response bias.

Third, in some cases the selected questions are not enough to explore the multifaceted concepts of healthcare organizations, service planning, healthcare investments and their contextualization to the Italian NHS.

Lastly, we didn't cross-checked by a collection of data at the user's level, which could be useful to assess their views or experiences, in order to effectively assess their perspective towards major changes.

Conclusion

The evaluation of the pandemic over time has highlighted stressful situations, weaknesses and vulnerabilities in hospitals and in the territory.
Therefore, it appears evident to redesign a uniform and effective model of interoperative management through learning and exchange processes among hospitals and territory, enhancing communication campaigns, implementing and investing in innovative digital services. The aim is to put the patient at the center and to predict its needs, supported by a more efficient and effective organization.

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Conflict of interests

Authors state no conflict of interest.

Authors' contribution

All authors actively participated in the study design, data analysis, and drafting of the manuscript.
Additionally, all authors read and approved the manuscript.

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COVID-19 - Health care management

Exploring the effectiveness of the Digital Green Certificate Law as Public Health instrument to increase anti-COVID-19 vaccination in a sample of working-age adult population in the Palermo Metropolitan Area

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Summary

Counteracting vaccine hesitancy should be considered an absolute priority for Public Health Authorities. A correct health communication represents one of the best ways to increase adhesion to vaccination among hesitant population.
In order to increase vaccination coverage rates against COVID-19, the Italian government has issued a legislative decree with a mandatory "Digital Green Certificate" (DGC) to access workplaces for some categories considered at risk.
Methods. *We conducted a cross-sectional study with the aim to highlight the factors associated with the anti-COVID-19 vaccine acceptance and to estimate the influence of the introduction by law of the Digital Green Certificate (DGC) on the adhesion to the COVID-19 vaccination campaign in a sample of individual accessing one of the main vaccination centres of the metropolitan area of Palermo, Italy. An anonymous and validated questionnaire*
was self-administered through the Google Documents® platform, between October 2021 and March 2022.
Results. *Among the 467 subjects enrolled, 43.3% were influenced on their vaccination choice by the introduction of the DGC. The multivariate analysis showed that among the respondents emerged contrasting feelings with a self-reported significantly higher sense of freedom (Adj-OR = 2.45, 95%CIs = 1.51-3.97, p-value: < 0.001) but a lower sense of safety (Adj-OR = 0.19, 95%CIs = 0.12-0.29, p-value: < 0.001) after vaccine administration.*
Conclusions. *Our findings, in line with the available literature, suggest that the introduction of DGC has led to a significant increase in the immunization rate and, together with an appropriate communicative approach, it could represent an effective strategy to counteract vaccine hesitancy.*

Introduction

On March 11, 2020, the World Health Organization (WHO) announced that the outbreak of "COronaVIrus Disease 2019" (COVID-19), which initially started in Asia in the city of Wuhan at the end of 2019, had become a pandemic [1]. The outbreak of COVID-19 led to an unprecedented global crisis, impacting on the political agenda, the economic and healthcare systems [2].

High pressure on healthcare systems, during the first wave, required a rapid international response to slow down the transmission of contagions, as well as the death rates associated with COVID-19 [3].

Due to the lack of vaccines or specific therapies to contrast the COVID-19 spread, drastic Public Health interventions, such as lockdowns and social distancing measures, were considered worldwide as the first step to counteract the first and second waves of the pandemic [4].

On December 2020, the European Medicines Agency (EMA) approved the use of the first COVID-19 vaccine in Europe and in Italy the first dose was administered on December 27 [5]. In the following weeks and months other vaccines were approved and, progressively, vaccination was extended to healthcare professionals, elderly, subject with comorbidities, teachers, and the general population [6].

In the middle of July 2022, in Italy, 91.5% of the population over 12 years old received a full COVID-19 vaccination cycle, with 83.5% of the target population vaccinated with the third (booster) dose. Unfortunately, in Sicily the first COVID-19 vaccination cycle was administered to 83.6% of the target, with only 77.7% receiving a booster dose [7, 8].

Many countries since the start of the COVID-19 vaccination campaign had to fight against vaccine hesitancy, consisting in a refusal of vaccination despite the availability of effective vaccines [9].

Media may play a role against the fight to SARS-CoV-2 by supporting vaccination campaigns, but may became also an enemy due to the spread of fake news [10].

To counteract the spread of COVID-19 and the vaccine hesitancy, in March 2021, the European Commission proposed the introduction of a vaccination certificate, namely Digital Green Certificate" (DGC) [11].

In the same direction, on July 2021, the Italian government issued a legislative decree implementing the use of the DGC [12], which was extended to a mandatory use for both public and private workers, health care professionals and subjects with more than 60 years old, starting from October 2021 [13].

We conducted a cross-sectional study with the aim to highlight the factors associated with the anti-COVID-19 vaccine acceptance and to estimate the influence of the DGC on the adherence to the COVID-19 vaccination campaign in a sample of individual accessing one of the main vaccination centres of the Metropolitan area of Palermo, Italy.

Material and methods

Since the beginning of the COVID-19 vaccination campaign, the vaccination centre of the Palermo University Hospital has administered 80,000 doses of COVID-19 vaccines, with more than 7,000 shots dispensed to subjects with severe allergy in secure environment, while serving the Palermo metropolitan area, one of the most density populated areas of Italy with 1,214,291 inhabitants [14].

A cross-sectional study was carried out between October 2021 and March 2022. An anonymous and previously validated questionnaire was administered to subjects accessing the COVID-19 vaccination centre of the Palermo University Hospital for COVID-19 immunization.

A simple random sampling procedure was used in order to select our sample through a Microsoft Excel spreadsheet that assigned randomly a number to enrolled subjects.

Participants were initially provided with information explaining the study aims and the personal data processing, according to Italian privacy policies, and received an informed consent before answering to the questionnaire.

QUESTIONNAIRE STRUCTURE

The questionnaire consisted of an introductive part, presenting the study aims and describing the method of treatment, conservation, and protection of personal data, as well as indicating the person responsible for the data treatment. The questionnaire, self-administered through the Google Forms® platform, consisted of 8 items distributed in four main sections investigating:
- socio-demographic information, including gender, residence, age;
- knowledge, perceptions and attitudes regarding COVID-19 vaccination;
- main information sources consulted, and considered reliable, on vaccination against COVID-19 and

influence of DGC on the decision process about COVID-19 vaccination;
- access to advertisements against COVID-19 promoted by the regional health authorities;
- factors leading to the vaccination choice.

Level of freedom and post-vaccination safety were both calculated using a Likert scale, with answer values ranging from 1 (very low) to 5 (very high).

The research team validated the questionnaire through a pilot study on a sample of 30 subjects to evaluate its reproducibility and comprehensibility. To this end, the Cronbach's alpha was calculated and corresponded to 0.92 with an adequate reliability of the test.

Once the questionnaires were completed, all data were automatically recorded on an Excel file (ver. 1997-2003) protected by password and accessible by the research group only to further ensure privacy.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Palermo Ethical Committee 1 (resolution no. 9, October 2022).

STATISTICAL ANALYSIS

Absolute and relative frequencies were calculated for the categorical (qualitative) variables.

The association between introduction of mandatory Digital Green Certificate and other qualitative variables was explored using Fisher test or Chi-square test. To guarantee a more conservative approach all the variables found to have a p-value ≤ 0.20 at the univariate analysis were included a multivariate backward stepwise logistic regression model. The crude and adjusted odds ratios (ORs and adj-ORs) with their 95% confidence intervals (CIs) were calculated. The level of significance was set at p-value < 0.05 (two tailed).

All the data were analysed using the statistical software package Stata/MP 12.1 (StataCorp LP, College Station, TX, USA).

Results

Table I summarizes the socio-demographic characteristics of the 467 respondents recruited in the survey, having an average age of 38.3 years old (SD ± 14.2), predominantly

Tab. I. Socio-demographic characteristics of the surveyed population (n = 467).

	N	%
Gender		
Male	215	46.1
Female	252	53.9
Residence		
Palermo	301	64.4
Other	166	35.6
Age distribution		
< 50 years	353	75.6
≥ 50 years	114	24.4
Age, Mean ± SD	38.3 ± 14.	

Tab. II. Information sources and decisive factors on vaccination against COVID-19 of the surveyed population (n = 467).

	N	%
Subjects that have seen promotional image against COVID-19		
No	95	20.4
Yes	372	79.6
Media consulted on COVID-19 vaccine		
TV	233	49.9
Journal, magazine, poster	48	10.2
Internet/web	186	39.9
Main factors associated with vaccination acceptance		
Own choice/fear of disease	341	73.0
Relatives or friends advice/ TV, internet	34	7.2
General practitioners' advice/trusted physician	92	19.8
Influence of the GP decree on vaccination acceptance		
Yes	202	43.3
No	265	56.7

female (n = 252; 53.9% of total) and resident in the Palermo city (64.4%).

In Table II are reported the results of the answers to the questions related to the main information sources consulted and considered reliable by respondents, the factors leading to the vaccination choice against COVID-19, and the DGC influence on the decision process about COVID-19 vaccination adhesion.

Within the study sample, 372 respondents (79.6%) confirmed to have had access to advertisements against COVID-19 promoted by the regional health authorities. Media sources consulted were mainly TV (49.9%), followed by internet/web (39.9%) and journals/magazines (10.2%).

An own choice and the fear for disease were the main factors leading to vaccination acceptance (73.0%), followed by the advice from the General practitioners or a trusted physician (19.8%) and the informal advice from relatives or friends (7.2%).

Lastly, 202 (43.3%) respondents declared to be influenced by the introduction of the DGC.

Table III and IV shows the results of the univariate and multivariable analyses aiming at estimating the impact of mandatory DGC on the decision process about COVID-19 vaccination adhesion of the 467 respondents in study.

At the univariate analysis the variables associated to the DGC influence on vaccination adhesion were the male gender (OR = 1.52, 95% CIs = 1.05-2.20; p-value: < 0.05), a high perception of post-vaccination safety (OR = 0.24, 95% CIs = 0.16-0.36; p-value: < 0.001) and the advice from the General Practitioner or a trusted physician (OR = 0.58, 95% CIs = 0.36-0.85; p-value: < 0.01).

The multivariable analysis highlighted a statistically significant association between the DGC influence

Tab. III. Univariate (crude OR) analysis between influence of mandatory Digital Green Certificate (DGC) on the decision process about immunization adherence anti COVID-19 with different dependent variables considered in the study (n = 467).

Influence of the DGC decree on vaccination acceptance, n (%)		
	Crude OR (95% CIs)	p-value
Gender		
Female	reference	< 0.05
Male	1.52 (1.05-2.20)	
Residence		
Palermo	ref	0.52
Cities outside Palermo	0.99 (0.67-1.45)	
Age classes		
≥ 50 years	ref	0.39
< 50 years	1.08 (0.70-1.65)	
Perception of post-vaccination freedom		
Low	ref	0.06
High	1.37 (0.92-2.04)	
Perception of post-vaccination safety		
Low	ref	< 0.001
High	0.24 (0.16-0.36)	
Main factors associated with vaccination acceptance		
Relatives or friends advice/ TV, internet	ref	
Own choice/fear of disease	0.82 (0.63-1.15)	< 0.01
General Practioners advice/trusted physician	0.58 (0.36-0.85)	
Media consulted on the COVID-19 vaccine		
Internet	ref	
TV	1.25 (0.75-2.34)	0.96
Journal, magazine, poster	1.36 (0.82-1.93)	

Tab. IV. Multivariate (adj-OR)* analysis between influence of mandatory Digital Green Certificate (DGC) on the decision process about immunization adherence anti COVID-19 with different dependent variables considered in the study (*multivariate analysis was performed only for variables with p-value ≤ 0.20 at the univariate) (n = 467).

Influence of the GP decree on vaccination acceptance, n (%)		
	Adj-OR (95% CIs)	p-value
Gender		
Female	ref	0.18
Male	1.31 (0.88-1.95)	
Perception of post-vaccination freedom		
Low	ref	< 0.001
High	2.45 (1.51-3.97)	
Perception of post-vaccination safety		
Low	ref	< 0.001
High	0.19 (0.12-0.29)	
Main factors associated with vaccination acceptance		
Relatives or friends advice/ TV, internet	ref	0.13
Own choice/fear of disease	0.86 (0.75-1.27)	
General Practioners advice/trusted physician	0.72 (0.49-1.07)	

on vaccination adhesion of respondents and their perception of a higher post-vaccination freedom (Adj-OR = 2.45, 95% CIs = 1.51-3.97; p-value: < 0.001) and of a lower post-vaccination safety (Adj-OR = 0.19, 95% CIs = 0.12-0.29, p-value: < 0.001).

Discussion

The COVID-19 vaccination campaign, started on December 2020 in the developed Countries and in Europe, was the biggest ever known universal mass campaign conducted in the history.
The scientific community and Public Health Institutions should spread the right messages and information about COVID-19 vaccination, also to tackle circulating of fake news and governments have the task of enacting decree laws useful for increasing vaccination coverage, such as laws that making vaccination 'mandatory'. [15].
Many countries have introduced some restrictions, such as lockdowns and the use of masks to reduce the surge in cases attributable to the pandemic [16].
With the arrival of vaccines, an attempt was made to reverse the trend by trying to return to normality and reducing stringent measures but in a short time the growth of the vaccinated rate stopped due to vaccine hesitancy especially in those countries where the vaccination offer was high; this leads us to speak of an 'unvaccinated pandemic' [17, 18].
The introduction of the mandatory vaccination has contributed in the countries where it has been adopted to drastically reduce hospitalizations, deaths and cases as demonstrated by some randomized and observational studies [19].
Specifically, in the present sample, was reported a prevalence of working-age adults that are mainly healthy and for which the personal protection of anti-COVID-19 vaccination it is considered less important than elderly people or people with comorbidities [18].
The Digital Green Certificate therefore, forcing workers to receive anti-COVID-19 vaccination, represented an

essential instrument of Public Health in order to ensure the health of general population and to contribute to indirect protection of fragile and elderly people [17, 20]. The need for large-scale vaccination has led to some concerns about the transparency of vaccines as well as their long-term safety; nevertheless, it would seem that the benefits of such a large vaccination campaign during this pandemic far outweigh the risks it could cause [20]. Mandatory vaccination policies are heterogeneous across countries, in all Europe.
Countries that adopt sanctions for those who have not vaccinated have lower incidence rates of vaccine-preventable diseases than countries who do not. Although financial penalties are useful for achieving high vaccination coverage, these must be accompanied by constant availability of vaccines but above all by education on the importance of prevention measures aimed at hesitant subjects. [21]
At the same time, correct health communication is increasingly becoming a fundamental tool to guide and educate citizens in taking responsible actions. The phenomenon of the dissemination of misleading news emerged in an intrusive way during this pandemic emergency, determining a pandemic of false information (Infodemic). Website and social network were one of the most important theater of spreading of fake news where everyone, with or without competence, could say his idea about pandemic, vaccines and government decision [22]. Islam MS et al. conducted a study where a team of epidemiologist, medical doctors and scientist were formed to examined a wide range of sources such as websites, Facebook and Twitter. They identified about 2311 reports related to COVID-19 infodemic from 87 countries, most of them, 2049 (89%), were classified as rumors while the rest conspiracy theories, and stigma (182 and 82, respectively) [23].
The Sicilian regional health authority has dedicated some specific efforts in the communication process during the management of the COVID-19 health emergency, implementing a promotional campaign in support of COVID 19 vaccination. Despite our study

didn't aim to assess the effectiveness of this institutional communication campaign against COVID-19, we were able to report that it reached the vast majority of the respondents to the survey. Anyway, not surprisingly, the main sources of information on COVID-19 vaccination were television and the web, suggesting the need to provide correct information through these means.

Furthermore, within the factors leading to vaccination the interviewees recruited in our cross-sectional study a predominant role was played by the fear of contracting the COVID-19 disease, overcoming the advice of medical-doctors [24, 25]. Moreover, a large part of the respondents declared that the introduction of GP influenced their adhesion to the COVID-19 vaccination campaign. Anyway, among the study sample population emerged contrasting feelings with a self-reported significantly higher sense of freedom but a lower sense of safety after vaccine administration, this could be related to fear of expected adverse events. Negative feelings about mandatory vaccinations have been already documented in healthcare workers by international literature, forced intervention and anxiety about physical injections being the main stated motivations toward this vaccination strategy when adopted to increase influenza vaccination rates [26].

There are some limitations of the present study that need to be discussed. Firstly, there can be a lack of representativeness due to the limited number of participants. However, the vaccination centre of the Palermo University Hospital represents one of the most important centres (in terms of vaccination administered) of Sicilian Region and the sample could be considered a proxy of general population of the Metropolitan area of Palermo.

Secondly, the survey was proposed to citizens voluntary accessing the vaccination centre to get vaccinated and, for this reason, it was not possible to involve in the analysis the so-called no-vax population, even if it would have been difficult to trace the reasons behind their refusal of the COVID-19 vaccine, as they are usually reluctant to provide their responses.

Conclusions

In conclusion, as compared to other strategies used in the past to implement the vaccination rate, the DGC may represent a ploy encouraging citizens to get vaccinated without imposing a direct obligation on them. Nevertheless, the introduction of DGC has led to several public debates on a potential discrimination based on the lack of privacy with regard to the individual vaccination status [27, 28]. This was the reason why, even in Italy, protests and strikes were organised against the government decision to introduce the DGC strategy [29].

However, the vaccination campaign in Italy benefited from the introduction of the mandatory DGC, which increased the COVID-19 vaccination rates, as further confirmed by our findings.

The data presented highlighted that the many hesitant respondents have been influenced by the mandatory

DGC in their choice to vaccinate against COVID-19, even if they reported to feel less confident after having the vaccine shots, therefore informative campaigns and communicative strategies should be improved to reassure vaccinated population on COVID-19 vaccines safety and effectiveness.

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Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

C.C., D.C., D.S. and D.M.: conceptualization; C.C., W.M., F.R., N.B. and M.S.: methodology; N.B., M.S., L.D., A.C.: software; M.M., G.G., C.M.M., V.R., F.T. and F.V.: validation; C.C., N.B., L.D. and A.C.: formal analysis; W.M., F.R., V.R., and F.V.: data curation; C.C., N.B., M.S., L.D. and A.C.: writing – original draft preparation; W.M., D.C., D.S., D.M., and F.V.: writing – review and editing; W.M.: visualization; F.V.: supervision; C.C: project administration. All authors have read and agreed to the published version of the manuscript.

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Monitoring influenza vaccination coverage among healthcare workers during the COVID-19 pandemic: a three-year survey in a large university hospital in North-Western Italy

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Keywords

Summary

Introduction. *Healthcare workers (HCWs) are one of the highest priority groups recommended for seasonal influenza vaccination (SIV). Greater awareness of the importance of influenza vaccination was observed among HCWs after the start of the COVID-19 pandemic. The aim of this study was to analyze SIV coverage rates in the 2019-2020, 2020-2021 and 2021-2022 seasons among HCWs employed at the IRCCS Ospedale Policlinico San Martino in Genoa, in order to observe how coverage has changed since the COVID-19 pandemic began.*

Methods. *A retrospective, single-center study was conducted among HCWs working at the IRCCS Ospedale Policlinico San Martino in Genoa. The vaccinated population was stratified by gender, age, qualification and area of activity, and the characteristics of vaccinated HCWs were analyzed.*

Results. *While SIV coverage was below the recommended target in*

all seasons, a sharp increase was observed in 2020/2021 (12.8%; 40.9% and 23% in 2019/2020, 2020/2021 and 2021/2022, respectively). The mean and median age of vaccinees also increased during the 2020/2021 vaccination campaign (46.7 and 49 years, respectively) in comparison with the 2019/2020 season (43.5 and 45, respectively). In the 2019/2020 and 2021/2022 seasons, a higher proportion of vaccinees were physicians. Vaccinated females outnumbered males, but the coverage rate resulted greater in males than females in all three seasons. While a higher proportion of vaccinated subjects worked in medical areas, the most evident increase over the three years was seen among subjects working in the services area.

Conclusions. *This survey highlights the importance of studying the determinants that influence vaccination adherence and how the COVID-19 pandemic has affected SIV coverage.*

Introduction

Influenza is a viral respiratory disease of global importance. Indeed, a study published in 2018 reported that around 1 billion influenza cases worldwide occur each year, 3-5 million of which are severe cases and 290,000-650,000 lead to influenza-related respiratory deaths [1]. Healthcare workers (HCWs) are considered one of the highest priority groups recommended for annual influenza vaccination. After the start of the COVID-19 pandemic, owing to the possible concomitant circulation of influenza viruses and SARS-CoV2, awareness of the importance of influenza vaccination increased among HCWs [2, 3].

The 2009 Council of the EU encouraged Member States to implement national, regional and local plans and policies to improve the seasonal influenza vaccination (SIV) coverage rate among at-risk categories, including HCWs, and also to measure coverage rates. Although almost all European jurisdictions recommend free influenza vaccination for HCWs, less than half of the

Member States are able to report on vaccination coverage among HCWs [4].

As HCWs are often in contact with many people, they run a greater risk of exposure to influenza viruses than the general population. In addition, once infected, they are potential vectors of contagion to their patients [5]. Not only is influenza vaccination among HCWs important in terms of saving financial resources and preventing mortality among patients (6), it also aims to avoid the interruption of essential services for the community [7]. SIV coverage goals have been set at a minimum of 75% and an optimal value of 95% for populations at risk, including HCWs. In Italy, there is no systematic surveillance system for collecting coverage data among HCWs; however, single local studies have reported coverage rates ranging from 5% to 34% in different Regions and hospitals [8, 9]. The mean prevalence of SIV is lower in Italy than in other European countries [10].

HCWs' perception of the risks engendered by influenza varies according to the working setting; for example, differences between tertiary hospitals and community

hospitals have been reported [11, 12]. Moreover, physicians display higher SIV coverage rates than nurses, midwives, nursing assistants and nursing aides [11, 13]. In the 2020/2021 season, the Italian Ministry of Health recommended introducing initiatives to promote SIV of health personnel "on all possible occasions" [14].

Official recommendations for the 2020-2021 season suggest influenza vaccination starting with all children aged six and above who have no known contraindications. The recommendations identified health care workers and the elderly as highly recommended vaccination groups. Other categories covered by the recommendations are: pregnant women, patients with an underlying disorder that can affect the immune response and children mainly those in the 6 months to two years age range.

Several recent studies have shown that the COVID-19 pandemic has improved influenza vaccination rates among HCWs [15, 16]. Among the factors responsible for this more proactive attitude towards influenza vaccination, increased awareness of the severity of symptoms associated with airway infections has been hypothesized [17]. Furthermore, according to some studies, SIV coverage has also been found to have improved in professionals not directly involved in patient care (administrative staff, etc.), suggesting a link between increased SIV coverage and the fear of SARS-CoV-2 infection [18].

To increase the SIV coverage of HCWs, in particular those working in hospitals, a number of initiatives have been implemented and evaluated. According to the Centre for Disease Control and Prevention (CDC), a proven and cost-effective strategy is to administer influenza vaccination on site [19].

The purpose of the present study was to analyze and compare SIV coverage rate in the 2019-2020, 2020-2021 and 2021-2022 seasons in the IRCCS Ospedale Policlinico San Martino in Genoa, in order to observe how HCWs' compliance has changed since the start of the COVID-19 pandemic. The characteristics of vaccinated HCWs were also studied.

Methods

A retrospective, single-center study was conducted among HCWs working at the IRCCS Ospedale Policlinico San Martino in Genoa. This hospital has always been a reference point for the health needs of the citizens of the metropolitan area of Genoa, the regional capital of Liguria, North-Western Italy, which has a population of about 650,000. San Martino is a research and clinical institute officially recognized by the Italian Ministry of Health and specializes in oncology (Istituto di Ricovero e Cura a Carattere Scientifico or IRCCS). Besides these activities, the duties of the hospital also include teaching and academic research in all major fields of medicine, in collaboration with the University of Genoa. Indeed, the centre handles the teaching of clinical medicine for the Medical School and post-graduate training to qualify in all medical specialties and sub-specialties [20].

Most recent studies in the literature suggest that combined interventions can moderately increase SIV coverage among HCWs [11, 21]. For these reasons, the strategies implemented in our hospital in all three years considered in our study were: the offer of on-site vaccination during working hours, the distribution of vaccines provided by the hospital pharmacy, and the publication of ministerial recommendations on the hospital network (hospital Intranet platform). In the 2019/2020 season, the SIV campaign began in the first week of November, while in the following seasons it started one month earlier (first week of October) [22].

This study adopted a retrospective cohort design. When vaccinations were carried out, HCWs' consent forms were collected by the Hygiene and Preventive Medicine Unit. Our dataset included all the consent forms collected in the period 2019-2022, which included three flu seasons: 2019-2020, 2020-2021 and 2021-2022. The administrative databases of the hospital were queried in order to retrieve the data of the HCWs currently employed in the hospital.

The vaccinated population was stratified by gender, age, qualification and area of activity. In terms of qualification, three groups were created: physicians (including resident doctors), nurses and others. The "Others" category included: medical assistants, administrative staff, technicians, pharmacists, biologists, engineers, psychologists, veterinarians and rehabilitation staff. With regard to the area of activity, three categories were identified: medical, surgical and services.

Descriptive statistics were reported for the collected variables: quantitative variables were summarized with median and interquartile range, while for describing qualitative variables, absolute and relative (percentage) frequencies were reported.

Associations between vaccination status and other characteristics were tested by mean of chi-square tests.

As this was a non-interventional study involving the analysis of routinely collected data, no ethical approval was required.

Results

The study considered a total of 6194 HCWs employed at the IRCCS Ospedale Policlinico San Martino in Genoa for whom records were available for all three seasons. Table 1 shows the characteristics of the vaccinated HCWs and the vaccination coverage rates in the three-year period. Data on the last three flu seasons (2019/2020, 2020/2021 and 2021/2022) are reported.

A total of 4753 influenza vaccinations were carried out during the entire three-year period: 794 in the 2019/2020 season, 2536 in 2020/2021 and 1423 in 2021/2022. Vaccination coverage rose from 12.8% in 2019/2020 to 40.9% during the 2020/2021 season. The rate subsequently fell to 23.0% in the 2021/2022 season. Both the increase between the 2019/2020 and 2020/2021 vaccination coverage rates and the decrease

Tab. I. Characteristics of vaccinated HCWs: 2019/2020, 2020/2021 and 2021/2022 seasons.

	2019/2020 season	2020/2021 season	2021/2022 season
Total HCWs vaccinated (n)	794	2536	1423
Total hospital HCWs (n)	6194	6194	6194
Vaccination coverage rate (%)	12.8	40.9	23.0
Gender (n, %)			
Total male vaccinated (n)	277	924	512
Total hospital male (n)	2120	2120	2120
Vaccination coverage rate in male (%)	13.1	43.6	24.2
Total female vaccinated (n)	517	1606	911
Total hospital female (n)	4074	4074	4074
Vaccination coverage rate in female (%)	12.7	39.4	22.4
Age of vaccinated HCWs			
Mean, SD	43.6	12.34	46.7
Median, IQR	45	31-54	49
18-39 (n, %)	311	39.1	755
40-59 (n, %)	392	49.4	1420
>60 (n, %)	91	11.5	345
Missing	-	-	16
Qualification of vaccinated HCWs (n, %)			
Physicians	447	56.3	854
Nurses	249	31.4	886
Other	97	12.2	634
Missing	1	0.1	162
Area of activity of vaccinated HCWs (n, %)			
Medical area	478	60.2	1117
Surgical area	209	24.2	614
Services area	107	13.5	664
Missing	-	-	141

observed during the following year resulted statistically significant (P < 0.01).

Regarding the gender of the vaccinated HCWs, more females than males were vaccinated in all three seasons. For both gender, vaccination coverage rose from 2019/2020 to 2020/2021 and then decline from 2020/2021 to 2021/2022. Vaccination coverage in males was greater than in females for all the three seasons. A statistically significant difference in vaccine coverage rates between males and females was observed in the 2020/2021 season.

Both the mean and median ages were higher in the 2020/2021 season (46.7 and 49, respectively) than in the 2019/2020 season (43.6 and 45 respectively). In the 2021/2022 season, however, the mean (44.9) and median (47) ages declined. Both the increase in mean age from 2019/2020 to 2020/2021 and its decrease from 2020/2021 to 2021/2022 were statistically significant (P < 0.01).

Data on age were missing in 16 subjects in the 2020/2021 season and in 85 subjects in the 2021/2022 season. In all three seasons, the percentage of vaccinated subjects was higher among those aged between 40 and 59 years. The highest percentage of vaccinated subjects aged between 40 and 59 years was observed in the 2020/2021 season (56%), while the lowest percentage (43.6%) in this age-group was seen in the 2021/2022 season; in 2019/2020, the figure was 49.4%.

Concerning the occupational categories of the HCWs, physicians displayed the highest coverage rates in the 2019/2020 and 2021/2022 seasons. The difference between categories was greatest in the year before the start of the COVID-19 pandemic, the percentages being 56.3% in physicians, 31.4% in nurses and 12.2% in the category "others". The 2020/2021 season saw a decrease in the differences between the occupational categories (33.7%, 34.9% and 25% among physicians, nurses and others, respectively). In the last season, however, the initial differences partially re-emerged (44.6%, 25.6% and 25.9% in physicians, nurses and others, respectively). In all three vaccination campaigns, a higher proportion of vaccinated subjects worked in medical areas (60.2, 44 and 52.1% in 2019/2020, 2020/2021 and 2021/2022, respectively). The most evident increase in the proportion of vaccinees was observed among subjects working in the service area: 13.5% in 2019/2020, 26.2% in 2020/2021

Fig. 1. Characteristics of vaccinated HCWs, stratified by occupational category and gender: 2019/2020, 2020/2021 and 2021/2022 seasons.

Physicians

	Males	Females
2019/2020 season	207 - 46.3%	240 - 53.7%
2020/2021 season	437 - 51.2%	414 - 48.5%
2021/2022 season	278 - 43.8%	356 - 56.1%

Nurses

	Males	Females
2019/2020 season	44 - 17.7%	205 - 82.3%
2020/2021 season	200 - 22.6%	683 - 77.1%
2021/2022 season	91 - 24.9%	274 - 75.1%

Others

	Males	Females
2019/2020 season	26 - 26.8%	71 - 73.2%
2020/2021 season	224 - 35.3%	409 - 64.5%
2021/2022 season	123 - 33.3%	246 - 66.7%

and 30.6% in 2021/2022. Conversely, a decrease was observed in the last two seasons among those working in the surgical area (24.2% in 2020/2021 and 17.2% in 2021/2022). Figure 1 shows the populations of physicians, nurses and "others" vaccinated in the three-year period, divided by gender.

Among physicians, males accounted for 46.3 and 51.2% of vaccinees in the 2019/2020 and 2020/2021 seasons, respectively, and females for 53.7 and 48.5%. The greatest gender difference was seen in the last influenza season (43.8% males and 56% females in 2021/2022). Regarding the population of nurses and "others", a higher proportion of vaccinees were females in all three influenza seasons. In the population of nurses, the proportion of vaccinated males steadily increased over the three-year period (from 17.7% in 2019/2020 to 24.9% in 2021/2022). In the

Fig. 2. Characteristics of vaccinated HCWs, stratified by occupational category and age-group: seasons 2019/2020, 2020/2021 and 2021/2022.
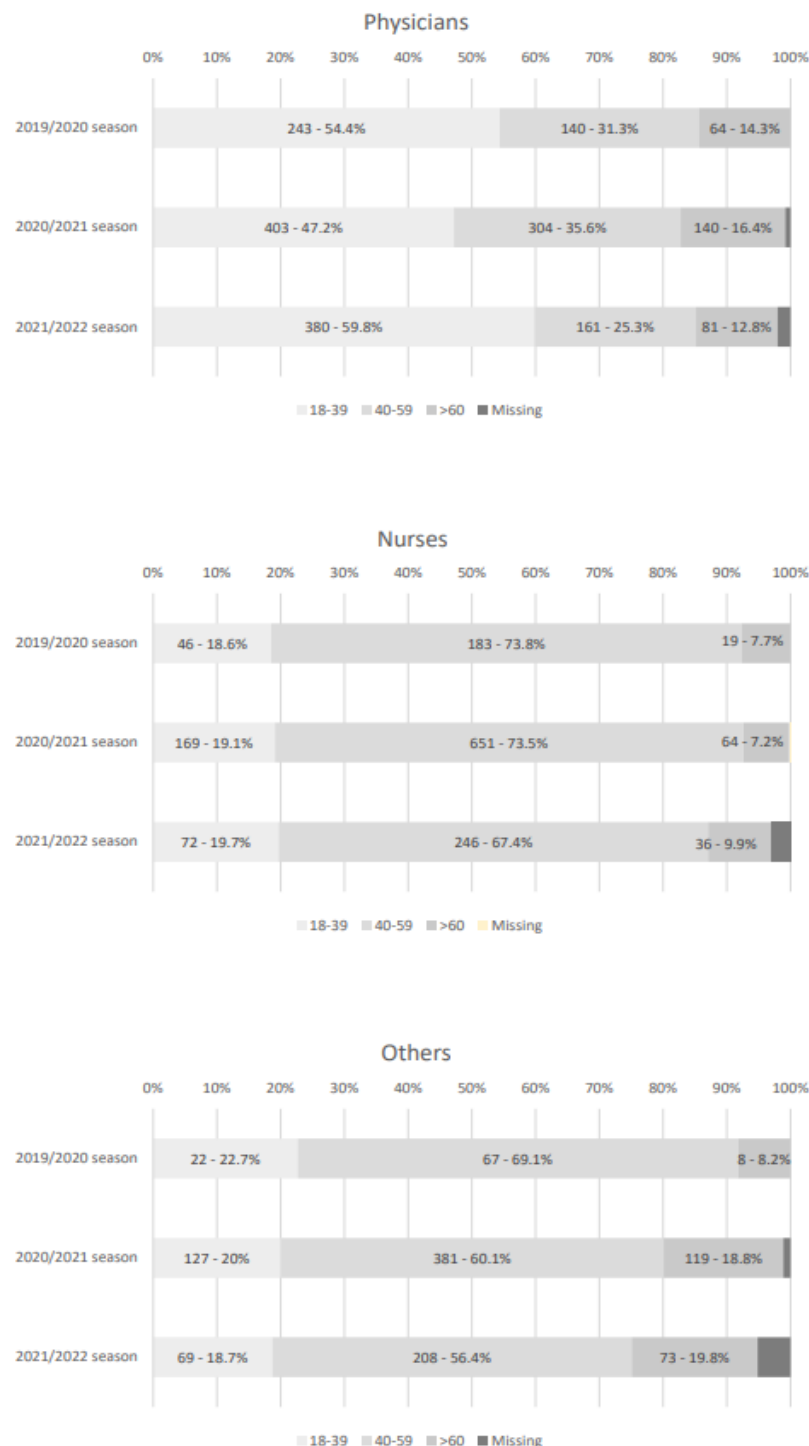
category "others", the proportion of vaccinated males increased in 2020/2021 and then decreased in 2021/2022, though remaining above the initial level (26.8%, 35.3%, 33.3% in the seasons 2019/2020, 2020/2021 and 2021/2022, respectively).

Figure 2 shows the populations of vaccinated physicians, nurses and "others", stratified into three age-groups: 18-39, 40-59 and > 60 years.

With regard to physicians, the largest proportion of vaccinees belonged to the youngest age-group in all three seasons, (54.4%, 47.2% and 59.8% in 2019/2020, 2020/2021 and 2021/2022, respectively). The difference in the distribution of proportions of the young and the middle age groups in the physician's population over the past two seasons was statistically significant (P < 0.01).

Fig. 3. Characteristics of vaccinated HCWs, stratified by area of activity and gender: seasons 2019/2020, 2020/2021 and 2021/2022.
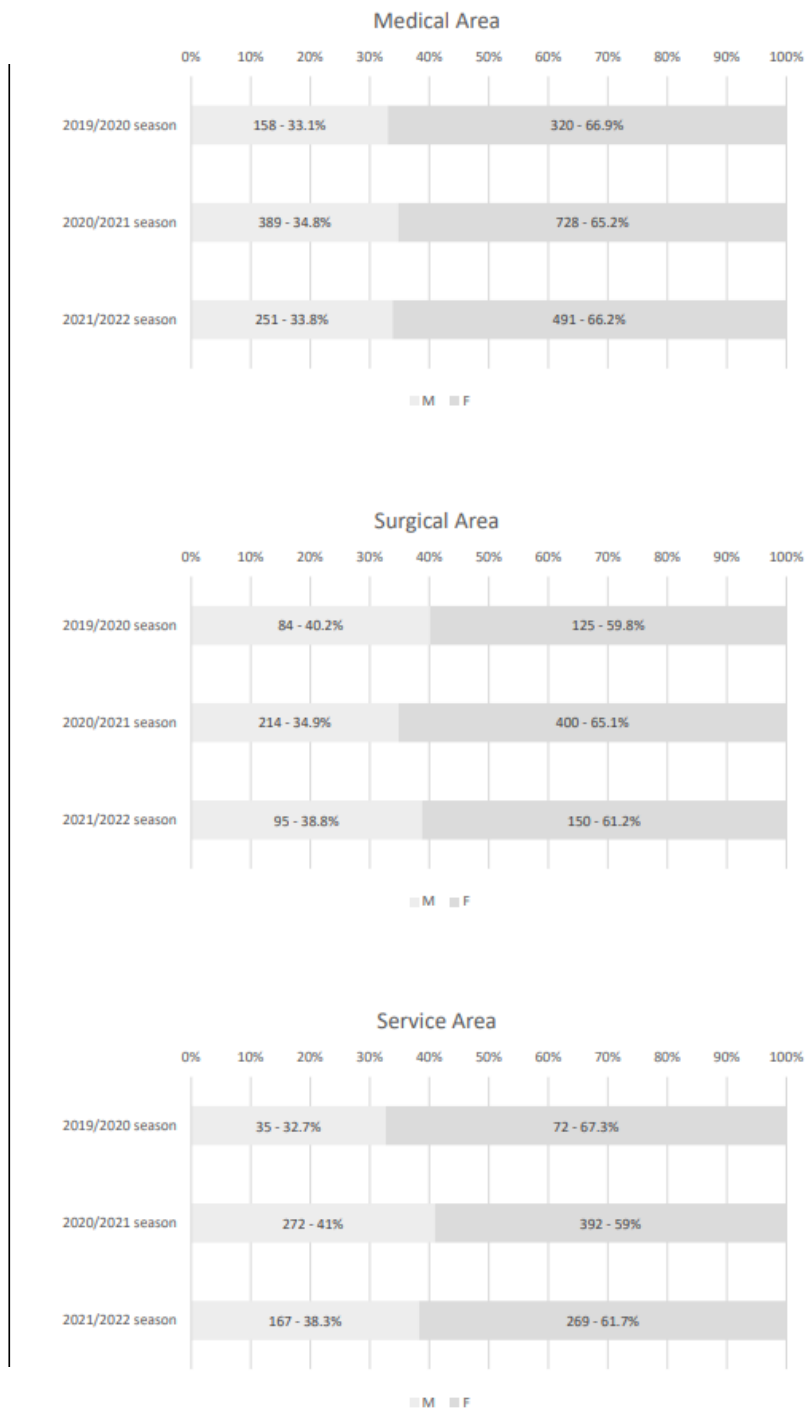
Regarding both nurses and "others", the largest proportion of vaccinees was seen in the intermediate age-group (40-59 years): 73.8%, 73.5% and 67.4% of vaccinated nurses and 69.1%, 60.1% and 56.4% of "others" in the 2019/2020, 2020/2021 and 2021/2022 seasons, respectively. Among physicians, the oldest age-group (> 60 years) remained almost constant over the three years studied. Among nurses, the oldest group showed a slight increase (7.7%, 7.2% and 9.9% in the 2019/2020, 2020/2021 and 2021/2022 seasons, respectively). The greatest increase in this age-group 60 was seen in the category "others": from 8.2% in 2019/2020 to 18.8% in 2020/2021 and 19.8% in 2021/2022.

The HCWs' areas of activity were grouped into three categories: medical, surgical and services. Within these categories, vaccinees were divided according to gender, and the proportions of males and females vaccinated during the three years were observed (Fig. 3).

Fig. 4. Characteristics of vaccinated HCWs, stratified by areas of activity and age-group: seasons 2019/2020, 2020/2021 and 2021/2022.
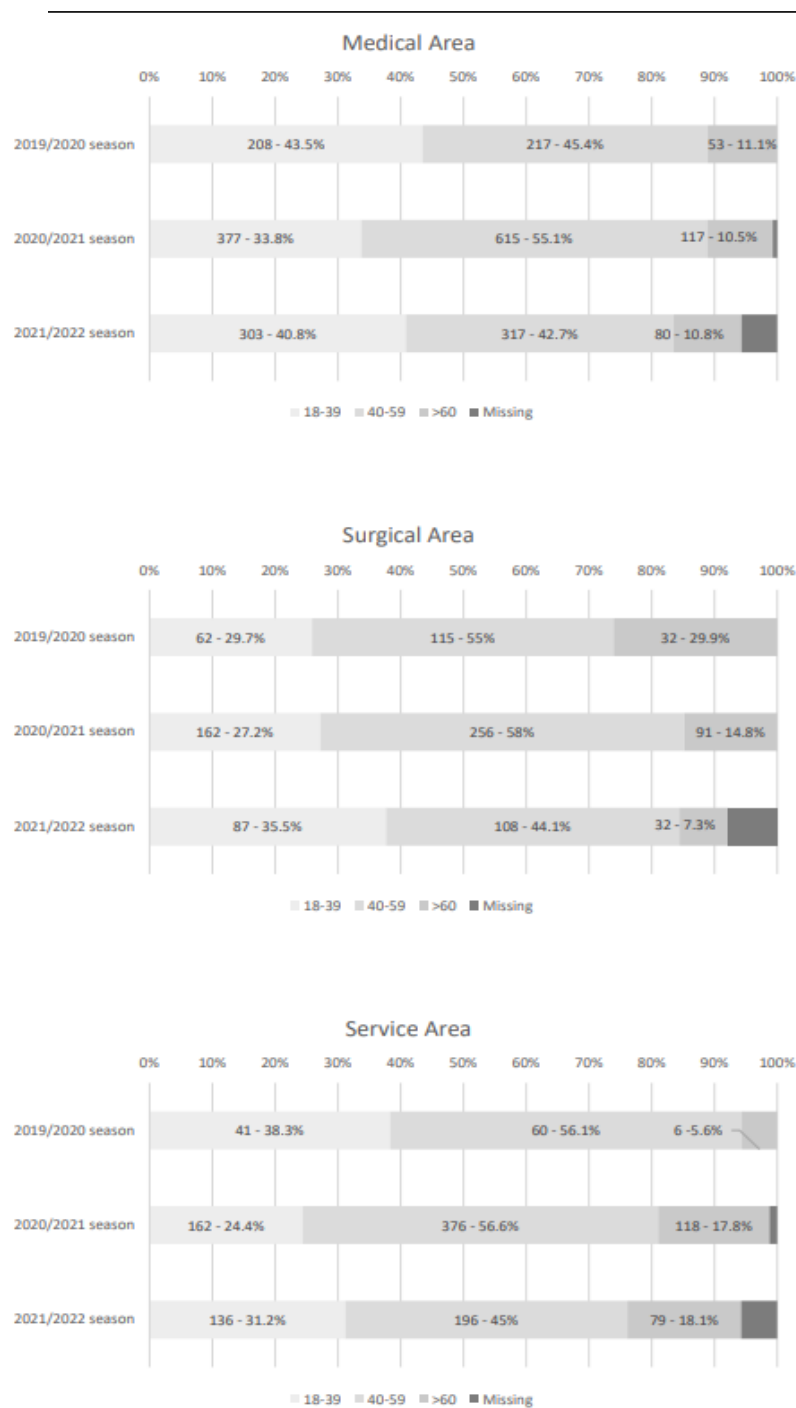
In all areas, the proportion of vaccinated females exceeded 50% in all seasons surveyed. In the medical area, the male/female ratio remained fairly constant. In the surgical area, the percentage of vaccinated males decreased in the 2020/2021 season, but increased again in the following season (40.2%, 34.9% and 38.8% in the 2019/2020, 2020/2021 and 2021/2022 seasons, respectively). In the services area, males accounted for 32.7%, 41% and 38.3% of vaccinees in 2019/2020, 2020/2021 and 2021/2022, respectively.

The vaccinated population in each area of activity was also stratified by age-group (Fig. 4).

In all three flu seasons, the proportion of vaccinees in the 40-59 age-group was the highest. The greatest increase (+9.7%) in the proportion of vaccinees in this age-group was seen in the medical area: from 45.4% in 2019/2020 to 55.1% in 2020/2021 (P < 0.01). In the services area,

the proportion of vaccinated subjects belonging to the > 60 age-group rose from 5.6% in 2019/2020, to 17.8% in 2020/2021 (+ 12.2%, P < 0.01) and 18.1% in 2021/2022. Instead, for the surgical area, the proportion of > 60 age group decreased from 29.9 to 14.8% and the decline of this proportion was statically significant (P < 0.01).

Discussion

This study evaluated SIV coverage rates among HCWs at the IRCCS Ospedale Policlinico San Martino in Genoa in the last three flu seasons (2019/2020, 2020/2021 and 2021/2022). The percentage of HCWs who underwent vaccination was unstable over the years.

The study confirmed the low compliance of Italian HCWs with the national and international recommendations for SIV. Indeed, the overall SIV coverage rates observed were below the recommended threshold in all seasons (12.8%; 40.9%; 23%). In Italy, current coverage data are not available, but these results agree with the findings of other Italian studies, which show that HCWs' knowledge and coverage of recommended vaccinations are often insufficient [9, 23]. Moreover, the results of our study agree with those of a 2010 review by Prato R et al. [24], which found that SIV coverage among Italian HCWs in the period 1999-2007 ranged between 12% and 37%.

As revealed by the recent literature [18, 25, 26, 27], influenza vaccination rates showed an increasing trend in the first influenza season following the start of the COVID-19 pandemic.

In our hospital, a higher proportion of physicians than other professionals were vaccinated in the 2019/2020 and 2021/2022 seasons. This result agrees with literature reports that physicians are more inclined to accept seasonal influenza vaccination than other HCWs [28].

Among vaccinated HCWs, females outnumbered males in all categories studied, but the coverage rate resulted greater in males than females in all the three seasons.

Regarding gender, according to some studies, female HCWs are less likely to be vaccinated than male HCWs [29]. Indeed, in an Italian survey conducted during the 2009-2010 A/H1N1 influenza pandemic, males were more likely than females to be vaccinated and to perceive vaccination as more effective [30]. A statistically significant difference in vaccine co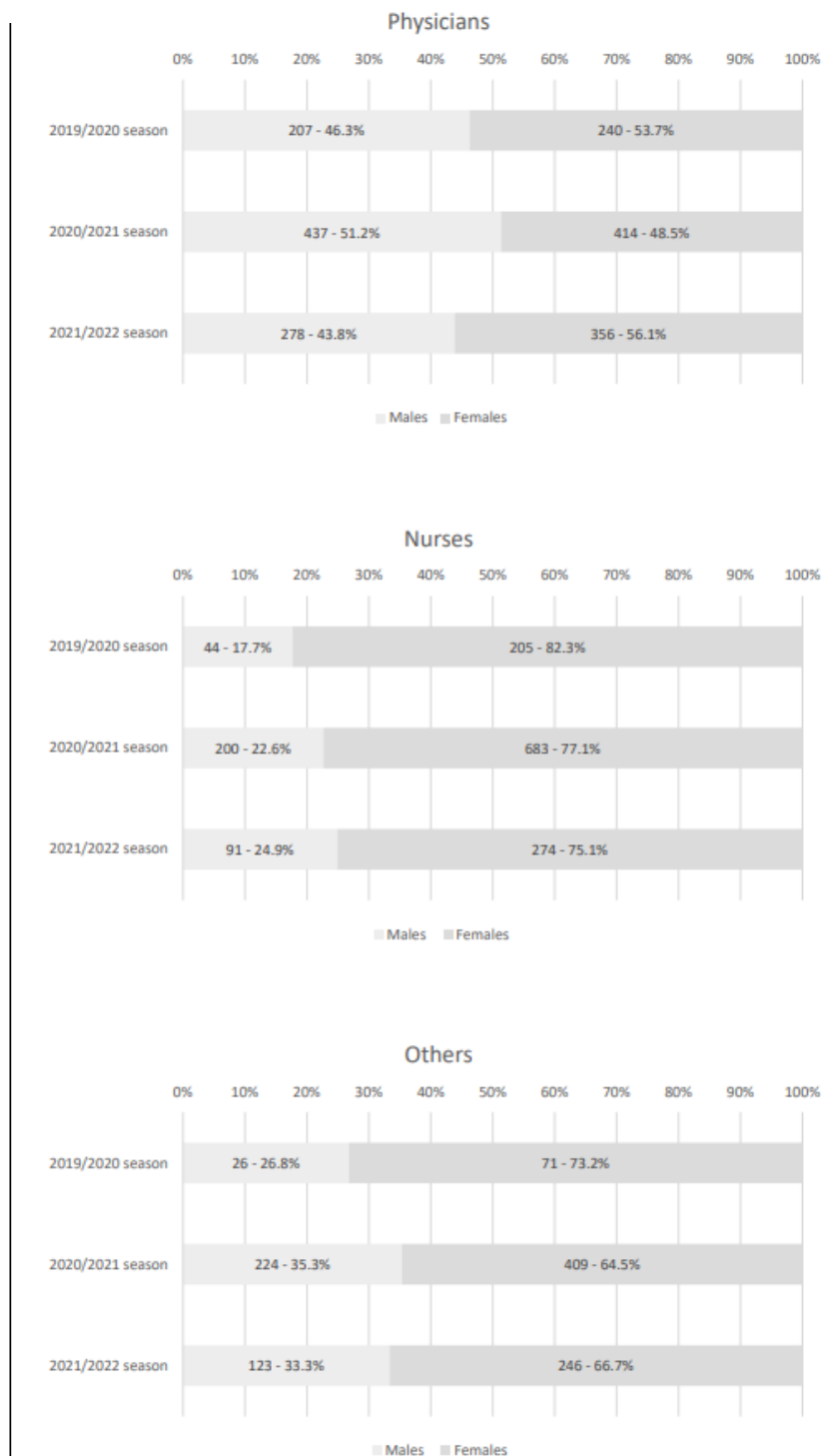verage rates between males and females was observed in the first influenza season after the start of COVID-19 pandemic; this can be partly explained by the fact that the risks of COVID-19 disease have been indicated in the literature as being greater for males [31]; males may therefore feel at higher risk.

The increase in the mean and median ages of vaccinated subjects suggests that the COVID-19 pandemic may have had a greater influence on the older population, owing to their heightened perception of risk, as evidenced by other studies [32]. The vaccines in each occupational category and area of activity were stratified in three age-groups (18-39, 40-59 and > 60 years).

The category of nurses displayed less variation in the percentages of vaccinees in the various age-groups in the three seasons. By contrast, in the 2020/2021 season, physicians and "others" displayed an increase in the percentages of vaccinees in the 40-59 and > 60-year age-groups, respectively. This could mean that, after the start of the COVID-19 pandemic, older physicians and older "other" professionals were more compliant with influenza vaccination, while older nurses did not show a similarly sustained increase in SIV compliance. Our results confirm what was observed in a survey published in 2021 by Kwok et al. [33], which reported low compliance with influenza vaccination among older nurses.

Regarding the areas of activity, in both the medical and surgical areas, the proportion of vaccinees in the 40-59 age-group increased markedly from the 2019/2020 season to the 2020/2021 season. This finding, however, needs to be further investigated, as the distribution of age-groups in the different areas of activity may have been affected by the unequal representation of the various occupational categories.

The main limitation of this study is that the number of employees of the Polyclinic was considered constant throughout the three seasons. However, new employees in the years 2020 and 2021 accounted for less than 3% of the total. Moreover, as data were collected retrospectively, some information was missing. Despite this limitation, the data were processed by means of company software and, with regard to the latest anti-flu campaign, the regional internet platforms were used for the purpose of creating the database. Another limitation is that HCWs may have been vaccinated outside our hospital; thus, the SIV coverage data may be underestimated. Finally, as this was a single-center study, the data refer to a single hospital. However, our Polyclinic is representative of many national and international hospitals, since it is a university hospital, committed to research and training.

Conclusions

The study of adherence to influenza vaccination among HCWs has aroused increased interest in recent years. The goal of such studies is to evaluate the coverage and effectiveness of vaccination campaigns, and to identify new strategies to reduce vaccine hesitancy [34]. In the literature, SIV coverage among healthcare professionals continues to be unsatisfactory, a finding which was also confirmed in our study.

In agreement with the recent literature, we observed that the COVID-19 pandemic was an incentive for HCWs to undergo flu vaccination. However, in the years following the start of the pandemic, adherence to vaccination declined. It is important to study the determinants that influenced the increased compliance with influenza vaccination, in order to develop vaccination strategies.

Our results confirm that being a physician increases the likelihood of adhering to flu vaccination. In addition, we observed that the average age of vaccinated subjects

increased after the start of the COVID-19 pandemic; this finding confirms the greater propensity for vaccination among older subjects.

Acknowledgments

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

M.O., A.D., A.O.: conceptualization; M.O., A.D., A.O.: methodology; M.O., R.B.: formal analysis; M.O., R.B., E.C., A.F., E.M., V.T.: investigation; G.I., A.O.: resources; L.S., A.D., P.D.: data analysis; M.O., A.O.: writing-original draft preparation; M.O., L.S., A.D., P.D., G.I., A.O.: writing-review and editing; M.O., R.B., E.C., A.F., E.M., L.S., A.D., V.T., P.D., G.I. and A.O.: visualization; A.O: supervision.
All authors have read and agreed to the current version of the manuscript.

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INFECTIOUS DISEASE

Cervical, oral and anal Human papillomavirus infection in women attending the Dermatology Unit of a regional reference hospital in Genoa, Italy: a prevalence study

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Keywords

Human papillomavirus infection • Prevalence • Cervical infection • Anal infection

Summary

Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI) worldwide. In women with genital infection, the virus can be transmitted by sex to the oral cavity of their partners and then to their own oral cavity. The aim of the present study was to establish the prevalence of cervical/anal/oral HPV infection in women attending the Dermatology Unit of the Policlinico San Martino of Genoa, the regional reference hospital in Liguria, Italy.
Methods. *Between January 2016 and December 2018, the female patients attending the STI center (cases) and those requiring a full body skin examination for skin cancer screening ("supposed" healthy population: controls) were recruited. Cervical/anal/oral samples were collected with ThinPrep liquid based cytology preparation system: polymerase chain reaction for HPV and cytologi-*

cal evaluation were performed. Overall, 85 cases and 31 controls were recruited.
Results. *Cervical HPV infection was detected in 60% of the cases and 48% of the controls; anal HPV infection in 44% of the cases and 26% of the controls. Cervical and anal HPV infection resulted associated, especially in the control group. Moreover, 32% of the cases and 29% of the controls proved HPV positive in the oral cavity. In the cases of our series, prevalence of cervical, anal and oral HPV infection was higher compared with the controls.*
Conclusions. *The high prevalence of anal-oral infections and the frequent association between anal and cervical infections, provide reason to suggest HPV screening also in the anal and oral regions, which may represent HPV reservoirs and grounds for cancer development.*

Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI) worldwide and a causative agent for cancer of the cervix uteri, vagina, vulva, penis, anus and oropharynx [1]. Especially women pay a high price for HPV infection: the majority of cancers attributable to HPV worldwide are cervical cancers representing the fourth most common cause of death from cancer in women [1]. After establishing infection, HPV can spread from one region of the body to another anatomically close area: indeed, patients with genital infection have an increased risk of anal infection. Moreover, in women with genital infection, the virus can be transmitted by sex to the oral cavity of their partners and then to their own oral cavity [1, 2].

Data on the prevalence of genital HPV infection are disparate, depending on demographic, geographic and clinical factors of the studied populations. The different prevalence of genital HPV infection among countries and even among regions of the same countries is influenced by migration, sexual behavior, type of

cervical lesion in women sampled, and diagnostic methods.

In 2014, the Center for Disease Control and Prevention (CDC) estimated the prevalence of cervical HPV infection of any type (both high and low risk genotypes) at 42.7% in a nationally representative US population [3]; similarly, an Italian studies from Southern Italy found overall prevalences of HPV infections of 45% in pregnant women during the first trimester [4]; a recent report from southern Mexico observed a higher prevalence of genital HPV infection (54.2%) among 7313 females aged 14-97 years: the cohort included women who had no intraepithelial lesions, women with low-grade and high grade squamous intraepithelial lesions, and women with cervical cancer [5]. In our previous study involving patients attending the STI clinic and healthy subjects, we found an overall prevalence of genital HPV infection of 50%, with a slightly higher prevalence in STI patients (51%) than in the healthy population (43%) [6].

Data on the prevalence of anal and oral HPV infection and their association with genital HPV infection in Italian women are few.

The present study aimed to establish the prevalence of HPV infection not only in cervical but also in anal and oral samples collected in the women attending the Dermatology Unit of the Policlinico San Martino, Genoa, the regional reference hospital in Liguria, Italy.

Methods

Between January 2016 and December 2018, the female patients attending the Dermatologic Unit of the Policlinico San Martino, Genoa, were asked to participate in the study, after giving written informed consent. The patients attending the STI outpatient clinic were recruited as "cases", since we assumed they could be at moderate-high risk of HPV infection; the age-matched patients attending the Dermatology Unit for skin cancer screening were recruited as "controls", since they could represent a supposed healthy population from the point of view of STI. Inclusion criteria were: to be over 18 years old and to show no overt clinical signs of ano-genital/oral/cutaneous HPV infection. Exclusion criteria were: age under 18, presence of cutaneous, ano-genital and/or oral warts, or having undergone treatment for warts in the last 6 months. Cervical, anal, oral samples were collected through a cytobrush by F.D. and G.C. in the STI outpatient clinic; samples were stored using the ThinPrep liquid based cytology preparation system, as previously described [7]. Polymerase chain reaction (PCR) for HPV and cytological evaluation were performed at the Pathology Unit of the Galliera Hospital, Genoa.

Statistical analysis

Data from cases and controls were statistically compared using the Fisher's exact test and chi-square test, considering a p-value < 0.05 as significant.

Results

Overall, 116 female patients were recruited: 85 cases (median age: 37 years, [interquartile range 25-46 years]) and 31 controls (median age: 38 years, [interquartile range 27-42 years]).

Cervical HPV infection was detected in 66 of the total 116 recruited women (57%), 60% of the cases (17 low-risk [LR] HPV, 34 high-risk [HR] HPV) and 48% of the controls (5 LR-HPV, 10 HR-HPV).

In the anal region, 45 of the 116 women (39%) proved positive for HPV: they were 44% of the cases (18 LR-HPV, 19 HR-HPV) and 26% of the controls (4 LR-HPV, 4 HR-HPV).

In the oral cavity, 36 of the 116 women (31%) proved positive for HPV: they were 32% of the cases (14 LR-HPV, 13 HR-HPV) and 29% of the controls (4 LR-HPV, 5 HR-HPV).

Cytological results are detailed in Table 1. The difference in the prevalence of cervical, anal and oral HPV infection among cases and controls was not statistically significant (p > 0.05).

Overall, simultaneous HPV infection in the anal site (regardless to genotype) was detected in 30 of the 66 women with cervical HPV infection (45%). Considering the healthy subjects, among the 15 women with cervical HPV, 7 had also anal HPV infection

Tab. I. Citological findings in HPV positive STI patients (cases) and apparently healthy subjects (controls).

site of infection	Cases			Controls			All 116 patients		
	85 STI patients			31 supposed healthy subjects					
	HPV+			HPV+			HPV+		
	global positivity	HR-HPV	LR-HPV	global positivity	HR-HPV	LR-HPV	global positivity	HR-HPV	LR-HPV
cervix	51 (60%)	34 (12 normal citology, 21 L-SIL, 1 H-SIL)	17 (3 normal citology, 14 L-SIL)	15 (48%)	10 (1 normal citology, 9 L-SIL)	5 (5 L-SIL)	66 (57%)	44 (38%)	22 (19%)
anus	37 (44%)	19 (19 normal citology)	18 (19 normal citology)	8 (26%)	4 (4 normal citology)	4 (4 normal citology)	45 (39%)	23 (20%)	22 (19%)
oral cavity	27 (32%)	13 (13 normal citology)	14 (14 normal citology)	9 (29%)	5 (5 normal citology)	4 (4 normal citology)	36 (31%)	18 (15.5%)	18 (15.5%)

STI sexually transmitted infections; HR-HPV high-risk HPV; LR-HPV low risk HPV; L-SIL low-grade squamous intraepithelial lesion; H-SIL high-grade squamous intraepithelial lesion. In the group of cases, cervical and anal HPV infections were not statistically associated (p > 0.05); conversely, in the control group, cervical and anal HPV infection resulted significantly associated (p = 0.0154 at Fisher's exact test).

(47%) versus 1 of the 16 (6%) women that were cervical HPV-negative. Considering the STIs women, anal HPV infections were detected in 23 of the 51 (45%) women with cervical HPV infection versus 14 of the 34 (41%) women that were cervical HPV negative. Therefore, in the control group, cervical and anal HPV infection resulted significantly associated (p = 0.0154 at Fisher's exact test); conversely, in the group of cases, cervical and anal HPV infections were not statistically associated (p > 0.05).

Oral HPV infection was detected in 16 of the 66 women with cervical HPV infection (29%) and in 18 of the 45 women with anal HPV (40%). Oral-cervical and oral-anal HPV infection were not statistically associated (p > 0.05) using chi-square test.

Discussion

As we have previously observed in a cohort of male and female patients [7], in the STI women of the present series, the prevalence of cervical, anal and oral HPV infection (regardless of genotype) was only slightly higher (respectively 60, 44, 32%) than in the "presumed" healthy women (48, 26, 29%), without statistically significant difference between the two groups.

The prevalence of HR-HPV genital infection in this study resulted in line (38%) with one of our previous works (39%) [7] but definitely lower than that reported in a similar recent study from Czech Republic (53%) [8]. According to our work, the Czech authors observed that all HPV infections occurred more often in cases than in controls and found a frequent association between cervical and anal HPV infection (especially in the group of cases) [8].

Another recent study from Hungary showed a cervical HR-HPV infection prevalence of 11.1% among 4,000 eligible samples from a screening target population of women without histories of hysterectomies, immunosuppression and/or operations or samplings that affected the cervix [9], confirming the different prevalence in very close geographical areas.

Also in extra-European studies, the overall prevalence of genital HPV infection in women varies widely, especially based on the population studied. A study from Ghana recruiting women who had never attended cervical screening prior to the study, found a prevalence of 37.2%, with 31% of women carriers of HR-HPV infections [10]. A work from Nigeria investigating prevalence and concordance of cervical, vulval, oral and anal HPV infection among female sex workers showed a very high prevalence and concordance of HPV infections in these sites: 88% in the vulva, 84% in the cervix, 75% in the anus and 24% in the oral cavity [11].

Regarding the association between cervical and anal HPV infection, more than 10 years ago Goodman et al. found that it appears common for anal and cervical HPV infections to occur simultaneously. The high degree of genotype-specific concordance between sites suggests that the cervix (or vagina) and anus may serve as reservoirs for HPV infection for the other anatomic sites [12]. Another study including 304 female sex workers in Amsterdam found a strong and significant concordance in vaginal and anal HR-HPV infection: logistic regression analyses demonstrated that having an anal HR-HPV infection was a risk factor for vaginal HR-HPV infection; likewise, vaginal HR-HPV infection was a risk factor of anal HR-HPV infection [13].

According to these studies [11-13], our work suggests that the presence of HPV genital infection in women is a risk factor for detection of HPV in the anal region. Although sexual intercourse is the primary route of anal infection, several authors have found that a history of anal intercourse is not the single risk factor for incident anal HR-HPV infection or anal cancer, suggesting alternative routes of transmission, including non-penetrative sex or inoculation through fomites or vaginal discharge. Concomitant HPV infection in different anatomical sites (cervix-vagina-anus, for example) might be due to viral shedding between contiguous anatomic structures and/or to autoinoculation through fingers [12, 14] or unhygienic practices, as the use of sex toys [15]. Also during hygienic practices the virus can spread from the vagina to contiguous regions such as the anus.

Therefore, the presence of HPV infection in an anatomic site suggests the need for a screening protocol in multiple anatomic sites. For example, in a subject with genital HPV infection associated with premalignant lesion of the cervix should also be taken into account the possible presence of HPV infection in other sites and offered the opportunity to screen for HPV DNA and premalignant lesions of the anus.

Unfortunately, despite the evidence of the association among cervical, anal, and oral HPV infections in women and men, to date, the Center for disease Control and Prevention (CDC) states that data are insufficient to recommend routine anal HPV infection and cancer screening among populations at risk for anal cancer (persons with HIV infection, men who have sex with men and those having receptive anal intercourse). However, the last CDC guidelines on STI treatment admit that certain clinical centers perform anal cytology to screen for anal cancer among high risk populations, followed by high resolution anoscopy (HRA) for those with abnormal cytological findings; the CDC guidelines report also that "HRA can be useful for diagnosis of high grade-squamous intraepithelial lesions (H-SIL), to monitor response to therapy or to conduct surveillance of H-SIL for evidence of progression" [16].

Conclusions

In conclusion, despite the limitation of the small sample size of our study, our data confirm the wide circulation of HPV not only in the genital sites but also

in the anal and oral ones; we therefore emphasize the need to improve the screening protocols for preventing HPV related cancers not only in the cervix but also in multiple anatomic sites, especially the anus.

Our results underlie the diffuse lack of awareness on this subject among the general population that is often unaware of having contracted a STI and highlight the urgent need of effective information campaigns [17]. The increase of knowledge on STIs to educate to sexual health through the rules of safe sex, the early diagnosis of STIs through screening tests for discovering asymptomatic infections, and prevention strategies (as anti-HPV vaccination) especially in high risk populations as the prison inmates [18], should all be encouraged by institutions like health services and schools.

Acknowledgements

Conflict of interest statement

Authors' contributions

F.D. and G.C. conceived of the presented idea; A.H. developed the theory and performed the computations; A.H. and A.P. verified the analytical methods; all the authors discussed the results and contributed to the final manuscript. The manuscript has been approved by all authors.

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INFECTIOUS DISEASE

Indirect hyperbilirubinemia and jaundice during chronic hepatitis C in an HIV-infected patient treated with glecaprevir/pibrentasvir (GLE/PIB) and antiretroviral therapy (ART). The first reported case in Italy

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Keywords

Glecaprevir • Pibrentasvir • HCV • HIV • Chronic hepatitis C • Direct-acting antiviral • Adverse drug reaction

Summary

Glecaprevir (GLE)/pibrentasvir (PIB) is a pangenotypic direct-acting antiviral regimen approved for treating chronic hepatitis C virus. Primary treatment and re-treatment with GLE/PIB are effective and safe for patients without decompensated liver cirrhosis and chronic hepatitis C in a real-world clinical setting. However, in the context of compensated cirrhosis and concomitant administration of inhibitors of cytochromes, a careful monitoring of liver biomarkers, as well as therapeutic drug monitoring (TDM), may be advisable during GLE/PIB therapy. The GLE / PIB combination is very effective and safe in achieving a sustained virological response, but it can be associated with the development of severe hepatic adverse events, which require virological and serum concentration monitoring of the two drugs to prevent a serious liver damage. The possible onset of hyperbilirubinemia must not necessarily lead to the suspension of therapy, because the phenomenon may be transient. We report what is likely the first known case of severe jaundice after treatment with GLE/PIB in Italy in a patient with compensated chronic hepatitis in the context of HIV disease.

Introduction

Real-world evidence indicates that Glecaprevir (GLE)/pibrentasvir (PIB) 300 mg/120 mg once daily (Mavyret/Maviret), Hepatitis C Virus Direct-Acting Antivirals is a well-tolerated and highly effective for a broad range of HCV-infected patients.

The combination of GLE and PIB, a pan-genotypic and ribavirin-free direct acting antiviral agent regimen, has shown significant efficacy and very few serious complications and was recently approved for chronic hepatitis C virus (HCV) infection

These drugs block two essential enzymes for the replication of HCV. GLE blocks the action of NS3/4A protease, while PIB blocks a NS5A, a key enzyme in HCV RNA polymerization [1]. The most common side effects with GLE/PIB are headache and tiredness. According to EASL guidelines, no dose adjustment of Maviret is required in patients with mild hepatic impairment (ChildPugh A). GLE/PIB is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C). Presence of cirrhosis, older age, and high body weight were identified as significantly associated with increased GLE/PIB exposure (high body weight is associated with increased exposure to PIB) [2].

CASE REPORT

We report the first case of serious indirect hyperbilirubinemia and jaundice observed in Italy in an HIV-infected patient treated with GLE/PIB and antiretroviral therapy (ART). A 55-year-old man with a history of HIV infection in ART (Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg) and compensated liver disease (without cirrhosis), due to chronic hepatitis C virus (HCV) genotypes 4, was admitted to our hospital because of jaundice, tiredness, fatigue, and asthenia. It is well known that no dose adjustment of elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide is recommended in patients treated with GLE/PIB. However, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3 inhibition by cobicistat, and OATP inhibition by elvitegravir may lead to an increase plasma concentration of glecaprevir and pibrentasvir that are P-gp, BCRP, and OATP inhibitors. At 10 weeks following treatment with GLE/PIB, our patient showed evidence of jaundice and severe hyperbilirubinemia (Total bilirubin 12.76 mg/dL, direct bilirubin 7.14 mg/dL). The ALT and AST levels were within the

normal range. At baseline: Cd4+ cells count 374, HIV-RNA < 20 copies/mL, HCV-RNA 1.490.000 UI/mL. Fibrosis stage: F3. Plasma concentrations of GLE/PIB was performed using blood samples taken 1 hour before taking Maviret tablets and 6 and 12 hours after this dose. Plasma samples for determination of GLE and PIB concentrations were analyzed through a UltraHigh Performance Liquid Chromatography coupled with Tandem Mass Spectrometry (UHPLC-MS/MS) method at the Laboratory of Clinical Pharmacology and Pharmacogenetics, University of Turin. Plasma levels of GLE and PIB were as follows: GLE 2472 ng/mL, PIB 92 ng/mL (T0); 8758 ng/mL, PIB 187 ng/mL (T2); GLE8239 ng/mL, PIB 272 ng/mL (T4); GLE 7314, PIB 256 ng/mL (T8), respectively (for GLE higher than the drug concentration in healthy adults). The mean value of glecaprevir maximum plasma concentration level was reported as 1,150 to 1,390 ng/mL in normal healthy adult subjects [3]. Patient was treated with ursodeoxycholic acid, sibylline, vitamin E and he received adequate rehydration therapy. He completed GLE/PIB treatment, maintaining an excellent virological response during a close monitoring of liver function. Completed 12 weeks after the end of the treatment, total bilirubin has returned to normal values. Blood examinations were performed at end of treatment (EOT), and at 3, 6, and 12 months post-treatment during the 12-month follow-up period.

Discussion

GLE/PIB are direct-acting antiviral agents with pangenotypic activity and a high barrier to resistance. GLE/PIB are primarily eliminated via biliary excretion; they are minimally metabolized with < 1% renal excretion and have high percentages of plasma protein binding (98% for glecaprevir and > 99% for pibrentasvir) [4]. The safety of PIB and GLE was evaluated in phase II and III clinical trials. Some caution is needed administering for the co-administration of drugs that are substrates of CYP3A, since GLE is a weak CYP3A inhibitor [5]. In HIV-HCV coinfected patients, GLE/PIB is contraindicated with atazanavir-containing regimens and is not recommended with other HIV protease inhibitors. Similarly, the inducing non-nucleoside reverse transcriptase inhibitors efavirenz, etravirine and nevirapine are not recommended because of an expected reduction in plasma exposure of glecaprevir/pibrentasvir. All other antiretroviral drugs can be co-administered, including cobicistat when used with integrase inhibitor elvitegravir [5]. However, co-administration of GLE/PIB with medicinal products that inhibit P-gp and BCRP (e.g. ciclosporin, cobicistat, dronedarone, itraconazole, ketoconazole, ritonavir) may slow elimination of GLE/PIB, increasing their plasma levels.

Since cobicistat is an inhibitor of OATP1B3, of P-gp and BCRP, it is expected to increase the systemic exposure to GLE [6].

In a study that evaluated the drug-drug interaction and safety of GLE/PIB coadministration in healthy volunteers,

the combination of GLE/PIB at doses up to 400 mg was well tolerated by the healthy subjects in this study, while high GLE exposures at 700 and 1200 mg were associated with grade 2/3 elevations in alanine aminotransferase, aspartate aminotransferase, and/or bilirubin [7]. Elevations in total bilirubin of at least 2x ULN were observed in 1% of subjects related to glecaprevir-mediated inhibition of bilirubin transporters and metabolism. Bilirubin elevations were asymptomatic, transient, and typically occurred early during treatment. Bilirubin elevations were predominantly indirect, mostly in patients with pre-existing elevated bilirubin levels (consistent with Gilbert's Syndrome), and not associated with ALT elevations [8]. GLE/PIB was safe and efficacious in a dedicated Phase III trial [9] for patients with compensated liver cirrhosis (EXPEDITION-1) who had not elevations in ALT and no patients prematurely discontinued treatment because of adverse events. No cases consistent with a drug-induced liver injury were reported in an integrated analysis from 9 Phase II and III clinical trials, assessing the efficacy and safety of GLE/PIB treatment in patients with compensated liver disease [10]. Grade 3 transient elevations in indirect bilirubin were observed in 1% in patients, particularly in patients who had already grade 1 or 2 elevations before treatment. Most of these elevations were transient in nature and predominantly resulted from increased, indirect bilirubin fractions, which is consistent with the known capability of GLE to inhibit bilirubin transport and conjugation. Higher GLE and/or PIB exposures may be expected in HCV-infected patients with Child-Pugh-B and CP-C hepatic impairment than in HCV-infected subjects with compensated cirrhosis [11]. Co-administration of GLE/PIB with medicinal products that inhibit P-gp and BCRP (e.g. ciclosporin, cobicistat, dronedarone, itraconazole, ketoconazole, ritonavir) may slow elimination of GLE/PIB, increasing their plasma levels. Furthermore, drugs that inhibit OATP1B1/3 (e.g. elvitegravir, ciclosporin, darunavir, lopinavir) increase systemic concentrations of glecaprevir [6]. GLE plasma levels were increased by ritonavir boosted protease inhibitors and cobicistat boosted elvitegravir [12]. Zhang J et al. observed presented reported two patients with hyperbilirubinemia as a side effect and potential for cirrhotic decompensation with renal failure during treatment with GLE/PIB. After GLE/PIB was held bilirubin showed rapid improvement [13]. Yoon JH et al. reported the first known case of severe jaundice after medication with GLE/PIB in a patient with compensated liver cirrhosis, with a plasma drug concentration level of GLE more than 15 times higher than the drug concentration level verified in normal adults [14]. This phenomenon was related to a low activity of CYP3A. In a Taiwanese investigation on the profile of GLE/PIB, 3 (2%) patients had Grade 3 elevation of total bilirubin level [15]. One of them had active HCC and received sorafenib along with radiotherapy before the initiation of GLE/PIB. The patient temporarily discontinued GLE/PIB for 5 days and resumed the scheduled treatment after the recovery of hyperbilirubinemia. The other 2 patients had total bilirubin levels peaked at 4.05 mg/dL and 3.42 mg/

dL, respectively; both completed the assigned treatment without interruption. In the CERTAIN-1 Study, a phase 3, open-label, multicenter study assessing the safety and efficacy of GLE/PIB (300/120 mg) once daily in Japanese patients with chronic HCV GT1 infection, blood bilirubin increased in 3 (2%) patients of Arm A (Patients randomized to 8 weeks of treatment with GLE/PIB), in 3 (6%) patients in the Arm B (Patients randomized to 12 weeks of treatment with ombitasvir/paritaprevir/ritonavir), and in 1 (3%) patient in the Arm C (Patients with compensated cirrhosis assigned to 12 weeks of GLE/PIB, 300/120 mg) [16]. In the CERTAIN-2 Study, assessing the safety and efficacy of GLE/PIB in treatment-naive patients without cirrhosis, blood bilirubin increased in 1 (1%) patient in arm A (Patients administered GLE/PIB for 8 weeks) and in 7 (15%) patients in the Arm B (Patients administered sofosbuvir + ribavirin for 12 weeks) [17].

For patients (with or without compensated cirrhosis) treated with G/P, no grade ≥ 3 abnormalities occurred in hemoglobin, ALT, AST, or total bilirubin levels. Clinically significant laboratory abnormalities occurred in less than 1% of patients and four patients (1 patient was HIV+) had grade 3 elevations in total bilirubin levels. All patients with bilirubin elevations of grade 3 also had bilirubin elevations of grade 1 or 2 at baseline [18].

The Food and Drug Administration (FDA) has received reports that the use of GLE/PIB, elbasvir+grazoprevir (Zepatier), or sofosbuvir + velpatasvir + voxilaprevir (Vosevi) to treat chronic hepatitis C in patients with moderate to severe liver impairment has resulted in rare cases of worsening liver function or liver failure identified in 63 cases (Mavyret, n = 46, Zepatier, n = 14, and Vosevi, n = 3), reported in the FDA Adverse Event Reporting System (FAERS) database and in the medical literature through January 8, 2019 [19]. This occurred most commonly in the first 4 weeks of therapy, most of the patients had Child-Pugh B or C cirrhosis, and liver related events included hyperbilirubinemia (n = 42), jaundice (n = 32), ascites (n = 27), and hepatic encephalopathy (n = 12). Ten cases reported isolated hyperbilirubinemia and jaundice without concomitant evidence of increased transaminase levels or other hepatic decompensation events, and eight cases reported deaths. The median time to onset of a liver-related event or liver decompensation after initiating treatment was 22 days, ranging from 2 days to 16 weeks. The most frequently reported liver related events were hyperbilirubinemia (n = 42), jaundice (n = 32), ascites (n = 27), and hepatic encephalopathy (n = 12). Discontinuation of the drug resulted in resolution of symptoms or reduced liver biochemical values in 39 of the 63 cases, and there were two cases of recurrence of symptoms upon re-initiating treatment [19].

In conclusion, our described case suggests that the concomitant boosting effect of COBI and the reduced elimination of GLE related to cirrhosis can be capable of increase GLE exposure up to potentially toxic levels, causing bilirubin elevation and jaundice. Nevertheless, even in such a particular case, the elevations in bilirubin resulted not associated with liver injury and did not lead to treatment discontinuation or failure due to toxicity. Therefore, we suggest that, in the context of compensated cirrhosis and concomitant administration of inhibitors of cytochromes, a careful monitoring of liver biomarkers, as well as therapeutic drug monitoring (TDM), may be advisable during GLE / PIB therapy. The possible onset of hyperbilirubinemia must not necessarily lead to the suspension of therapy, because the phenomenon may be transient. In cases of elevation of grade 2-3 of bilirubin, hospitalization for direct, more regular and prudent observation, may be advisable; the administration of liver protective agents and adequate rehydration can favor and improve the adverse event.

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Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

All the authors contributed to the study of the clinical case and to the drafting of the manuscript.

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Prediction of Hepatitis disease using ensemble learning methods

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Keywords

Hepatitis B virus • Hepatitis C virus • Ensemble learning • Data analysis

Summary

Objective. *Hepatitis is one of the chronic diseases that can lead to liver cirrhosis and hepatocellular carcinoma, which cause deaths around the world. Hence, early diagnosis is needed to control, treat, and reduce the effects of this disease. This study's main goal was to compare the performance of traditional and ensemble learning methods for predicting hepatitis B virus (HBV), and hepatitis C virus (HCV). Also, important variables related to HBV and HCV were identified.*

Methods. *This case-control study was conducted in Hamadan Province, in the west of Iran, between 2014 to 2019. It included 534 subjects (267 cases and 267 controls). The bagging, random forest, AdaBoost, and logistic regression were used for predicting HBV and HCV. These methods' performance was evaluated using accuracy.*

Results. *According to the results, the accuracy of bagging, random forest, Adaboost, and logistic regression were 0.65 ± 0.03, 0.66 ± 0.03, 0.62 ± 0.04, and 0.64 ± 0.03, respectively, with random forest showing the best performance for predicting HBV. This method showed that ALT was the most important variable for predicting HBV. The the accuracy of random forest was 0.77±0.03 for predicting HCV. Also, the random forest showed that the order of variable importance has belonged to AST, ALT, and age for predicting HCV.*

Conclusion. *This study showed that random forest performed better than other methods for predicting HBV and HCV.*

Introduction

Hepatitis is one of the dangerous diseases that result from viral infections [1, 2]. This virus attacks the liver leading to its inflammation. Inflammation may lead to the death of the liver cells and affect the functionality of the liver [3]. Five main types of hepatitis have been identified, namely hepatitis A, B, C, D, and E viruses [4]. The most common types of these are hepatitis A virus, hepatitis B virus (HBV), and hepatitis C virus (HCV). Among these, HBV and HCV will cause chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma [2, 5, 6].

It is estimated that 257 and 71 million people around the world are currently infected with HBV and HCV, respectively [7, 8]. The prevalence of HBV depends on the geographic area, and its overall prevalence was estimated at 3.6% in the world [9]. The HCV global prevalence in adults is 2.5% [10]. Furthermore, the incidence of HCV was estimated between 0.5% and 2.8% in various studies [11, 12]. According to previous studies, African and Asian countries have the highest prevalence of HBV and HCV [13, 14]. In Iran, the prevalence of HBV and HCV was about 2.2 and 0.5% in the general population, respectively [15, 16].

Prediction of chronic diseases plays an important role in health informatics. Hepatitis is one of the chronic diseases that can lead to liver cirrhosis and hepatocellular carcinoma, which cause deaths around the world.

Therefore, early diagnosis is needed to control, treat, and reduce the effects of this disease [17-19]. In the past few years, machine learning methods have been widely employed for predicting chronic diseases [2, 5, 13, 17, 20-23]. Among them, ensemble learning methods such as bagging, random forest, and AdaBoost are powerful methods. These methods can achieve better learning performance by combining several weak learners [24-26]. Despite the several studies that have used ensemble learning methods for the prediction of hepatitis disease, only a few of them have been performed in Iran [27, 28]. Furthermore, hepatitis is a public health concern, especially in developing countries such as Iran [29, 30]. Hence, this study's main goal was to compare the performance of three ensemble learning methods (including bagging, random forest, Adaboost) and logistics regression as traditional methods for predicting hepatitis diseases (HBV and HCV). Important variables related to HBV and HCV were also identified.

Methods

STUDY DESIG

This case-control study was conducted in Hamadan Province, Western Iran. This study was approved by the ethics committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1396.330).

Between 2014 and 2018, 267 patients with a definite diagnosis of HBV or HCV (131 HBV, 131 HCV and 5 HBV and HCV), as the case group, were referred to the hepatitis clinic and the infectious diseases clinic of Hamedan Health Center. The control group was selected from among 267 people referred to Sina Hospital and Dey Hamedan Laboratory during 2018-2019. The second author collected case and control group data using a checklist. The checklist included data related to demographic characteristics (age, sex) and the results of laboratory tests. All participants were over 15 years of age. Non-cooperation of the participants to perform further laboratory tests, ultrasound or any other follow-up was excluded from this study. Informed consent was obtained from the participants after explaining the objectives of the study.

Data Collection and preparation

The data collection tools included an information form on demographic characteristics (age, sex) and laboratory tests. Of any contributor, under sterile conditions, a 10 cc blood sample was obtained by an expert sampler. At the time of admission to the laboratory, alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol (CHOL), triglyceride (TG), fasting blood sugar (FBS), body mass index (BMI) were measured and recorded. Missing values of these variables were imputed with the multiple imputations method. For an exact evaluation of probable causes of elevated ALT, including viral hepatitis and fatty liver, HBsAg, HBCAb, and HCVAb as well as liver sonography were requested for all of the non-hepatitis groups with high ALT. An abnormal measure of CHOL, TG, and blood sugar is defined as above 200, 200, and 115 respectively. The aforementioned cutoffs were determined according to the recommendation of the kit's manufacturer (Roche Biotech).

Statistical Analysis

Bagging, proposed by Breiman, is one of the most popular and earliest ensemble learning methods. This method uses bootstrap resampling to create multiple training subsets from the given original training dataset. Then each training subsets is used to construct a classifier, which is also called a based learner. Eventually, all based learners aggregate into the final prediction model [24].

Random forest, also proposed by Breiman, is a tree-based ensemble learning method. In this method, each tree is grown by a bootstrap sample, which is obtained by randomly resampling from the training dataset. When building each tree, at each nodeot tree, a subset of predictors was selected randomly and among which, the best predictor is chosen for splitting. Eventually, predictions are obtained by averaging the results of all the trees. The random forest can also estimate the importance of predictors using the Gini Index, which makes the results more interpretable [25].

AdaBoost, proposed by Freund and Schapire, is one of the most popular ensemble learning methods that was used boosting algorithms. This method creates a subset of the training dataset. Then an initial classifier-based model is constructed by assigning the same weight for

instances. Each boosting iteration assigns weight to the training instances so that the next learner concentrates on reweighted instances that were misclassified previously. Eventually, the final model is a weighted sum of all the classifier-based models [26].

Logistic regression as a traditional method was performed to assess the effect of prognostic factors on HBV and HCV. This method can determine the direction of association of variables on outcome. The results are also easy to interpret [31].

The cross-validation method has been used for evaluating the performance of three ensemble learning methods and logistic regression, in which the dataset was randomly divided into training (70%) and test (30%) sets. Then, the discrimination ability of each methods was assessed by accuracy. This procedure was repeated 100 times and the average values of accuracy were computed.

Software packages

The statistical analyses were performed using R Version 3.6.3 [32], with the following packages "adabag", "CORElearn" and "randomForest".

Results

The study involved 534 subjects (267 cases and 267 controls). The case group included 131 patients with HBV, 131 patients with HCV, and 5 patients with HBV and HCV. The control group also included 267 healthy subjects. The characteristics of cases and controls are given in Table I.

Tab. I. Characteristics of the study population.

Variables	Cases N = 267	Controls N = 267	Total N = 534
Age (Year)	38.82 ±10.99	43.05±13.86	40.94 ±12.67
ALT	59.08 ± 58.83	39.33 ± 38.08	49.20 ± 50.49
AST	42.15 ± 33.81	28.06 ± 20.57	35.11 ± 28.83
Sex			
Male	210 (78.7)	157 (58.8)	367 (68.7)
Female	57 (21.3)	110 (41.2)	167 (31.3)
BMI			
Underweight/ Normalweight	89 (33.3)	63 (23.6)	152 (28.5)
Overweight/ Obese	178 (66.7)	204 (76.4)	382 (71.5)
FBS			
≤ 115	252 (94.4)	240 (89.9)	492 (92.1)
> 115	15 (5.6)	27 (10.1)	42 (7.9)
CHOL			
≤ 200	187 (70.0)	177 (66.3)	364 (68.2)
> 200	80 (30.0)	90 (33.7)	170 (31.8)
TG			
≤ 200	189 (70.8)	204 (76.4)	393 (73.6)
> 200	78 (29.2)	63 (23.6)	141 (26.4)

Data are expressed as Mean ± SD and N (%). HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHOL: Cholesterol; TG: Triglyceride; FBS: Fasting blood sugar; BMI: Body mass index.

Fig. 1. The variable importance for HBV and HCV.
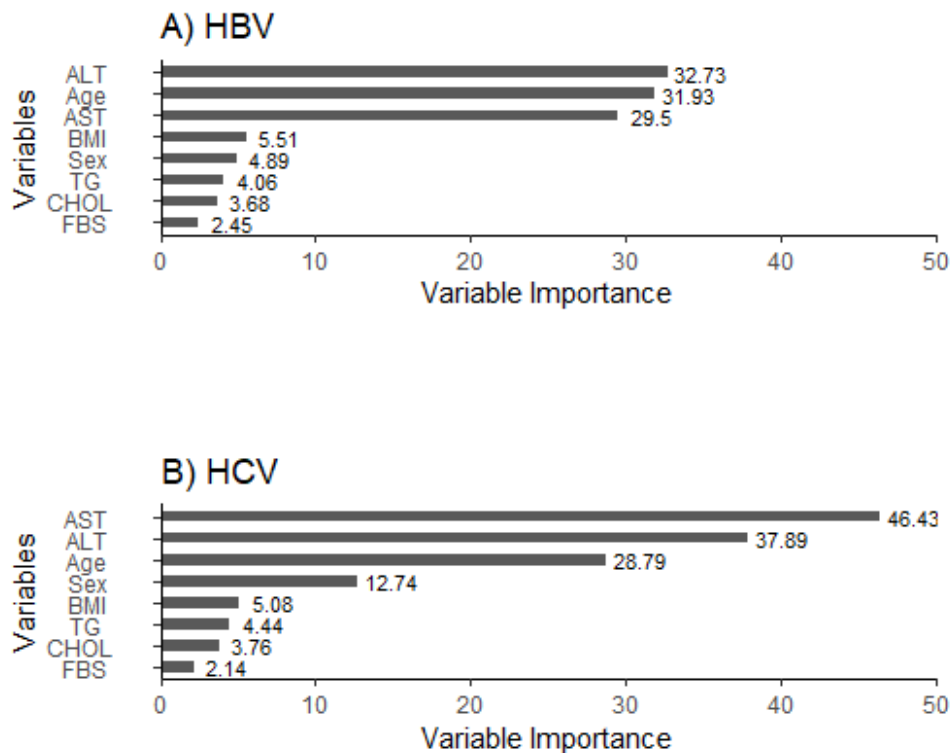
A) HBV

B) HCV

HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHOL: Cholesterol; TG: Triglyceride; FBS: Fasting blood sugar; BMI: Body mass index.

Figure 1 displays the variable importance obtained from random forest for HBV and HVC. The results showed that ALT, age, and AST as the three most important variables for predicting HBV [Fig. 1 (A)]. The random forest also identified that the order of variable importance has belonged to AST, ALT, and age for predicting HCV [Fig. 1 (B)].

Table II shows the performance of three ensemble learning methods (bagging, random forest, Adaboost) and logistics regression for predicting HBV and HCV in testing datasets. As seen, the accuracy of bagging, random forest, Adaboost, and logistic regression were 0.65 ± 0.03, 0.66 ± 0.03, 0.62 ± 0.04, and 0.64 ± 0.03, respectively, with random forest showing the best performance for predicting HBV. Also, the performance of random forest compared to other methods was better for predicting HCV.

Tab. II. The performance criteria of methods.

Test	Methods	Accuracy
HBV	Bagging	0.65 ± 0.03
	AdaBoost	0.62 ± 0.04
	Random Forest	0.66 ± 0.03
	Logistic regression	0.64 ± 0.03
HCV	Bagging	0.76 ± 0.03
	AdaBoost	0.75 ± 0.02
	Random Forest	0.77 ± 0.03
	Logistic regression	0.74 ± 0.03

HBV: Hepatitis B Virus; HCV: Hepatitis C Virus.

Discussion

In the current study, the performance of traditional and ensemble learning methods was assessed for predicting HBV and HCV. The results showed that the random forest performs better than other methods for predicting HBV and HCV. This method identified age, ALT, and AST as the top three most important variables for predicting both hepatitis.

According to previous studies, ALT and AST were identified as important variables in discriminating between healthy controls and patients with hepatitis [18, 33-35]. These findings are consistent with our results. The AST was an important variable that was identified by random forest in the present study. Also, the random forest identified ALT as one of the most important variables for predicting HBV and HCV. It seems that due to lifestyle changes and the addition of factors effective in increasing ALT such as BMI and blood lipids, high ALT is not caused by infectious hepatitis in most cases. However, because of the importance of HBV and HCV in endemic areas, it is best to screen individuals for abnormally high levels of transaminases for hepatitis virus.

Based on our findings, age was identified as another important variable in predicting both types of hepatitis. This results in agreement with Yasin et al., who used data mining techniques for the classification of HCV and concluded that age was associated with it [36].

Several studies have been performed in predicting hepatitis disease using machine learning methods. For instance, Karthikeyan and Thangaraju [4] applied six different machine learning methods to classify hepatitis patients. They showed that the Naive Bayes has the highest performance, and the random forest was also relatively good. Syafa'ah et al. [21] also evaluated the performance of classification machine learning methods for predicting HCV. In their study, neural networks and random forests had a good performance. Nandipati et al. [37] compared the performance of different machine learning methods for predicting HCV. They found that random forest had better performance in comparison to other methods in the binary class. Similar results were also reported in a study conducted by Orooji and Kermani [18]. In another study, Kumar and Sikamani [22] showed that the accuracy of random forest was higher than logistic regression to predict hepatitis. Chicco and Jurman [33] used an ensemble learning method for enhanced classification of patients with hepatitis and cirrhosis. The results of their study confirmed the usefulness of random forest for HCV and cirrhosis diagnosis prediction. The results of these studies were in agreement with our study, which indicates that random forest has the best performance.

The main limitations of this study were the small sample size and failure to consider some risk factors associated with hepatitis. Despite these limitations, our study showed that ensemble learning methods perform reasonably well for HCV and HBV prediction. The results could help doctors better identify people at high risk for hepatitis.

In fact, early detection of this dangerous virus can increase the chance of treatment and prevent the complications of hepatitis, including more deaths caused by it.

Conclusions

This study showed that the performance of random forest provided better results compared to other methods for predicting HBV and HCV based on accuracy.

Acknowledgments

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Authors' contributions

M.M., S.N. and H.M. contributed to the study design, analysis, and interpretation of data. A.H. participated in data collection. R.N.V. participated in data analysis and drafting of the manuscript. All authors read and approved the final manuscript.

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INFECTIOUS DISEASE

Assessment of the knowledge, attitude, and practice related to visceral leishmaniasis among residents of Al-Suwaira city, Wasit Governorate, Middle East of Iraq

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Summary

Introduction. *It is important to assess the knowledge, attitudes, and practice (KAP) related to visceral leishmaniasis (VL) to implement an effective control program. Hence, this study aimed to highlight KAP among residents of Al-Suwaira city in Wasit Governorate, Middle East of Iraq.*
Methods. *During March to May 2021, a cross-sectional study was done on 121 randomly selected residents. A normal self-administered questionnaire was used to measure KAP. Descriptive analysis was used to present the results.*
Results. *Overall, participants indicated average knowledge towards VL. However, the incubation period of VL (23.9%), the symptoms of VL (57.9%), and the diseases' transmission ways (54.5%) were recognized as knowledge gaps. Participants had a positive attitude towards VL, as the majority of them (more than*

70.0%) agreed that VL causes health problems in local populations and local communities should be actively involved in the fight against VL. Also, the majority of participants agreed that VL is a treatable disease. Regarding the practice towards VL, 110 (90.9%) participants had taken preventive measures against sand fly bites. The majority of respondents (44.6%) chose cleanliness as a preventive measure. The main sources of information that participants used to learn about the disease were the Internet (57.0%) and television (19.8%).
Conclusion. *Overall, participants had good knowledge, positive attitudes, and good practice when it came to VL prevention. However, there were also some gaps. Hence, it is recommended that knowledge-based strategies be strengthened and implemented consistently to raise awareness among residents in the region.*

Introduction

Visceral leishmaniasis (VL), often known as kala-azar (Hindi for black fever), is the most severe form of leishmaniasis caused by protozoan parasites of the genus *Leishmania* [1, 2]. Fever, weakness, weight loss, lymphadenopathy, pancytopenia, hepatosplenomegaly, and death are the symptoms and consequences of this chronic systemic disease [1, 3]. In the Old World, the etiologic agents are *Leishmania donovani* and *Leishmania infantum*; and in the New World, *Leishmania chagasi* is the contributing agent [1]. Transmission of the Old World and New World species occurs through members of the genus *Phlebotomus* and *Lutzomyia* sand flies, respectively. The parasite penetrates macrophages, where it replicates and causes disease, and is known to infect humans, wild and domestic animals [1, 2, 3]. Currently, the number of annual VL cases has decreased significantly (less than 100,000), compared with previous estimates of 400,000 cases [1]. Currently, leishmaniasis is endemic in the Mediterranean region, Africa, Americas, Asia and is found in 89 countries [4]. According to a report by World Health Organization (WHO), Sudan, Brazil, Nepal, Bangladesh, and India

accounted for 90.0% of all VL cases until 2010 [4]. VL is frequently found in distant places with few or no healthcare facilities, inadequate patient assessment and identification tools, inadequate personal protection, and most importantly, few or no skilled personnel [3, 5].
Both forms of cutaneous and visceral leishmaniasis occur in Iraq, and it has been classified as a high burden country by the WHO [6]. Iraq is one of the Middle Eastern countries with a higher incidence of VL in the city of Al-Suwaira in Wasit Governorate, which is located in the endemic area of Iraq between Baghdad and Misan. Most cases occur in rural areas where hygienic measurement and educational programs are lacking. The most important prerequisite for the success of any disease prevention and control program is community engagement. The cooperation of the affected population is necessary for the implementation and use of the program activities. Community knowledge, attitudes, and practices (KAP) related to the disease need to be assessed in order to implement successful prevention and control programs [3]. Also, the KAP study provides an opportunity to explore possible misconceptions about the disease in the community that may influence disease control and prevention [3].

To the best of our knowledge, there have been few studies evaluating KAP in the context of the VL cases in the Iraqi population. Hence, this study aimed to assess the KAP of residents in relation to VL to develop disease control programs that would contribute to the reduction of disease cases in Iraq, particularly among residents of Al-Suwaira city in Wasit Governorate.

Methods

Ethical consideration

This study was approved by the Ethics Committee of the Middle Technical University, Baghdad, Iraq (January, 01 2021) in accordance with the Helsinki Declaration of 1975. Written informed consent was obtained from all participants.

Study area and participants sampling

From March to May 2021, a descriptive cross-sectional survey was conducted among the population of Al-Suwaira city. Al-Suwaira is located in eastern Iraq at 32°56′25″N 044°38′04″E in the Wasit Governorate about 35 km south of Baghdad, the capital of Iraq. The residence registration number was used as the sampling frame for selecting individuals using a simple random sampling method.

Inclusion and exclusion criteria

Individuals 18 years of age and older from the city of Al-Suwaira in Wasit Governorate who had lived there for at least one year or longer participated in this study. Individuals under 18 years of age and those who had lived in the area for less than one year, as well as those who were unable to answer the questionnaire, were excluded from the study.

Data collection

Data were collected using a self-administered questionnaire that was sent to the relevant participants for their responses. The questionnaire had been previously reviewed. After a thorough assessment of content validity, the first draft was forwarded to three experts for feedback on the relevance, simplicity, and importance of the content. The questionnaire was divided into five parts: the first part addressed participants' demographic data such as gender, age, occupation, qualification, marital status, and place of residence; the second part contained 12 questions assessing participants' knowledge of VL including causes, symptoms, transmission, incubation time, and disease prevention; the third part included seven statements assessing attitudes towards VL prevention and treatment; the fourth part addressed four questions assessing the participants' practices related to VL prevention and control; and the fifth part captured respondents' sources of information about VL. Demographic data were expressed in frequencies and

percentages using descriptive analysis. The response options for the knowledge questions were yes, no, and don't know. Participants' responses to the attitudes questions were scored with three agreement points : agree, disagree, and don't know. Response options for the practice questions were recorded as yes and no. Finally, the percentage of each category was calculated.

Data analysis

Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM Corporation, Armonk, NY, USA) was used to analysis of the responses of the participants.

Results

Demographic information of the participants

A total of 121 individuals took the time to complete the survey. The demographic characteristics of the participants were shown in Table I. The majority of participants were under 30 years old (n = 77, 63.6%), and female participation was higher (n = 62, 51.2%) than male participation (n = 59, 48.8%). In terms of education, the majority of participants (n = 51, 42.1%) had a bachelor's degree, while only 5 (4.1%) individuals were unable to read and write. However,

Tab. I. Demographic information of the participants.

Demographic information Percent		Number	Percent
Age Groups	< 30	77	63.6
	(30-40)	25	20.7
	(41-50)	14	11.6
	> 50	5	4.1
	Total	121	100.0
Gender	Male	59	48.8
	Female	62	51.2
	Total	121	100.0
Qualifications	Unable to read and write	5	4.1
	Primary school	21	17.4
	Secondary school	44	36.4
	Bachelor's	51	42.1
	Total	121	100.0
Occupation Status	Farmer	9	7.4
	Government employee	37	30.6
	Student	47	38.4
	House wife	21	17.4
	Others	7	5.8
	Total	121	100.0
Marital Status	Married	51	42.1
	Unmarried	70	57.9
	Total	121	100.0
Residence	Rural	23	19.0
	Urban	98	81.0
	Total	121	100

Tabl. II. Knowledge of contributors towards visceral leishmaniasis (VL) in Al-Suwaira city, Wasit Governorate, Middle East of Iraq.

Statements	Yes (%)	No (%)	I do not know (%)
VL is a parasitic disease.	65 (53.7)	10 (8.3)	46 (30.0)
VL is a very serious disease.	40 (33.1)	29 (23.9)	52 (42.9)
Incubation period of VL is 2 weeks-several years.	29 (23.9)	27 (22.3)	65 (53.7)
In a number of cases symptoms appear during 2-6 months.	40 (33.1)	30 (24.8)	51 (42.1)
Traveling to a VL endemic area is a risk factor for the disease.	80 (66.1)	10 (8.3)	31 (25.6)
VL is spread by sand fly.	55 (45.5)	14 (11.6)	52 (42.9)
VL is spread through malaria mosquitoes.	40 (33.1)	41 (33.9)	40 (33.1)
VL is spread by the carriers' worms.	50 (41.3)	40 (33.1)	31 (25.6)
Symptoms of the disease are high fever, loss of weight, hepatosplenomegaly, abdominal swelling, and muscle fatigue.	51 (42.1)	40 (33.1)	30 (24.8)
VL can affect all ages.	75 (61.9)	6 (4.9)	40 (33.1)
It is highly recommended to take preventive measures against this disease.	99 (81.8)	5 (4.1)	17 (14.0)
VL is a life-threatening disease in the absence of treatment.	62 (51.2)	16 (13.2)	43 (35.5)

when occupational status is taken into account, students (n = 47, 38.8%) were the most common respondents in this survey. The number of married participants (n = 51, 42.1%) was lower than single respondents (n = 70, 57.9%). The number of rural participants (n = 23, 19.0%) was also lower than urban participants (n = 98, 81.0%).

KNOWLEDGE OF THE PARTICIPANTS TOWARDS VL

In total, more than 50.0% of the participants selected "yes" response for 5 of the 12 available questions, indicating that participants had an average knowledge of VL (Tab. II). In the knowledge part, 53.7% (n = 65) of participants knew that VL is a parasitic disease. Also, 66.1% (n = 80) of participants knew that travel to a VL endemic area was a risk factor for the disease. The role of prophylactic measures to prevent VL was well-understood by 81.8% (n = 99) of participants. Almost half of the participants (n = 62, 51.2%) knew the importance of treating of the VL patients. However, participants were least likely to know about the incubation period of VL (n = 29, 23.9%). Moreover, the majority of participants (n = 50, 41.3%) incorrectly answered that VL is spread by the worms of carriers.

ATTITUDE OF PARTICIPANTS TOWARDS VL

Overall, the vast majority of participants had a positive attitudes toward VL (Tab. III). The majority of respondents (n = 76, 62.8%) agreed that VL causes health problems in the local population. The majority of participants (n = 110, 90.9%) agreed that VL is a treatable disease. The majority of them (n = 87, 71.9%) also agreed that local communities should be actively involved in the fight against VL. Similarly, the majority of participants agreed that people infected with VL should be treated (n = 110, 90.9 %). A high percentage of participants (n = 107, 88.4%) felt that the disease should be completely cured. However, 20.7% (n = 25) of participants felt that they were unaware of the severity of the disease. Contrary, 40.5% (n = 49) of the participants answered that VL is not a serious problem in our area. Furthermore, 29.8 % (n = 36) of participants expressed no attitude towards the possibility of controlling the VL disease through community involvement in their area.

PRACTICE OF THE PARTICIPANTS TOWARDS VL

Regarding practice towards VL, 110 (90.9%) participants had used preventive measures against sand fly bites as follows: bed nets (28.1%), dichloro-diphenyl-trichloroethane (DDT) (3.3%), isolation

Tab. III. Attitudes of participants towards visceral leishmaniasis (VL) in Al-Suwaira city, Wasit Governorate, Middle East of Iraq.

Statements	Participant's responses N (%)		
	Agree	Disagree	I don't know
VL is a health problem in the local communities.	76 (62.8)	11 (9.1)	34 (28.1)
The problem of VL is severe in your area.	21 (17.4)	49 (40.5)	51 (42.1)
Local communities should be actively involved in the fight against the VL.	87 (71.9)	6 (4.9)	28 (23.1)
Treatability of the disease.	110 (90.9)	2 (1.7)	9 (7.4)
Complete cure of the VL is possible.	107 (88.4)	5 (4.1)	9 (7.4)
I am exposed to the seriousness of the VL disease.	61 (50.4)	25 (20.7)	35 (28.9)
It is possible to control the VL disease through community participation.	78 (64.5)	7 (5.8)	36 (29.8)

Tab. IV. Practice of participants towards visceral leishmaniasis (VL) in Al-Suwaira city, Wasit Governorate, Middle East of Iraq.

Practices		Number	Percent
Prevention of sand fly	Bed net	34	28.1
	Dichloro-diphenyl-trichloroethane (DDT)	4	3.3
	Cleanliness of living environment	54	44.6
	Isolation of patients	18	14.9
	Not use prevention methods	11	9.1
	Total	121	100.0
Use of bed net	Yes	57	47.1
	No	64	52.9
	Total	121	100.0
Sleeping outdoor	Yes	40	33.1
	No	81	66.9
	Total	121	100.0
Work time preference when temperature is high	Day time	46	38.0
	Night time	35	28.9
	Both	40	33.1
	Total	121	100.0

of patients (14.9%), and use of cleanliness of living environment (44.6%). The practice of the participants towards VL is shown in Table IV. In total, 11 (9.1%) participants did not use any measure to avoid VL. About half of participants (n = 54, 44.6%) chose cleanliness as a disease-prevention technique. Also, 46 (30.0%) participants favored daytime working when the weather was hot.

INFORMATION SOURCES OF RESPONDENTS TOWARDS VL

Participants learned about VL primarily through the internet (n = 69, 57.0%), television (n = 24, 19.8%), and university (n = 22, 18.1%). Also, other sources such as radio, books, and newspapers account for 4.9% (n = 6) of the total.

Discussion

The prevalence of visceral leishmaniasis isunclear in certain parts of Iraq. This study is unique in that it identified an area for which there is little information. The findings of this study could have major implications for the development of future VL education and data distribution systems aimed at improving people's knowledge and attitudes about VL control and prevention to improve public health in Iraq.

The results of the current study revealed that more than 50.0% of participants had good knowledge of some VL-related items as follows: VL is a parasitic disease (53.7%), travel to a VL endemic area is a risk factor (66.1%), VL can affect all age groups (61.9%), it is necessary to take preventive measures against VL (81.8%), and VL is a life-threatening disease if not treated (51.2%). However, almost half of the participants were unaware of other aspects of the disease. This highlights the need to improve knowledge in this

area through health education. The result of our study revealed that the majority of contributors (51.2%) knew that untreated VL is life-threatening, and 45.5% of them knew that VL is transmitted by sand flies. These findings were higher than a previous study from India, which indicated participants' low knowledge of VL [7]. Also, in a previous report from Brazil [8], 61.2% of participants were unaware of the mode of transmission of the VL that was lower than the current study. This could be due to the different study population, as the majority of participants in this study had a secondary school degree or higher, and thus were better informed about the VL disease. However, our results were lower than a previous report from Ethiopia [9], in which 68.1% of participants knew that sand fly was the main route of transmission, and 96.7% of them knew that untreated VL leads to irreversible damages. Also, in a previous study from India [10], 98% of respondents reported that VL can be fatal if untreated, which was higher than the current research. In this study, 42.1% of participants knew about the symptoms of VL. This was higher than a previous report from Brazil [8], in which 83.5% of respondents did not know about VL symptoms. However, in a study from Ethiopia [11], 87.5% of participants knew the VL symptoms, which was higher than our result. Early detection and treatment of VL are dependent on recognizing clinical symptoms. The gap across studies could be due to a lack of health education and awareness in the community, as well as the socioeconomic status of different communities. The recurrence and re-emergence of the disease in the cities of Wasit province allowed the community to have more knowledge and education about the disease and its transmission to people, which is most likely the reason for these differences. This study revealed that more than two-thirds of contributors (81.8%) strongly advised taking preventive measures against VL, while only 4.1% of respondents stated the disease could not be prevented.

These findings were consistent with prior findings from Ethiopia [9, 11] and Iraq [12]. Participants were well-informed that the disease was preventable. This could be due to people's awareness of the preventability of other parasitic diseases (which are largely vector-borne diseases), leading them to believe that VL is also preventable.

In this study, the vast majority of contributors had a positive attitudes toward VL, which was in line with previous studies from India [7] and Ethiopia [9, 11]. The results showed that 62.8% of the contributors agreed that VL was a health problem in local communities. In a previous study by Alemu et al. [9] from Ethiopia, 53.1% of the contributors thought that VL was a health problem in local communities, which was lower than the current research. In total, 71.9% of respondents said that local communities should be actively involved in the fight against VL, while 4.9% did not. This was in line with previous findings that about 80% of participants thought that communities should be actively involved in the fight against kala-azar, whereas 7.6% did not [9]. Likewise, the majority of respondents (90.9%) knew that VL is a treatable disease. This finding was consistent with the Ethiopian findings [9, 11], where more than 85.0% of the respondents knew that the disease was treatable. In this study, participants had a high attitude towards complete cure of VL. A large number of participants (88.4%) believed that the disease canbe entirely treated, which was consistent with previous findings from Ethiopia (86.4%) [9] and India (80.7%) [10]. The differences in people's attitudes toward completecure of the disease could be due to a number of factors, including community awareness and people's tradition of interviewing patients to learn more about VL [9]. This study also examined participants' attitudes toward community involvement in controlling VL. The results were positive, with 64.5% of participants believing that VL can be controlled through community involvement. These data were consistent with the results from Ethiopia [9, 11] which showed that more than 70.0% of the respondents believed in the control of VL through community involvement. However, our results were inconsistent with a prior report by Govil et al. [10] from India where only 24.0% of respondents believed that community participation can be effective in controlling kala-azar.

Regarding the practice of prevention and control measures implemented in the study area, 110 (90.9%) residents reported that they took the following preventive measures against sand fly bites: bed nets (28.1%), dichloro-diphenyl-trichloroethane (DDT) (3.3%), isolation of patients (14.9%), and cleanliness of the living environment (44.6%). While 9.1% of the contributors did not use any preventive measures against sand fly bites. Bed nets were used by almost half of the contributors (47.1%). A total of 40 (33.1%) respondents reported sleeping outdoors, especially during high temperatures. These findings were consistent with previous findings from India [7] and Ethiopia [9], where the majority of residents used preventive measures against sand flies. However, in our region, a lower percentage of residents used bed nets compared to the previous studies from India (97.9%) [7] and Ethiopia (93.7%) [9]. In contrast to the current study, a previous report by Gelaye et al. [13] from Ethiopia showed that more than half (59.5%) of the participants did not implement any preventive measures towards VL. Likewise, JS et al. [14] from India found thatpoor practices towards VL were prevalent among HIV patients, as 66% of them did not use bed nets. Sandflies can expand their geographic range due to changes in environmental and climatic conditions, which increase the risk of transmission of VL [14]. To reduce human-vector contact, it is important to educate people about the peak seasons, biting times, and breeding habitats of the sand flies [14].

In this study, 28.9% of the contributors preferred to work at night when temperatures were low, but even when temperatures were high, 38.0% of residents preferred to work during the day. This could be due to the lack of electricity, the socioeconomic status of the population, or people's habit of working throughout the day [9].

Our results revealed that donors mainly obtained information about VL from the Internet (n = 69, 57.0%), television (n = 24, 19.8%), and the university (n = 22, 18.1%). Other sources such as radio, books, and newspapers accounted for 4.9% (n = 6) of the total. Contributors reported using a variety of websites to learn more about VL. With the development of communication tools, the Internet has generally become the most common means of obtaining information about diseases. In a previous report from Ethiopia [3], friends (80.8%) and pamphlets (34.1%) were the most commonly used sources of information.

It is crucial to note that this study had some limitations as it was conducted in one location in Wasit Governorate and the results may not be generalizable to other areas. Therefore, it is helpful to study a large sample in different locations to find out what is going on. Despite the limitations, our findings have important implications for VL prevention and future studies.

Conclusion

Overall, participants had good knowledge, positive attitudes, and good practice when it came to VL prevention. However, diseases transmission, signs and symptoms, and incubation period of VL were still not well understood. Hence, it is recommended that knowledge-based strategies be strengthened and consistently implemented to raise awareness of the modes of transmission, symptoms, and incubation period of VL. This will enablethe community to effectively participate in the prevention and control of the disease. The findings of this study could have far-reaching implications for future VL education and information activities targeting people in rural and urban areas of Iraq to improve their knowledge and attitudes towards VL. To close the gap in knowledge implementation, further research is needed in areas such as continuous communication of behavior change and activities related to social use.

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Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

All authors contributed to the study conception and design. M.H.G.K., I.D.S., and S.S.A. participated in the design of the study. I.D.S. and A.M.T. performed data collection, wrote the manuscript, and helped with statistical analysis. A.M.T. and S.S.A. edited the manuscript. All authors read and approved the final manuscript.

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Non Comunicable Diseases

Relationship between dietary energy intake, nutritional status and cardiovascular risk in adults from the communes of Quellón and Chonchi, Chiloé, Chile

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Keywords

Dietary energy intake • Malnutrition by excess • Nutritional adequacy of the diet •Chronic diseases • Cardiovascular risk

Summary

Introduction. *Behavioural and metabolic risk factors are responsible for the greatest burden of disease; an unhealthy diet, along with abdominal obesity, are risk factors related to Non-communicable diseases (NCDs).*

Methods. *Data concerning food patterns were determined by the application of an interview-type instrument, used to assess the daily and weekly frequency of consumption; cardiovascular risk was assessed using waist circumference, and nutritional status via Body Mass Index. Student's t test was applied to evaluate the differences between variables and the Pearson's chi-square test for the association of variables.*

Results. *Dietary energy intake (kcal/capita/day) was 3000 kcal, with an average distribution of 12.2% (proteins), 46.9% (carbo-hydrates), and 40.9% (total fats). The 78% of the sample suffered from malnutrition by excess. About 37.5% had Non-Communicable Diseases, with high blood pressure being the most frequent disease among both genders, with the highest prevalence among women, along with diabetes mellitus and dyslipidaemia. Depending on the nutritional status, the presence of obesity is associated with high cardiovascular risk (p = 0.000), greater energy availability (p = 0.012), and an increased occurrence of non-communicable diseases (p = 0.004).*

Conclusions. *Malnutrition by excess figures support the global alert for obesity and overweight, which are considered to be a pandemic; in addition, Chiloé is not immune to the increasing trend of processed and ultra-processed food consumption.*

Introduction

Behavioural and metabolic risk factors are responsible for the greatest burden of disease. It is observed that an unhealthy diet, along with abdominal obesity, are some of the risk factors related to Non-communicable diseases (NCDs) [1], therefore, having knowledge of the diet and eating patterns of the population is a priority, in order to establish actions to improve them.

The burden that NCDs represents for health and economic development is one of the greatest challenges of the 21st century, causing 71% of all deaths globally, besides being the primary cause of disability [2]. Each year, 15 million people aged between 30-69 years die from a NCD, and more than 85% of these deaths occur in low and middle-income countries [3]. Because of the high costs of reducing deaths and the impact of NCDs on the economies of the countries, NCDs are targeted in the United Nations Sustainable Development Goals (SDG) set out for 2030 [4].

In Chile, 74.2% of the population aged 18 years and older suffer from malnutrition by excess, showing an increase sustained over time, as shown by the latest National Health Surveys (NHS 2009-2010, NHS 2016-2017) and the Organisation for Economic Co-operation and Development (OECD 2019) [5, 6]. With respect to NCDs, 26.9% have High Blood Pressure (HBP), and 38.5% have Hypercholesterolemia, combined with unhealthy eating patterns, alcohol consumption, tobacco

use and a sedentary lifestyle, all this contributing to Cardiovascular Diseases (CVDs), which represent the leading cause of death in Chile [5]. On the other hand, there is no enough background information about the diet quality of the population and its evolution, and this information is even more limited in extreme zones of the country, such as the Chiloé Island. The first National Food Consumption Survey (NFCS, 2010) showed a low consumption of health protective foods, and a gap with respect to the consumption recommended in the Dietary Guidelines for the Chilean Population. Furthermore, the same survey indicated that 95% of the population required major changes in their diet [7], showing that in Chile, as is happening in other countries, accelerated changes have taken place during the last decades, impacting the habits, dietary practices and consumption patterns, affecting the health of the population [8]. In these context, given the importance of healthy diet and nutrition as protective factors to prevent NCDs, it is of great interest to know the dietary energy intake, nutritional adequacy of the diet, and nutritional status, and how they are related to cardiovascular risk (CVR) in a sample of adult patients of the Family Healthcare Centres (CESFAM, as per its acronym in Spanish) in isolated localities of Chile, as in the case of the communes of Quellón and Chonchi, in the Chiloé Island.

In the light of the above, the objective of this study is to know the energy intake and nutritional adequacy of

the diet, and to establish an association with nutritional status, cardiovascular risk and non-communicable diseases, in a sample of users of the Family Healthcare Centres (CESFAM) of Quellón and Chonchi, which are part of the primary healthcare network of the Chiloé Island.

Methods

A comparative, correlational-associative, cross-sectional study, with a non-experimental design, and a quantitative and qualitative approach was conducted. Dependent variables: nutritional status and cardiovascular risk; independent variable: nutritional adequacy of the diet. A convenience sample consisting of 200 adults (women n = 153, and men n = 47) aged between 18 and 89 years, who are users of the Family Healthcare Centres (CESFAM) of the communes of Quellón and Chonchi, of the Chiloé Island, Chile, was recruited for the study. The subjects voluntarily agreed to participate and signed the informed consent. Inclusion criteria were: to be a user of the CESFAM (subjects must be registered patients), voluntarily agree to answer the questionnaire the day it was applied, and to sign the informed consent. Exclusion criteria were: to be under 18 years old, and to not fully complete the questionnaire.

The study was developed following the Declaration of Helsinki regarding work involving human beings, and approved by the Bioethics Committee of the Academic Vice-Presidency of the Universidad de Playa Ancha, Chile. The field work was carried out in November 2017 by students of the last year of the Nutrition and Dietetics degree program of the Universidad de Playa Ancha, who were previously trained on the standardization of measurement protocols and application of the instruments. A questionnaire was developed and validated by expert judgment before its application. The judges who evaluated the questions were five experts with experience in the field of foods and nutrition, and they did not take part in the wording of the questions of the instrument. The questionnaire was applied as an interview and collected general background information such as age, gender, place of residence, occupation, income level, level of education, family size, family type, main NCDs (high blood pressure, diabetes mellitus, dyslipidaemia, and others), and anthropometric data such as weight, height and waist circumference. Body weight (kg) was measured with participants wearing the least amount of clothes possible, using a digital Omron scale with a maximum capacity of 220 kg and an accuracy of 50 g. Height (m) was measured using a SECA stadiometer, with a measuring range of 20-205 cm. A SECA measurement tape was used to measure waist circumference, at the midpoint between the last rib and the iliac crest. The body mass index (BMI) variable was calculated using the measurements of weight and height or Quetelet index defined as (weight[kg]/height[m]2); nutritional status was categorized according to the criteria established by the World Health Organization (WHO) as: normal

weight (18.5 to 24.9 kg/m2), overweight (25 to 29.9 kg/m2) and obese (≥ 30 kg/m2) [9]. CVR was evaluated by the measurement of abdominal fat, obtained by measuring waist circumference, and it was assessed according to the WHO standards. It was classified in: Low CVR: < 80 cm (women) and < 94 cm (men); Moderate CVR: ≥ 80 cm (women) and ≥ 94 cm (men); High CVR: ≥ 88 cm (women) and ≥ 102 cm (men) [10]. Dietary history was obtained by the application of a 24-hour recall questionnaire (R 24h) and a questionnaire of weekly frequency of consumption, applied as an interview. The food products consumed were recorded in household measures, and then standardized in g/ml, as appropriate, in order to subsequently make an estimation of energy intake, macronutrients, fibre and sodium.

Energy requirement was assessed by using the Resting Energy Expenditure (REE) formula provided by the WHO, and a correction factor of 1.3 was added (sedentary activity level). The distribution of nutritional adequacy was determined according to the classification of the Institute of Medicine (IOM) [11] in: proteins 15%, lipids 30%, carbohydrates 55%, fibre = 30 g/day, and sodium < 2000 mg/day (salt added to homemade meals was not included in this recommended intake). The calculation of nutritional adequacy (the ratio between estimated intake and recommended intake) was expressed as a percentage; an adequacy ranging from 90% to 110% was considered good. The following categories were established to distribute dietary energy intake of the sample (kcal/capita/day): < 2200 kcal; 2201-3000 kcal; and > 3000 kcal [12].

STATISTICAL ANALYSIS

Microsoft Excel 2013 (v15.0) was used to tabulate data. Absolute and relative frequencies were calculated for the categorical variables; arithmetic mean and standard deviation were used for the description and analysis of quantitative variables. The confidence interval was set at 95%, and the Student's t test was used to evaluate differences between the variables (Tab. I). Pearson's chi square test was used for the linear association of the variables, with a significance level of 95%. Statistical processing was performed with the Statistical Package for Social Science (SPSS) software version 22.0.

Results

The sample consisted of 200 adults enrolled in the public health system, who were patients at the Quellón and Chonchi Family Healthcare Centres; 76.5% of the subjects were women and 23.5% men.

Mean age was 42.6 ± 16.1 years; 99% of the participants have lived in the Chiloé Island during the last ten years, with the greatest proportion of them (61%) residing in Quellón. With regards to education, 47% only completed primary education (which starts at 6 years old and consists of a cycle of 8 years of training), and 2% had no schooling at all. The 59% of the sample were engaged in household work, and only 36% reported having a paid

Tab. I. Characteristics of the sample.

	N	%
Place of residence (10 years)		
Chonchi	76	38
Quellón	122	61
Other places	2	1
Gender		
Men	48	24
Women	152	76
Age		
18-39 years	89	44.5
40-64 years	85	42.5
≥ 65 years	26	11
Level of education		
Primary education	94	47
Secondary education	79	39.5
Technical education	15	7.5
Higher education	8	4.0
Unschooled	4	2.0
Family		
Nuclear	139	69.5
Single parent	27	13.5
Extended	10	5.0
Blended	24	12.0
Number of members		
< 3	97	48.5
4 to 6	93	46.5
> 6	10	5.0
Income level		
< 270,000 (< 465 USD)	59	29.5
270,000-500,000 (465-862 USD)	67	33.5
> 500,000 (> 862 USD)	18	9.0
Did not answer	32	16.0
Did not know	24	12.0
Occupation		
Unemployed	5	2.5
Housewife	90	59.0
Paid employment	99	35.5
Student	3	1.5
Retired	3	1.5

employment. About 30% received a monthly salary of less than $ 270,000 (465.42 USD), and only 9% reported having an income greater than $ 500,000 (861.89 USD) (Tab. II).

NUTRITIONAL STATUS

The classification, according to the BMI, indicated that 78.5% of the sample presented malnutrition by excess, with women having higher rates, reaching 81%. More than 50% have High CVR; among women the value is three times greater than among men. Moreover, 37.5% of the total sample suffer from NCDs, with HBP being the most frequent disease among both genders. The highest prevalence of HBP, diabetes mellitus, and dyslipidaemia occurs in women (Tab. I). With respect to the comparison of variables, differences were found in the mean weight, being greater in men than in women (p = 0.008), and in height, with a difference of almost 10 cm more in men than in women (1.67 ± 0.1 versus 1.56 ± 0.1, respectively) (p=0.000). No significant differences were observed when comparing by gender in the variables age (p = 0.673), waist circumference (p = 0.251) and BMI (p = 0.055) (Tab. III).

DIETARY ENERGY INTAKE

The mean dietary energy intake was almost 3000 kcal/ capita /day. In more than 50% of the participants, energy availability was over 3000 kcal/capita/day and around 20% have an average intake of 2200 kcal/capita/day. A difference of 500 kcal/capita/day was found between the mean energy consumption of men and women.

The average distribution of macronutrients was as follows: 12.2%, 46.9%, and 40.9% for proteins, carbohydrates and total fats, respectively. We observed a greater consumption for all macronutrients among men; however, women maintained significantly higher adequacy values in energy and lipids, equal to 30% and 85%, respectively. Dietary fibre and sodium were within the recommended ranges for the total sample; however, regarding sodium, men have an average consumption of almost 22% more than recommended (Tab. IV).

Tab. II. Distribution of nutritional status, cardiovascular risk and non-communicable diseases. Number (n) and percentage (%). According to total sample and by gender.

	Total	Men	Women
Normal: n (%)	43 (21.5%)	15 (29.8%)	29 (19.0%)
Overweight: n (%)	70 (35%)	16 (34.0%)	54 (35.3%)
Obesity: n (%)	87 (43.5%)	17 (36.2%)	70 (45.7%)
Low Cardiovascular Risk: n (%)	45 (22.5%)	24 (51.1%)	21 (13.7%)
Moderate Cardiovascular Risk: n (%)	42 (21.0%)	13 (27.7%)	29 (19.0%)
High Cardiovascular Risk: n (%)	113 (56.5%)	10 (21.3%)	103 (67.3%)
Presence of Non-communicable Diseases	75 (37.5%)	18 (38.3%)	57 (37.3%)
Does not have Non-Communicable Diseases	125 (62.5%)	29 (61.7%)	96 (62.7%)
High blood pressure	51 (44.3%)	16 (31.4%)	35 (68.6%)
Diabetes Mellitus	32 (27.8%)	6 (18.8%)	26 (81.3%)
Dyslipidaemia	21 (18.3%)	3 (14.3%)	18 (85.7%)
Other diseases* (HT-AKF-CKF-ASTHMA)	11 (9.6%)	2 (18.2%)	9 (81.8%)

*HT: Hypothyroidism; AKF: Acute kidney failure; CKF: Chronic kidney failure.

Tab. III. Distribution of anthropometric measurements. Mean and Standard Deviation (SD). According to total sample and by gender.

Anthropometric measurements	Total	Men	Women	95% CI*	p
Age: mean (SD)*	43.5 (16.1)	44.7 (16.9)	43.2 (15.9)	2.68 - 6.43	0.673
Weight (kg): mean (SD)*	75.2 (13.8)	79.8 (14.6)	73.8 (13.2)	2.25 - 10.51	0.008
Height (m): mean (SD)*	1.59 (0.1)	1.67 (0.1)	1.56 (0.1)	0.01 - 0.13	0.000
Waist circumference (cm): mean (SD)*	92.3 (12.1)	94.1 (11.4)	91.8 (12.3)	2.02 - 6.31	0.251
Nutritional status (IMC): mean*	29.9	28.7	30.2	-3.43-.035	0.055

*SD: Standard deviation; CI: Confidence interval for the difference.

When making associations between the variables, a dependence between nutritional status, cardiovascular risk, dietary energy intake and the presence of non-communicable diseases was noted. Depending on the nutritional status, the presence of obesity is associated with high cardiovascular risk (p = 0.000), greater dietary energy intake (p = 0.012), and an increased occurrence of non-communicable diseases (p = 0.004) (Tab. V). It was found that old age and high cardiovascular risk were associated with a higher prevalence of NCDs (p = 0.000 and p = 0.001, respectively). No direct relationship was observed between age and dietary energy intake; age and CVR; and between energy intake and CVR.

Discussion

Data assessment shows that the occurrence of malnutrition is overwhelming, with a prevalence of obesity in almost 50% of the total sample. Overweight is dominant in both genders (78.5%), but in the case of women it reaches 80%. Lower values were found in the National Health and Nutrition Examination Survey (NHANES 2014), where obesity reached 37.7%, being higher in women (40.4%) than in men (35.0%) [13]. the prevalence of obesity increased significantly among adult men and women in the United States; further significant increases were observed through 2003-2004 for men but not women. Subsequent comparisons of data from 2003-2004 with data through 2011-2012 showed no significant increases for men or women. To examine obesity prevalence for 2013-2014 and trends over the decade from 2005 through 2014 adjusting for sex, age, race/Hispanic origin, smoking status, and education. Analysis of data obtained from the National Health and Nutrition Examination Survey (NHANESOn the other hand, the prevalence of overweight was significantly lower among adults from 20 European countries, reaching 53.1%. The highest numbers were found in Hungary (61.6%), the Czech Republic (60.1%), and Lithuania (59.6%), as opposed to countries such as Switzerland (43.3%), France (45%), and Denmark (45.2%), with lower rates of overweight and obese people. Unlike what was found

Tab. IV. Distribution of nutritional adequacy of the diet. Macronutrients, fibre and sodium /capita / day. Energy (kcal), grams (g), and percentage (%). According to total sample and by gender (kcal; g; %).

Energy intake (kcal)	Amount (n)	%	Kilocalories mean (SD*)	Proteins (g) mean (SD)	Carbohydrates (g) mean (SD)	Lipids (g) mean (SD)	Fibre (g) mean (SD)	Sodium (mg) mean (SD)
< 2200	43	21.5	1840.1 (215.24)	60.8 (16.06)	227.5 (48.39)	77.7 (24.02)	21.9 (7.61)	1271.3 (721.79)
2201-3000	64	32	2587.3 (218.90)	79.4 (21.38)	317.3 (47.67)	112.9 (25.55)	26 (6.59)	1668 (778.15)
> 3000	93	46.5	3615.7 (473.31)	109.4 (31.72)	413.2 (99.22)	172.2 (47.82)	31.7 (14.16)	2454 (1106.50)
Total	200	100	2904.8 (801.27)	89.4 (32.56)	342.6 (105.7)	132.9 (53.80)	27.8 (11.60)	1947.9 (1054.28)
Energy and nutrients requirement Total sample			2119.6	79.5	291.4	70.7	30	< 2000
Men	47	23.5	3298.9 (788.85)	107.8 (34.59)	400.2 (123.33)	144.6 (52.84)	29.7 (9.53)	2448.3 (1223.39)
Women	153	76.5	2783.8 (767.76)	83.7 (29.80)	324.9 (93.13)	129.3 (53.75)	27.2 (12.14)	1794.3 (949.25)
Adequacy for energy and nutrients requirements Total sample (%)			138%	113%	118%	188%	93%	97%
Adequacy Men			130%	113%	115%	171%	99%	122%
Adequacy Women			140%	112%	119%	195%	91%	90%

Tab. V. Associations. Pearson's Chi Square.

Energy consumption							
		< 2200	2201-3000	> 3000	Total	X2	p
Age	18-39	17	28	44	89		
	40-64	20	26	39	85	1.365a	0.850
	≥ 65	6	10	10	26		
Total		43	64	93	200		
Cardiovascular Risk							
		Low CVR	Moderate CVR	High CVR	Total	X2	p
Age	18-39	23	22	44	89		
	40-64	17	13	55	85	4.971a	0.290
	≥ 65	5	7	14	26		
Total		45	42	113	200		
Diseases							
		None	1	2 or more	Total	X2	p
Age	18-39	77	10	2	89		
	40-64	42	23	20	85	47.802a	0.000
	≥ 65	6	10	10	26		
Total		125	43	32	200		
Energy consumption							
		< 2200	2201-3000	> 3000	Total	X2	p
Cardiovascular Risk	Low CVR	7	16	22	45		
	Moderate CVR	11	15	16	42	2.633a	0.621
	High CVR	25	33	55	113		
Total		43	64	93	200		
Non-communicable diseases							
		None	1	2 or more	Total	X2	p
Cardiovascular Risk	Low CVR	34	9	2	45		
	Moderate CVR	34	3	5	42	18.912a	0.001
	High CVR	57	31	25	113		
Total		125	43	32	200		
Cardiovascular Risk							
		Low CVR	Moderate CVR	High CVR	Total	X2	p
Nutritional Status	Normal	19	16	9	44		
	Overweight	20	15	34	69	46.520a	0,000
	Obese	6	11	70	87		
Total		45	42	113	200		
Energy consumption							
		< 2200	2201-3000	> 3000	Total	X2	p
Nutritional Status	Normal	15	18	11	44		
	Overweight	12	24	33	69	12.866a	0.012
	Obese	16	22	49	87		
Total		43	64	93	200		
Non-communicable diseases							
		None	1	2 or more	Total	X2	p
Nutritional Status	Normal	32	8	4	44		
	Overweight	50	14	5	69	15.306a	0.004
	Obese	43	21	23	87		
Total		125		43	32	200		

in this sample, men were more overweight than women (44.7% versus 30.5%) [14].

According to data published by the MINSAL (Ministry of Health), overweight in Chile has increased from 64.4% to 71% during the last 7 years [5, 15]; globally, the prevalence of obesity has doubled in more than 70 countries over the last 30 years and keeps rising steadily [16].

Obesity, besides increasing central distribution of adipose tissue, among other complications, increases morbidity [17], since it leads to a greater incidence of diseases that affect multiple organs, such as CVD, DM2, HBP, among others [18, 19].

With respect to diet, 76% of the sample had an energy intake higher than their requirements (> 110%), and 57% had high CVR (cardio-metabolic risk); these data

are consistent with what was stated by FAOSTAT in relation to dietary energy intake, which in Chile reaches an average of 3029 kcal/day [20], and 2929 kcal/day worldwide [21]. Additionally, in a cohort of adults in the United States (USA), a positive association was found between the intake of a diet high in low-quality carbohydrates and an increase in WC, with a mean of 92.6 cm [22].

About 80% have a high lipid intake (> 110% adequacy), with a mean consumption of 133 g/capita/day, corresponding to 40% of the daily energy value. Similar values were found in adults from the USA between 1971-1975 in the NHANES, with lipids intake ranging from 36 to 37.5%; by 2016, a decrease to 33.2% was observed [23]. In addition, high fat consumption has been associated with weight gain, but the effect of fats on lipoprotein levels varies depending on the type of fat consumed. Several studies have associated the consumption of trans fats with an increased risk of CVD, atherosclerosis, sudden death, DM2, non-alcoholic fatty liver disease, dysbiosis.

There are studies indicating that the Chilean population maintains a low consumption of health-protective foods [7, 20]. In addition, it is clear that in Chile [24], as well as in countries from Europe [25, 26] and America [27-29] among others [30], there have been changes in the dietary habits and consumption patterns, shifting from traditional diets to processed and ultra-processed foods [31, 32] mainly in urban households, affecting the health of the population, a situation that is observed in Chiloé, where the diet has gone through significant transformations [8].

Conclusions

It has been shown that a restriction of dietary energy intake and weight reduction positively contribute to lower blood pressure [33-35], as well as moving towards a Mediterranean diet and practising physical activity may lower high blood sugar levels. Malnutrition by excess figures support the global alert for obesity and overweight, which are considered to be a pandemic; in addition, Chiloé is not immune to the increasing trend of processed and ultra-processed food consumption.

LIMITATIONS

Since the study was conducted on a convenience sample and data were collected from two family healthcare centres of the two aforementioned communes, and from patients who were seen at the centres and voluntarily agreed to participate, results are only valid for the sample in question.

Acknowledgments

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

M.C. and M.J.S. share responsibility for the conceptualization, methodology, software use, formal analysis, resources, data curation, writing – original draft preparation, redaction – review and editing, visualization, supervision, project administration, funding acquisition.

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Evaluation of the effects of diabetes self-management education based on 5A model on the quality of life and blood glucose of women with gestational diabetes mellitus: an experimental study in eastern Iran

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Summary

Introduction. *Gestational diabetes mellitus (GDM) is an important condition during pregnancy. The aim of the current study was to evaluate the effects of self-management education based on 5A model on the quality of life and blood glucose level of women with GDM.*

Methods. *This quasi-experimental study was conducted on 54 pregnant women referred to the urban health care centers affiliated to the Gonabad University of Medical Sciences from March 2019 to March 2020 based on purposive sampling method. Participants were randomly allocated into intervention and control groups based on stratified random sampling using permuted block randomization method. The intervention group received self-management education program based on 5A model in five sessions during two months. Demographic data, blood glucose level, and*

diabetes quality of life (DQOL) questionnaire were collected for each participant. Data analysis was performed using the SPSS software version 16 and the level of statistical significance was set at 0.05.

Results. *Mean age of the participants was 33.11 ± 5.35 years old. At the end of the intervention, the mean blood glucose level of the participants in the intervention group was significantly lower compared to the control group (p < 0.001). The quality of life in the intervention group was significantly improved at the end of the intervention compared to the control group (p < 0.001).*

Conclusions. *Self-management education based on 5A model can effectively improve quality of life and blood glucose levels in women with GDM.*

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disorder in pregnancy and is considered as the most common pregnancy complication [1]. GDM usually occurs in the second half of the pregnancy, when the body of pregnant mother is not capable of secreting enough insulin to compensate increased blood glucose due to increased nutritional intake of carbohydrates [2]. Globally, GDM affects up to 15% of pregnant women worldwide, and accounts for 90% of all cases of diabetes in pregnancy [3, 4]. In Asia, the prevalence of GDM was reported to be 11.5% [5]. The prevalence of GDM in Iran was reported to be 5.88% [6].

Various changes and complications that occur in pregnancy affect physical, psychological, and social aspects of a pregnant woman's life. Overall, these changes affect the quality of life in pregnancy at different gestational ages [7]. Many of these complications are preventable by performing prenatal care and active participation of pregnant women in their health care

process [8]. There is no definite cure for GDM and the most effective management method for GDM is through internalizing self-management behaviors in pregnant women as more than 95% of the patient care in GDM is performed by the pregnant women themselves [9, 10]. Therefore, considering the increasing trend of GDM and its economic burden, it is necessary to treat and manage GDM effectively. However, the currently available education to improve quality of life and blood glucose management in GDM that are provided in health care centers in Iran are limited and passive. Furthermore, the level of understanding and implementation of the provided education in personal life of pregnant women are not evaluated in health care centers.

One of the methods of GDM management by the individual is through the implementation of self-management programs [11]. One of the recommended self-management programs in GDM is based on the 5A model. Self-management program based on 5A model is an evidence-based approach and is used to change health behaviors and improve individual's health status. The 5A model is composed of five stages, including

Awareness, Appeal, Ask, Act and Advocacy [12]. Simplicity and briefness are the unique characteristics of self-management programs based on 5A model that makes them distinguishable from other self-management models [13]. The main goal of self-management program is improving the quality of life through reaching the maximum independence, self- management, and reliance on ones abilities in performing self-management [14].

Few studies have evaluated the effects of self-management programs based on 5A model. To the best of our knowledge, the effects of self-management interventions based on 5A model have not yet been evaluated in pregnant women with GDM. As improving the quality of life requires active patient cooperation, self-management programs are of great importance in the management of GDM. Therefore, the current study was conducted to evaluate the effects of diabetes self-management education on the quality of life and blood glucose levels of pregnant women with GDM.

Materials and method

The current study was an experimental study with two groups (intervention and control groups). Study participants were selected from pregnant women with the diagnosis of GDM who referred to Gonabad city Health Care Centers from March 2019 to March 2020. The study was approved by the Ethical Committee of the Gonabad University of Medical Sciences (IR. GMU.REC.1398.103). A written informed consent was obtained from all participants before entering the study. Participants were ensured about the confidentiality in data collection and analysis.

Sample size was determined based on mean difference equation and considering 80% power and 95% confidence interval. The mean difference for quality of life and blood glucose were determined based on previous study

The inclusion criteria were willingness to participate in the study, ability to read and write, fasting blood glucose greater or equal to 93 g/dl, no history for systemic, neurologic or psychological diseases; no history for drug abuse, smoking, or alcohol consumption; not being diagnosed as high-risk pregnancy, and documented diagnosis of GDM by an endocrinologist. Exclusion criteria were failing to participate in the intervention sessions for more than two sessions, complicated pregnancy (either maternal or fetal complications), and exposure to stressful conditions during the study duration, including serious illness in spouse, or children; death of close relatives, accidents, or labor. Participants were selected based on inclusion and exclusion criteria using purposive sampling method. Participants were then instructed about the aims and procedures of the study and pregnant women who were willing to participate in the study by giving a written informed consent were randomly assigned to intervention (n = 27) and control (n = 27) groups based on stratified sampling using permuted blocks.

This study used a two-part questionnaire that comprised of 1) demographic data, including age, gender, gestational age, gravida, number of children, height, weight, place of living, education, job, insurance status, economic level, spousal characteristics, and 2) the diabetes quality of life questionnaire (DQOL). DQOL is a 15-item questionnaire that evaluates the quality of life of patients with type 1 and 2 diabetes. DQOL items are scored using a 5-point Likert scale ranging from 1 (completely disagree) to 5 (completely agree). The minimum and maximum score of the questionnaire are 15 and 75 with higher scores indicating better quality of life. Quality of life is then categorized into three groups; acceptable (achieving 75% of the maximum score), somehow acceptable (achieving 50% to 75% of maximum score), and poor (achieving less than 50% of the maximum score) quality of life. Reliability and validity of the DQOL was previously approved on a sample of Iranian population [16]. Furthermore, blood glucose level of the participants was recorded in a researcher made checklist.

Intervention

The intervention group received self-management educations based on 5A model. The intervention duration was two months. Based on the findings of a pilot session, three sessions were planned to conduct the intervention. Education sessions were designed to last for 1.5 hours based on the five following steps:

1. **Evaluation:** This step included data collection from medical records of the participants as well as in person interviews (filling the study questionnaire and recording blood glucose levels). This step was conducted to evaluate participants in terms of risk factors, medical history, medication history, and sleep status, as well as type of diet, physical activity and stress level.

2. **Guidance:** This step included informing the participants about their condition based on the collected data from the previous step. Individual health threats, including unhealthy eating, inappropriate eating times, low or inadequate physical activity level, and lack of stress management strategies in pregnancy. In this step the benefits of behavior change were highlighted for the participants.

3. **Agreement:** This step included an agreement between the participants and researchers on choosing the right behavioral goals based on the condition of each participant and to design a functional plan to reach these goals. Each goal was given a scale ranging from 0 to 10 and participants were asked to rate their behavior every day during the first month and record the scores in their behavior goal logbook. Steps 2 and 3 were held for each participant separately in the first session (1.5 hours in total).

4. **Aid:** this step was held either in the form of group session or individual session based on the number of

participants who required the specific intervention. Education materials that were provided in this step emphasized on healthy eating, adequate physical activity, and suitable time for physical activity, stress, and blood glucose management. The education material was also provided to the participants in the form of pamphlets. This step was conducted in the second intervention session.

5. **Follow up**: This step included following up the practice of participants for two months. In order to ensure proper action by the participants, phone calls were conducted daily in the first two weeks, twice weekly in the next two weeks and weekly afterwards till the end of the follow up duration. During the phone calls, participants were reminded to follow their planned behavior instructions. Furthermore, participant progress was evaluated every four weeks through phone call or in-person interview (third session). In the interview sessions the agreed operational plan and behavior goals were reviewed and the level of progress toward these goals were evaluated. Goals or operational plans were changed in order to fit the condition of the participants.

The control group received routine education based on the Ministry of Health recommendations. The education focused on healthy eating and adequate physical activity. At the end of the intervention duration all the study questionnaires and checklists, including the DQOL, and blood glucose level were filled for all participants in both the intervention and control groups. All the documents and modules were given to the control group at the end of the study for ethical considerations.

STATISTICAL ANALYSIS

Normality of the continuous variables was evaluated using the Kolmogorov-Smirnov test. Comparison of the qualitative variables between groups at baseline was performed using the chi-square test. The independent t-test or Mann-Whitney test were used to compared continuous variables between groups at baselines and follow up based on normality of the data. The paired-t-test or Wilcoxon test were used to compare continuous variables between baseline and follow up based on normality of the data. Data analysis was performed using the statistical package for social sciences (SPSS) software version 16. Level of statistical significance was considered as $p < 0.05$.

Results

The mean age of the participants was 33.11 ± 5.35 years old. Demographic characteristics of the participants are shown in Table I. There was no significant difference between the intervention and control groups in terms of demographic data except for gestational age and education level.

The Mann-Whitney test indicated no significant difference in terms of DQOL total score between the intervention and control groups at baseline (37.62 ± 10.89 and 37.29 ± 4.05, respectively, $p = 0.23$). Based on the DQOL total scores participants in both groups were categorized as "somehow acceptable" to "poor".

Changes in DQOL and its domains in study groups are shown in Table II. The total and domain scores of the DQOL questionnaire significantly increased at the end of the study compared to the baseline values in the intervention group ($p < 0.001$) and reached from "somehow acceptable" to "acceptable" level ($p < 0.001$). The DQOL total score was significantly lower in the control group at the end of the study (36.62 ± 5.49) compared to the baseline values (48.29 ± 6.49, $p = 0.02$) (Tab. II).

Blood glucose level significantly reduced at the end of the study compared to the baseline values in the intervention group ($p < 0.001$), while blood glucose level was not significantly different at the end of the study compared to the baseline values in the control group ($p = 0.54$). Blood glucose level was significantly higher in the control group compared to the intervention group at the end of the study ($p < 0.001$) (Tab. III).

Discussion

The results of the present study showed that self-management education based on 5A model improved

Tab. I. Comparison of demographic variables between study groups at baseline.

Variable		Intervention N (%)	Control N (%)	p-value
Education level	Primary	3 (11.1)	6 (22.2)	0.02*†
	Secondary and above	24 (88.9)	21 (77.8)	
		Mean ± SD	Mean ± SD	p-value
Age (years)		33.55 ± 5.23	32.66 ± 5.23	0.64‡
Gestational age (week)		28.40 ± 3.28	30.22 ± 3.20	0.03*‡
Age of marriage (years)		23.25 ± 4.24	22.66 ± 4.93	0.63‡
Gravida		2.44 ± 1.01	2.40 ± 0.97	0.84‡
Pre-conception weight (kg)		72.14 ± 10.81	67.51 ± 9.18	0.09‡
Height (cm)		162.40 ± 3.99	159.59 ± 16.02	0.66‡
Weight (kg)		80.74 ± 10.23	77.44 ± 8.15	0.19‡
BMI (kg/m²)		27.48 ± 4.88	28.18 ± 14.11	0.38‡

SD: Standard Deviation. † The chi-square test was used for the comparison. ‡ The Mann-Whitney test was used for the comparison. ‡ The independent t-test was used for the comparison. * Significant difference

Tab. II. Comparison of DQOL total and domain scores between baseline and end of study among study groups.

DQOL	Group	Baseline Mean ± SD	End of study Mean ± SD	p
Satisfaction	Intervention	16.40 ± 4.65	22.51 ± 2.19	< 0.001*†
	Control	15.96 ± 1.50	15.11 ± 2.69	
	p	0.23‡	0.86‡	-
Self-management	Intervention	16.33 ± 4.73	22.85 ± 1.48	< 0.001*†
	Control	16.14 ± 2.38	15.55 ± 2.60	
	p	0.85‡	< 0.001‡	-
Total score	Intervention	37.62 ± 10.89	48.29 ± 6.49	< 0.001*†
	Control	37.29 ± 4.05	36.62 ± 5.49	
	p	0.89‡	< 0.001*‡	-

SD: Standard Deviation.
† The Wilcoxon test was used for the comparison. ‡ The Mann-Whitney test was used for the comparison. ‡The independent t-test was used for the comparison. * Significant difference

Tab. III. Comparison of blood glucose levels between baseline and end of study among study groups.

Blood glucose	Intervention Mean ± SD	Control Mean ± SD	p
Baseline	101.96 ± 6.62	103.37 ± 12.08	0.86‡
End of study	88.14 ± 6.28	104.11 ± 16.01	< 0.001*‡
p	< 0.001*†	0.54†	

SD: Standard Deviation. † The Wilcoxon test was used for the comparison. ‡ The Mann-Whitney test was used for the comparison. * Significant difference

the quality of life in pregnant women with GDM. Similar to the findings of the present study, regardless of the differences in the study population, Soleimani et al. reported the quality of life of diabetic patients was somehow acceptable [17]. In addition to the maternal complications caused by diabetes, the fetuses of pregnant women with GDM are also at risk of developing dangerous complications, which can affect the quality of life of pregnant women with GDM. In a study aimed at investigating the effect of spiritual education on reducing anxiety and improving the quality of life of pregnant women with GDM, Beigi et al. stated that spiritual education could reduce anxiety and improve quality of life in pregnant women with GDM [18].

Azari et al. also reported that group spiritual therapy was effective in reducing anxiety and could improve the quality of life of pregnant women with GDM [19]. Spiritual teachings reduce anxiety in mothers and increase their satisfaction. Furthermore, reducing anxiety in pregnant women can reduce their worries and helps them perform self-management activities with peace of mind. In general, it can be said that these findings were consistent with the findings of the present study.

In another study by Makki et al. the effect of problem-solving skills training on the quality of life of pregnant women with GDM was evaluated. The study indicated that all domains of the quality of life gradually improved during the training period [20]. These findings were in line with the findings of the present study. Ghiasvandian et al. reported that self-management education was effective in improving the quality of life of patients with type 2 diabetic [21]. Saeedpour et al. investigated the effect of self-management education on the quality of life of diabetic patients and reported that quality of life of diabetic patients was poor. They found self-management

education effective in improving the quality of life of diabetic patients. The self-management education intervention was implemented using group discussion, face-to-face training, pamphlets, educational videos and tracts related to each of diabetes complications in three sessions over a period of three weeks [22]. Although these two studies deferred from the present study in terms of education method, educational content, time of presenting the education, and target population, their results were similar to the findings of the present study and all the three studies indicated that self-management promotion improved the quality of life in diabetic patients. Other studies used different methodologies to study the effect of educational interventions. Sharifi Rad et al. [23], Rezaei et al. [24], Baghianimoghadam et al. [25], Aghmolaei et al. [26], Wattana et al. [27] and Dunn et al. [28] pointed out that education intervention was effective in improving performance and quality of life in diabetic patients. These findings were consistent with the findings of the present study. Javanvash et al. used 5A model to conduct education intervention to elderly with acute coronary syndrome and showed that this education intervention had no effect on the quality of life of these elderly [29]. This finding was not consistent with the findings of the present study. The reason for this difference might be due to the difference in the sample size of the studies. Despite disease related complications, the elderly also face many age-related problems and disability that can have a great impact on their quality of life.

Another finding of the present study was the positive effect of self-management education based on 5A model on blood glucose level of pregnant women with GDM. Similarly, Moattari et al. used 5A model to conduct self-management education in patients with insulin-dependent diabetes and reported that this intervention

could reduce blood glucose and glycosylated hemoglobin in these patients

Improving self-management skills of pregnant women with GDM improves their skills and can help improve symptoms and psychological problems caused by anxiety and pregnancy. Furthermore, due to its simplicity and ease of use and the cultural and social appropriateness of its educational concepts, 5A model-based education can increase the motivation of pregnant women with GDM to deal with their disease.

One of the limitations of this study was the heterogeneity of the participants in terms of spiritual, psychological, and cultural characteristics; as well as the level of knowledge of the participants. This heterogeneity may have affected the results and could not be controlled by the researcher. Another limitation of this study was excluding illiterate pregnant women, which makes it impossible to generalize the results to this group of patients. Therefore, it is suggested that 5A model be taught to the staff of health care centers and the effect of this education be evaluated on illiterate patients. It is also recommended to implement 5A model for self-management education in other chronic diseases and to evaluate long term effectiveness of education programs based on 5A model in future studies.

Conclusions

The findings of the present study showed that self-management education based on 5A model was effective in improving the quality of life and blood glucose control of pregnant women with GDM. As maintaining the health of pregnant women and preventing the fetal complications of GDM are important goals of care during pregnancy, the findings of the present study could be of great value in nursing. Due to the fact that pregnant women are not always reachable to the health care staff to receive the necessary care, the best way to maintain their health is through self-management promotion. The 5A model can be effective in achieving this goal. Therefore, while emphasizing on the need for additional studies and considering the consistent results of many similar studies, education based on 5A model can be considered as a simple, practical, and effective alternative to somehow less effective traditional methods.

Some clinical implications of this study are discussed as follows: Nurses' and families' awareness of the importance of providing self-management based on the 5A model on the quality of life and blood glucose levels in women with GDM can have good results in improving nursing services. It can also take a practical step in improving patients' status and dependence on the medical staff, enabling them to manage their problems.

Some clinical implications of this study are discussed as follows: Nurses' and families' awareness of the importance of providing self-management based on the 5A model on the quality of life and blood glucose levels in women with GDM can help to improve nursing services. It can also take a practical step in improving patients' status and it is depending on the healthcare workers and enabling them to manage their problems.

Overall, the findings of the present study showed that self-management education, including the concepts of blood glucose management, diabetes complications, exercise and nutrition, lifestyle modification, stress management, medication, and foot hygiene through pamphlet, slide and movie presentation, lectures, group discussions, and workshops based on 5A model (evaluation, guidance, agreement, aid, and follow up) effectively improved the quality of life and reduced blood glucose levels in pregnant women with GDM. Considering the point that pregnant women are not always accessible by the health care staff to receive their health care services, the best approach for maintaining their health is through improving their self-management skills. One of the methods to achieve this goal is through educating mothers based on the 5A model.

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Conflict of interest statement

The authors declare no conflict of interest

Authors' contributions

S.R.: conception and design, data collection, writing and revision of the manuscript; A.N.D. and M.S.: concept and study design, critical revision and editing; Z.R.: participated in the study design, critical revision and editing of the manuscript; A.M.: supervisor, concept and study design, critical revision and editing. All authors reviewed and approved this manuscript.

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How do undergraduate nursing students learn about the fundamentals of care? A pilot cross-sectional attitudinal study

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Summary

Introduction. *Despite the growing importance of nursing fundamentals of care, nurses often overlook these aspects of care. In this study, we explored why this happens precisely where nursing education is initially provided. In fact, little is known about how undergraduate nursing students perceive the teaching of fundamentals of care and how they value them.*

Methods. *This pilot cross-sectional study used a questionnaire adapted and validated in Italian to assess the perceptions of first, second, and third-year undergraduate nursing students (n=150) in an Italian university about the teaching of fundamentals of care during theoretical lessons and clinical practice.*

Results. *In the first section of the tool, on general fundamentals of care (nutrition, hygiene, mobility, rest and sleep, the expression of sexuality, safety, etc), students reported high levels of agreement for all items: range between 61.2% (95% CI: 57.1-65.3) and 100%.*

In the section on nutrition, divided into nutrition, oral intake of fluids, and malnutrition high percentages of agreement from 53.1% (95% CI: 46.0-60.2) to 91.8% (95% CI: 87.9-95.7%) were obtained, but for questions regarding 'learning how to document food and fluid intake', first-year students reported low levels of agreement.

With regard to the 'Communication Section', the item about 'learning how to inform minor patients' presented low percentages of agreement throughout the three-year program. Of the first-year students, between 71.4% (95% CI: 64.9-77.9) and 77.6% (95% CI: 71.6-83.6) declared they had not received instructions about this.

Conclusions. *Understanding how nursing students perceive the importance of learning of fundamentals of care during their curriculum and how their multidimensional nature is highlighted by teachers and clinical supervisors, will enable educators to address the gaps in the way they taught and prioritized within the curriculum.*

Introduction

The fundamentals of care are a set of core nursing activities that underpin nurses' health care competencies. They include communication, nutrition, hygiene, mobility, rest and sleep, the expression of sexuality, safety (*e.g.,* prevention of infections and falls), general comfort (*e.g.,* maintenance of adequate temperature and pain control) and elimination [1]. The fundamentals of care are presented within a framework that consists of three domains: physical (patient's physiological needs), psychosocial (patient needs related to the context in which they live, in particular: the need to communicate, the need to be involved in the care process, privacy, dignity, psychological well-being, respect, being educated and informed about their health status and the need to see his beliefs and values respected) and relational (nurses' actions in their relationship with the patients such as: active listening, empathy, collaborating with the patient, being compassionate, supporting patients and their family members, and actively informing them on the progress made during the period of treatment and helping them maintain a state of psychological well-

being) [2]. Work on an agreed definition of fundamental care is ongoing, in particular by International Learning Collaborative (2020) [3], who are concerned with best practice in relation to fundamental care and supporting and encouraging research in this regard. A current working definition [4] is as follows: *"Fundamental care involves actions on the part of the nurse that respect and focus on a person's essential needs to ensure their physical and psychosocial wellbeing. These needs are met by developing a positive and trusting relationship with the person being cared for as well as their family/ carers"* [3].

Nutrition for instance has long been considered one of the basic needs that nurses are required to monitor, because it is one of the basic care activities provided to patients, and insufficient nutritional intake can compound or lead to health issues [5]. Adequate nutrition is a fundamental right of every human being and the basis for disease prevention and quality of life. However, in clinical practice nutrition is not always prioritized. [6].

Communication is another important aspect of care that should not be overlooked in the hospital setting, because it is vital to holistically address patients'

fundamental care needs [4, 5]. Yet patient education, giving information, and other aspects of communication are frequently overlooked [7]. Excellent communication with patients is an important contributor to positive healthcare outcomes and safety in healthcare practice. Patients who are fully informed about their procedures, for example, and have had the opportunity to express their doubts, fears and feelings will adhere more effectively to the proposed treatments and will feel more secure surrounded by professionals who build a relationship of trust with them [8].

There is emerging evidence that when these fundamentals of care are not fully implemented or missed, they can have direct consequences for patient care outcomes and patient satisfaction [9]. Therefore, there is an increasing consensus that the conceptualization of fundamentals of care, clearly outlined by the International Learning Collaborative [3], should be thoroughly integrated within undergraduate nursing curricula [10] and form part of the core competency set of nurses [11]. However, as there are many items competing for attention, the multidimensional nature of fundamentals of care are not always explicit in undergraduate nursing curricula [10, 12].

Nursing students often favor the more technical aspects of care, but if health care becomes increasingly technical, there are serious safety concerns when fundamentals such as communication and nutrition are not prioritized [13]. Therefore, teachers and clinical mentors play a crucial role in guiding students' attention towards understanding the importance and the multidimensional complexity of fundamentals of care [2, 8, 10]. Therefore, it is crucial to expand and develop the evidence base not only for fundamental care delivery but also its pedagogy. One recent study that investigated this aspect in the Netherlands, across three universities developed a research project called "Basic Care Revisited" [14]. This initiative significantly contributed to evidence-based basic nursing care by raising awareness of the importance of essential nursing activities within the curriculum [14].-

Given the increasing agreement of the need for fundamentals of care to become imbedded within the curriculum [15], this study aimed to explore Italian nursing students' perceptions of their theoretical and practical teachings received on fundamental care, with a particular focus on communication and nutrition.

Methods

Study design

This is a pilot cross-sectional study that uses a questionnaire adapted and validated in Italian to explore the perceptions of undergraduate nursing students about the teaching of fundamentals of care during theoretical lessons and clinical practice.

Tool validation before the current pilot study

A specifically designed questionnaire was developed in the Netherlands to investigate how students perceived the teaching of fundamentals of care during their three-year program, with a particular focus on their learning about nutrition and communication [11, 14]. It was validated for use across 6 universities. The instrument design was based on the "fundamentals of care template," developed by Kitson in (2010) which identified 14 discrete elements of fundamentals of care [1].

Before conducting the current pilot study, the questionnaire [11] was adapted and translated into Italian for the purposes of this project. The tool validation process included the following steps: 1) analysis of the original tool [11] and development of new items; 2) analysis of content and face validity; 3) reliability analysis (stability and internal consistency). The questionnaire showed excellent validity and reliability. The Item Content Validity Index (I-CVI) ranged from 0.80 to 1.00 and the Scale Content Validity Index (S-CVI) was 0.98. The Interclass Correlation Coefficient (ICC) confirmed the stability of the tool, and Cronbach's alpha its internal consistency (0.92). The adaptation took into account the Italian Nursing Code of Ethics and national and local programme requirements regarding nutrition and communication within the bachelor's degree in nursing.

Sampling

After the adaptation and validation process, the questionnaire was administered to first, second and third-year undergraduate nursing students. Convenience sampling was used and included all the nursing students who were attending their first, second- or third year and were ready for their clinical placements (n = 191) in September 2019. A hard copy of the questionnaire was administered after students had read the information sheet and the informed consent; the questionnaire was administered for two weeks. Participation was voluntary and data were collected ensuring the respondents' privacy and anonymity.

Ethical approval was sought from the Liguria Regional Research Ethics Committee (Italy) and deemed as not required according to the Italian laws and regulations. Permission to access the nursing students was gained from the Faculty of Nursing.

The questionnaire

The original questionnaire [11] was in digital format and consisted of 3 sections. In the first section demographic data were requested. In the second part, the questions focused on students' knowledge of the 14 fundamental care activities. In the last section, the questions focused on specific knowledge about nutrition and communication. The response grid of sections 2 and 3 consisted of a 5-point Likert scale, from 'completely disagree' to 'completely agree'.

The Italian version of questionnaire consisted of 3 sections and the responses to each item were based on a Likert scale (1-4) where students had to score their level

of agreement on learning a given aspect selected during their theoretical lessons and clinical internship.

Furthermore, unlike the original questionnaire, where the responses were based on a 5-point Likert scale, in the Italian version the responses were based on a 4-point Likert scale (from 'completely disagree' to 'completely agree'), because the intermediate response ('neither in agreement / nor in disagreement') of the original questionnaire was not relevant for the purpose of the present study. The responses of the 4-point Likert scale were dichotomized and attributed a score of 1 (disagree) for 'completely disagree' or 'disagree', and a score of 2 (agree) was attributed to the responses 'agree' and 'completely agree'. Section 1 deals with fundamentals of care, with 14 general questions regarding the elements of basic care: safety, communication, breathing, nutrition/hydration, elimination, hygiene, temperature, sleep and rest, comfort, mobility, dignity and privacy, and expression of sexuality. Section 2 focuses on some specific aspects of fundamentals of care: nutrition (divided into nutrition, hydration and malnutrition) (20 questions), and communication (11 questions), which were investigated through questions concerning all steps of the respective nursing process, from assessment to evaluation ["Where did you learn the identification of the right time to offer a food (e.g. diabetic patient, post-operative patient, healthy patient with the proposal of five daily meals)?"]. Finally, Section 3 includes questions on respondents' demographics. The average length of time taken to complete the questionnaire was 20 minutes.

Data analysis

Microsoft Excel sheets and IBM SPSS Statistics 22 software were used to analyze the results. A descriptive analysis using central tendency indexes, mean and frequencies to describe the sample was performed. The differences between students attending different years refer to separate samples where a comparative analysis was conducted. This happens because the nursing curriculum has not been changed in the last years.

Pearson's chi-square correlation was conducted to examine correlations between levels of agreement and gender, and between agreement answers and age [16].

Results

The study sample consisted of all the 191 students enrolled in the undergraduate nursing three years degree program (Tab. I). The response rate was 78.0% (n = 149).

Participant demographic characteristics

The research team decided to perform a stratification of the answers per course year to highlight the critical issues in more detail and the students' answers from the three different years of the undergraduate course both in terms of learning during theoretical lessons and clinical practice.

Tab. I. Sample characteristics.

Gender	n	%
Male	34	22.8%
Female	115	77.2%
Mean age	22.62 yrs (Age range 19-40 yrs)	3.08 (SD)
Year of Programme		
First-year students	49	32.8%
Second-year students	55	36.9%
Third-year students	36	24.1%
Out of course students	8	5.3%
Total sample	149	100%

General questions on Fundamentals of Care

In the first section of the tool, concerning questions on general fundamentals of care, students reported high levels of agreement for all items: from 61.2% (95% CI: 57.1-65.3) to 100%. Regarding safety-related care, prevention and therapy administration, the majority of students across all three years of the program reported receiving instructions on this topic in both the classroom and clinical practice. While a large percentage of first-year students reported receiving tuition, almost 40% did not appear to receive instructions. The level of perceived instructions across both lessons and clinical practice rose incrementally according to seniority, with high percentages reporting receiving this instruction in the final year.

Concerning communication and education assistance, students' agreement was high and increased from first- to second-year students but showed a higher percentage of disagreement (almost 28%) about perceived instructions on this topic among senior students

We found that for providing care during elimination, controlling temperature and ensuring rest and sleep students showed very high percentages of agreement in all years, reaching a level of total agreement also in first-year students. With regard to comfort care and pain management, students showed high levels of perceived instruction, but still with up to 20% of disagreement among earlier students that decreases to 11.1% of disagreement about learning this topic in third-year students.

The item 'providing care to ensure the expression of sexuality' showed the lowest levels of agreement about its learning among students, with a maximum of 52.7% (95% CI: 46.0-59.4) of agreement among second year students (Tab. II). These results revealed that undergraduate students from the three different years declared they learnt during lessons or clinical practice or both about the majority of basic nursing care items explored by the questionnaire. Overall percentages of agreement were almost all higher among second- and third- year students, who appeared to have received specific education about these topics.

Nutrition

The second section of the questionnaire, related to nutrition (divided into nutrition, oral intake of fluids,

Tab. II. Students' perceptions (stratified per year course) of receiving instruction regarding Fundamentals of Care across their nursing programmes.

	Level of Agreement (%)					
	(n = 49)		(n = 55)		(n = 36)	
	1st Year (L*) (95% CI)	1st Year (CP*) (95% CI)	2nd Year (L) (95% CI)	2nd Year (CP) (95% CI)	3rd Year (L) (95% CI)	3rd Year (CP) (95% CI)
GENERAL FUNDAMENTAL IDENTIFIED						
Safety-related care, prevention and therapy administration	61.2 (54.2-68.2)	73.5 (67.2-79.8)	90.9 (87.0-94.8)	98.2 (96.4-100)	100	97.2 (94.5-99.9)
Communication and education assistance***	85.7 (80.7-90.7)	91.8 (87.9-95.7)	94.5 (91.4-97.6)	96.4 (93.9-98.9)	72.2 (64.7-79.7)	89.9 (84.9-94.9)
Providing breathing assistance	83.7 (78.4-89.0)	81.6 (76.1-87.1)	78.2 (72.6-83.8)	89.1 (84.9-93.3)	88.9 (83.7-94.1)	91.7 (87.1-96.3)
Nutrition and hydration°	93.9 (90.5-97.3)	89.8 (85.5-94.1)	98.2 (96.4-100)	92.7 (89.2-96.2)	97.2 (94.5-99.9)	94.4 (90.6-98.2)
Providing care for elimination***	98.0 (96.0-100)	95.9 (93.1-98.7)	92.7 (89.2-96.2)	94.5 (91.4-97.6)	94.4 (90.6-98.2)	97.2 (94.5-99.9)
Providing care for personal hygiene and toileting***	93.9 (90.5-97.3)	95.9 (93.1-98.7)	85.5 (80.8-90.2)	90.9 (87.0-94.8)	91.7 (87.1-96.3)	88.9 (83.7-94.1)
Controlling temperature	93.9 (90.5-97.3)	98.0 (96.0-100)	89.1 (84.9-93.3)	96.4 (93.9-8.9)	94.4 (90.6-98.2)	100
Ensuring rest and sleep***	100	71.4 (64.9-77.9)	92.7 (89.2-96.2)	76.4 (70.7-82.1)	91.7 (87.1-96.3)	75.0 (67.8-82.2)
Comfort care (including pain management) **	79.6 (73.8-85.4)	81.6 (76.1-87.1)	92.7 (89.2-96.2)	89.1 (84.9-93.3)	91.7 (87.1-96.3)	88.9 (83.7-94.1)
Dignity care	87.8 (83.1-92.5)	75.5 (69.4-81.6)	83.6 (78.6-88.6)	76.4 (70.7-82.1)	80.6 (74.0-87.2)	83.3 (77.1-89.5)
Ensuring privacy**	91.8 (87.9-95.7)	73.5 (67.2-79.8)	94.5 (91.4-97.6)	80.0 (74.6-85.4)	94.4 (90.6-98.2)	83.3 ((77.1-89.5)
Respect the patient's choice	79.6 (73.8-85.4)	93.9 (90.5-97.3)	90.9 (87.0-94.8)	81.8 (76.6-87.0)	91.7 (87.1-96.3)	91.7 (87.1-96.3)
Ensuring mobility	93.9 (90.5-97.3)	93.9 (90.5-97.3)	98.2 (96-100)	85.5 (80.8-90.2)	94.4 (90.6-98.2)	91.7 (87.1-96.3)
Providing care to ensure the expression of sexuality**	46.9 (39.8-54.0)	44.9 (37.8-52.0)	45.5 (38.8-52.2)	52.7 (46.0-59.4)	50 (41.7-58.3)	50 (41.7-58.3)

*(L)= Lessons; (CP)=Clinical Practice. ** Significant correlation for Gender; *** Significant Correlation for Age;° Significant Correlation for Age and Gender

and malnutrition), revealed answers with a prevalence of high percentages of agreement [from 53.1% (95% CI: 46.0-60.2) to 91.8% (95% CI: 87.9-95.7%) regarding learning these aspects of nursing care in the undergraduate nursing program. For questions regarding 'learning how to document food and fluid intake during the work shift', first-year students showed low levels of agreement about this during classroom lessons: 26.5% (95% CI: 20.7-33.3%) and 28.6% (95% CI: 22.1-35.1%) respectively. These agreement values were higher in second- and third-year students: 47.3% (95%CI: 40.6-54.0) and 61.1% (95% CI: 54.5-67.7) respectively and, for all the three-year course, there were high percentages of agreement about learning this during clinical practice: 53.1% (95% CI: 46.0-60.2), 81.8% (95% CI: 76.6-87.0), 69.4% (95% CI: 62-77) for recording food intake; 63.3% (95% CI: 56-70); 81.8% (95% CI: 77-87), 86.1% (95% CI: 80.3-91.9) for fluid intake].

COMMUNICATION

With regard to the 'Communication Section', the item about 'learning how to inform minor patients'

presented low percentages of agreement about receiving instructions on this across the entire three-year program. Of the first-year students, between 71.4% (95% CI: 64.9-77.9) and 77.6% (95% CI: 71.6-83.6) declared they had not received instructions about this. During their third-year clinical practice, almost 70% of students perceived to have received education on this aspect (Tab. III). As in the first section, it is possible to see average higher percentages of agreement among the more senior students, meaning that at the end of the bachelor program, they received and learnt almost all aspects about fundamentals of care.

STATISTICAL ANALYSIS - CORRELATIONS

The chi-square test was used to investigate correlations and significant differences between agreement level (dichotomized dependent variable), and respondents' gender and age. The items that revealed statistically significant chi-square values between level of agreement and gender were: nutrition and hydration (chi-square = 4.061, p = .044); comfort care (chi-square = 6.297, p = .012); ensuring privacy (chi-square = 4.192, p = .041); and providing care to

Tab. III. Question 10, Communication section.

	Level of Agreement					
	(n = 49)		(n = 55)		(n = 36)	
	1st Year (L*) (95% CI)	1st Year (CP*) (95% CI)	2nd Year (L) (95% CI)	2nd Year (CP) (95% CI)	3rd Year (L) (95% CI)	3rd Year (CP) (95% CI)
Learning how to inform pediatric patients	22.4% (16.4-28.4)	28.6% (22.1-35.1)	40.0% (33.4-46.6)	54.5% (47.8-61.2)	41.7% (33.5-49.9)	69.4% (61.7-77.1)

ensure expression of sexuality (chi-square = 4.232, $p = .040$) (Tab. II).

With regard to the correlation between level of agreement and age, the results revealed statistically significant values for the following items: assisting with communication and education (chi-square = 28.023, $p = .021$); nutrition and hydration (chi-square = 39.757, $p = .000$); providing care for elimination (chi-square = 29.980, $p = .016$); providing care for personal hygiene and toileting (chi-square = 27.976, $p = 0.022$); ensuring rest and sleep (chi-square = 28.305, $p = .020$); factors related to malnutrition (chi-square = 39.953, $p = .000$); listening effectively to a patient (chi-square = 37.573, $p = .001$); respecting patient's opinions and ideas (chi-square = 27.599, $p = .024$); promoting patient participation (chi-square = 28.612, $p = 0.18$); and relationship with patients with communication limits (chi-square = 26.078, p = .037) (Tab. II).

Discussion

Through this survey we took a snapshot of the current situation in one Italian university, highlighting strengths and shortcomings about learning fundamentals of care among undergraduate nursing students, both theoretically and practically. Overall findings showed on average a good level of learning about fundamentals of care in contrast with the findings of lower levels of attention to explicit fundamentals of care in some other countries [12].

A thought-provoking finding from this study was that specific learning about addressing patients' sexuality appeared to be lacking and unaddressed throughout the three years curriculum. This may be linked to the students' cultural backgrounds and their geographical origins, whereby discussing sexuality may be perceived as a taboo. The current validated version of the questionnaire did not include items that explored students' cultural and geographical characteristics but would be worth exploring in the future. However, this finding is echoed in studies from other countries, such as the United States, where in one study only 16% of nursing educators believed that undergraduate students were prepared to manage the patient's needs in relation to sexuality and 27% reported that this aspect was not addressed in the curriculum [17]. These results highlight the need to strengthen and implement education in undergraduate nursing programs to ensure that future nurses learn and feel prepared to support patients' expression of sexuality,

and healthcare related needs, to provide truly holistic care to patients effectively [18]. The introduction of a graduate-level course on sexual health and sexual health disparities effectively increased perceived preparedness, comfort and confidence among nursing students in delivering comprehensive and culturally informed care to diverse populations and suggested to reinforce these implementation courses [18].

From this study it was also clear that from most of the students' perspectives, while safety issues appeared to be addressed both in the classrooms and clinical practice, a large percentage of students did not perceive to have gained this kind of instruction in their first year. While high levels of agreement with this was clear in the final years, it is of concern that this important aspect of nursing could have been neglected in the earlier stages of the program. This finding is consistent with other studies whereby senior students and qualified nurses were found to have an increased interest and concern with patient safety [19].

Since the relevance of the concept of patient safety concept enables to provide high quality care [20, 21, 22], we need to use the findings of this study to stress the importance of safety as an explicit subject within the nursing curriculum, and one that should be taught consistently across the duration of the program and varying levels of complexity. However, it is interesting to note that the undergraduate nursing program, where this survey was conducted and also in other settings [23], there were no specific classes based on safety. Rather it is often taught implicitly during lessons and through observation in clinical practice. Thereby, more junior students, understandably reported little learning on this topic, possibly because at that point they had limited clinical exposure. This finding is linked to Cresswell' s findings, which revealed that concept of safety was not taught consistently or explicitly across programs [23]. This finding is surprising even though the World Health Organization have actively developed a patient safety curriculum for multiprofessional education [21], and healthcare safety movements are growing globally [20]. Students' responses about specific fundamentals of care, such as elimination, nutrition, rest and sleep, demonstrated high levels of agreement thus reflecting an overt focus on these subjects within the nursing curriculum.

Another finding of importance was the students' experiences of learning about comfort care and pain management, where high percentages of students reported to have received instruction on these topics. However, the views were inconsistent, both within

each cohort and across the years, indicating an inconsistency in approaches to the teaching of pain management. Similar and even more negative results appeared in other studies where nursing students showed suboptimal levels of knowledge and attitudes towards pain management [24, 25]. Similar trends appeared in relation to students' views about learning about privacy, with high percentages of agreement among students, but inconsistences across the years of the program. Some previous studies have revealed the need to improve educational contents on this topic with the use of appropriate training methods [26, 27].

Students also declared teaching gaps throughout their three-year program regarding related to communication with children. This deficit may be due to the fact that Italy has a separate curriculum and professional profile for pediatric nurses, who were not included in this study. However, at the same time, nursing care of children is supported only be a small number of specialist hospitals [28] and many large public hospitals would also have children's units. This means that both students and staff may have opportunity to nurse children without necessarily having the specialist skill set. Indeed, gaps in graduates' communication skills are widely reported in relation to communication with both patient and family but also in relation to other areas such as reporting poor practice, using technology and intercultural communication. At the same time there is also some concern that communication proficiency is often not included within programme learning outcomes [29]. This may be because undergraduate outcomes predominately focus on ability to describe and reflect on practice and often lack emphasis on attaining objectively measured proficiency in these particular skills [29]. Evidence suggests that experimental/active teaching models such as simulation and role-play are perceived by students to be the preferred methods of educational interventions tentatively indicating that these may be effective nurse educational methods [19, 30].

Furthermore, this study found some correlations between being female and ensuring comfort care, dignity, and expression of sexuality. This can be linked to female students' vision of their professional role of altruism and caring by being a nurse [31], while male students focus on strengthening management, leadership, and technical aspects of nursing [31]. We should also point out that correlations between some general fundamentals of care (e.g., communication and education; nutrition and hydration; providing care for elimination; providing care for personal hygiene and toileting; ensuring rest and sleep; listening effectively to a patient; respecting patient's opinions and ideas, etc.) and students' age can be explained with the more senior and experienced students within the nursing program.

There is the need to consider the multifaceted reality of teaching and learning about fundamentals of care, as well as an approach that is more explicit. Conceptualizing the fundamentals of care within the curriculum according to the fundamentals of care framework would serve this purpose [10]. An additional benefit of this is that these fundamentals are interconnected and inter-reliant [10]. Thus, learning about one or two in isolation is not sufficient. Nursing students' learning about these must be in a holistic manner [10].

Consensus is also needed about the depth and necessity of learning across the stages of the program. Certainly, the early exposure without revisiting the topics again has limitations, and at the same time some topics might be best suited to the more advanced learner. Mapping the learning across the duration of the nursing program, using the fundamentals framework, and making teaching explicit, is one method so that the learning, regardless of its position within the curriculum, could be understood as important and reinforced [10]. Consideration also needs to be given to the best methods for teaching these fundamentals, particularly communication and nutrition, with additional research needed to explore the benefits of high-fidelity teaching and learning.

Of particular importance is the need to begin to consider these fundamentals as dynamic and interactive, and not static skills to be learnt in isolation and as a once off. Both high and low fidelity scenarios need to be developed that address the complexity of fundamentals of care and test the students' knowledge, skills and reactions to a combination of needs in these areas, rather than simply learning skills as standalone entities [10].

Nurse educators can use the findings of this study to tailor nursing programs so that they may emphasize the importance of teaching and learning fundamentals of care. Undergraduate education is a strategic time to start implementing a process of change in the way nurses perceive fundamentals of care, and to encourage students' awareness of the importance of this approach through consistent collaboration between the academic faculty and clinical mentors.

LIMITATIONS

This study has some limitations because it was conducted only in one academic setting, as well as being descriptive and cross sectional. Convenience sampling can determine another limitation for highly vulnerable selection bias and high level of sampling error. In addition, it is based on information reported by the students, without conducting a comparison with their learning outcomes or analyzing the contents of the undergraduate program.

Conclusions

This is the first study that attempts to investigate the learning of fundamentals of care in an Italian university. The results obtained through this pilot study are consistent with findings in the literature and reveal that interventions are needed to make the teaching and learning of fundamentals of care more explicit and structured. Also, more in-depth studies are needed, to expand the knowledge about the multifaceted approach of both teaching and learning fundamentals of care and enable students to develop the required skills to uphold safety standards and support excellence in practice.

Financial Competing Interests

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Conflict of interest

None.

Authors' contributions

M.Z., S.L., A.B., G.C., and L.S. contributed to the conception and the design of this study. S.R., N.D., G.O., G.C., and M.H. contributed to data collection, analysis, and interpretation. F.T., M.Z., G.C., G.A., S.L., G.O., N.D. and L.S. have been involved in drafting, editing and revising critically this manuscript.
All authors have read and approved the final manuscript.

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Probability of non-compliance to the consumption of Iron Tablets in pregnant women in Indonesia

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Summary

Introduction. *The low non-compliance to the consumption of Iron Tablets in pregnant women is an obstacle in the implementation of government programs to prevent and overcome the anemia problems in pregnant women. This study was conducted to determine the probability of non-compliance of pregnant women in the consumption of iron tablets in Indonesia.*
Methods. *A cross-sectional study using the 2017 IDHS data. The sample was 12,466 women of childbearing age 15-49 years in Indonesia who consumed Iron Tablets during their last pregnancy. Univariate analysis used proportion measure, the bivariate analysis using chi-square test and multivariate used binary logistic regression test. Statistical analysis using SPSS-26 software.*
Results. *The level of non-compliance to the consumption of Iron Tablets during pregnancy in Indonesia is only 48.47%. The risk factors for quantity (p = 0.000, OR 2.085), and quality (p = 0.000,*

OR 1.655) Antenatal Care (ANC) was not good, examiners were pregnancy not health workers (p = 0.000, OR 1.816), residence in rural areas (p = 0.000, OR 1.262), and very poor socioeconomic status (p value = 0.000, OR 2.041) were significantly related to non-compliance with Iron Tablets consumption. The probability of non-compliance to the consumption of Iron Tablets in pregnant women with risk factors is 88%.
Conclusion. *Quantity of ANC and socioeconomic have a high influence on compliance to consumption of iron tablets, so it is important to bring nutrition workers at ANC activities to educate pregnant women about the benefits, side effects, and ways of consumption of iron tablets, reactivate supervisors for consumption of iron tablets, increase access health services in rural areas and families with low socioeconomic status, as well as providing free health care programs for the poor.*

Introduction

Anemia is a public health problem that has a serious impact. Groups that are susceptible to anemia are women of childbearing age and pregnant women [1]. Anemia in pregnancy is a condition where the hemoglobin level is less than 11 g/dl. The impact of anemia in pregnancy results in abortion, easy infection, antepartum bleeding, shock, premature rupture of membranes, postpartum hemorrhage can occur. The World Health Organization (WHO) estimates that 40.1% of pregnant women worldwide experience anemia and the prevalence of anemia in pregnant women throughout Asia is around 48.2% [2]. The prevalence of anemia in pregnant women aged 15-49 years in Indonesia was 41.98% in 2016, where this percentage increased from the previous year's percentage of 40.53% in 2015 [3]. Based on the results of the Basic Health Research (2018), the prevalence of anemia in pregnant women in Indonesia increased to 48.9% when compared to the Basic Health Research (2013) which was 37.1% [4].

It is estimated that 50% of anemia in women worldwide is caused by iron deficiency. Most cases of anemia are due to iron deficiency from food, low iron absorption in the body, increased iron requirements during pregnancy or growth, and increased iron loss due to menstruation and worms (intestinal worms) [5]. Giving Iron Tablets to pregnant women at least 90 tablets is one of the

Indonesian government's efforts to prevent and overcome the problem of iron anemia [6]. WHO recommends the consumption of supplements of iron and folic acid in pregnant women with a daily dose of 30 to 60 mg of iron and 400 mcg (0.4 mg) of folic acid to prevent pregnant women have anemia, puerperal sepsis, low birth weight, and premature birth [7].

There are still many obstacles in the implementation of giving Iron Tablets in the community, one of which is the low compliance of pregnant women in the consumption of iron tablets according to the recommendation of at least 90 points during pregnancy [8]. Basic Health Research (2018) report, it was reported that only 38.1% of pregnant women in Indonesia consumed as recommended (≥ 90 tablets) [4]. The Indonesian Health Demographic Survey (IDHS) 2017 report shows that there are pregnant women who do not consumption of iron tablets during pregnancy 13% (2017), as many as 29.4% of pregnant women consume Iron Tablets < 60 tablets, consumption of 60-89 tablets by 8.9%, don't know 5.1% and the percentage of women who take Iron Tablet according to the recommendation of at least 90 tablets is only 44%, but this presentation has not changed in the last 10 years [9]. The achievement of pregnant women consumption of Iron Tablets has decreased from 2018 (81.2%) to 64% in 2019, and this figure is still far from the national target, which is 98% [10].

Fig. 1. Samples Selection Stage in the 2017 IDHS Data.

Total childbearing age IDHS 2017 = 49,627 people

Total Childbearing age ever gave birth = 34,199 people

Total Childbearing age experienced the birth of children in the last 5 years = 15,357 people

Complete Data (Available data on the number of iron tablets consumed by women of childbearing age) = 12,466 people
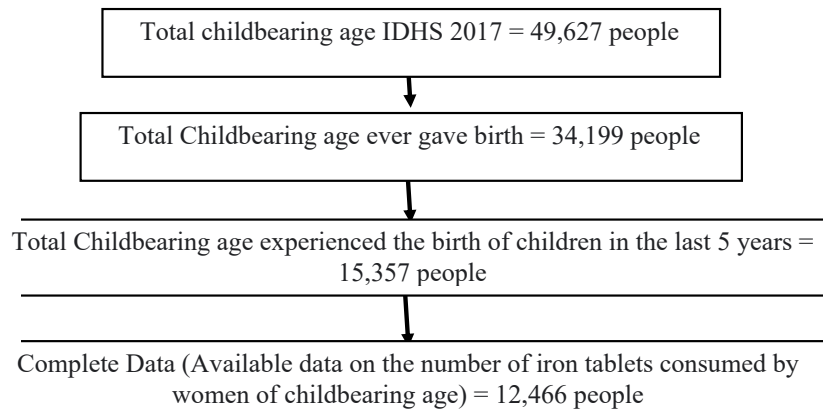
Compliance consumption of Iron Tablets in pregnant women is influenced by various factors, namely maternal age, occupation, education, parity, a quantity of ANC, a quality of ANC, place of residence, socio-economic status, and antenatal care workers [1, 11-15]. Research is generally in certain areas and locations with a small sample size so generalizations are limited. Research results that explain the determinants and the probability of compliance to Iron Tablets consumption in pregnant women using national survey data are still rarely done. This study used the 2017 IDHS data to determine the probability of non-compliance with the consumption of Iron Tablets in Indonesia based on risk factors for pregnant women. The results of this study are expected to be the basis for making policies to overcome anemia in pregnant women.

Methods

POPULATION AND SAMPLE

This study used the 2017 Indonesian Health Demographic Survey (IDHS) data with approach *cross sectional*. The population is all women of childbearing age (15-49 years) in Indonesia recorded in the 2017 IDHS survey. The research sample is women of childbearing age (15-49 years) with children born within 5 years prior to the 2017 IDHS survey. The unit of analysis for in this study, women of childbearing age (15-49 years) with their last child were pregnant. The sampling method used in this study follows the 2017 IDHS sampling process. The 2017 IDHS sampling design is designed to present estimates at the national and provincial levels. The 2017 IDHS sample covers 1,970 census blocks covering both urban and rural areas in Indonesia. The 2017 IDHS sample framework uses the master census block sample from the 2010 population census (PS 2010). While the household selection sample framework uses a list of ordinary households generated from updating the selected census block households [16] detect all complications of pregnancy and take the necessary actions, respond to complaints, prepare for birth, and promote a healthy lifestyle. This study aims to analyze interregional disparities in ≥ 4 ANC visits during pregnancy in Indonesia. Methods Data was acquired from the 2017 Indonesian Demographic and Health Survey (IDHS.

Of the 49,627 women of childbearing age, there are 34,199 childbearing age who have given birth, and childbearing age who have given birth to children in the last 5 years are 15,357 people and the number of childbearing age who become the research sample is 12,466 people. Based on the results of a survey conducted by the 2017 IDHS, the researchers selected a sample among the population that was in accordance with this study, namely childbearing age aged 15-49 years who consumed Iron Tablets during their last pregnancy. The stages of sample selection are described in Figure 1.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The 2017 IDHS activities received research ethics approval from the *Institutional Review Board* ICF (*International Classification of Functioning*) with ICF Project No. 132989.000. Whereas in this study itself, before the research was conducted, a research ethics permit was first submitted to the Health Research Ethics Commission of the Bengkulu Ministry of Health Polytechnic with the *Ethical Clearance* Number KEPK.M/021/05/2021. Respondents who had been involved in this study, had previously given written informed consent after explanation.

STATISTICAL ANALYSIS

Data analysis used univariate analysis to describe the characteristics of each research variable. Bivariate analysis used test *Chi Square* to show different test proportions of non-compliance to Iron Tablet consumption and to identify candidate variables that would be included in the multivariate analysis, and multivariate analysis used binary logistic regression to determine the determinants of compliance to Iron tablet consumption. Then calculated the probability of non-compliance to the consumption of Iron Tablets based on the final model of multivariate logistic regression.

Tab. I. Proportion of Iron Tablet consumption in Pregnant Women based on Indonesian Region.

Regional	Consumption of Iron Tablets	
	Recommendation (≥ 90 tablet)	Not Recommendation (< 90 tablet)
Region: Sumatera	38.17	61.83
Region: Java-Bali	65.65	34.35
Region: Nusa Tenggara	45.65	54.35
Region: Kalimantan	56.25	43.75
Region: Sulawesi	27.03	72.97
Region: Maluku Islands	41.99	59.01
Region: Papua	42.81	57.19
Indonesia	**48.47**	**51.53**

Results

Table I shows that 48.47% of pregnant women in Indonesia consume the number of Iron Tablets that are not as recommended. Based on the Indonesian region, the proportion of non-compliance with Iron Tablet consumption was highest in Sulawesi region (72.97%) and Sumatra region (61.83%). The proportion of pregnant women who consume Iron Tablets according to the highest recommendation in the Java-Bali region (65.65%) and Kalimantan region (56.25%).

Table II shows the majority of pregnant women in Indonesia aged 20-35 years (72.3%), most of the mother's education (57.5%) was secondary education (graduated from junior high school/equivalent and high school/equivalent), more than half (53.6%) of Pregnant women with working status, most (61.7%) Pregnant women with more than one parity (multipara), the majority (78.1%) with good ANC quantity (once in the

Tab. II. Frequency Distribution of Maternal Characteristics and Family Characteristics in Indonesia.

Characteristics	Frequency (n = 12,466)	Percentage (%)
Age		
20-35 Years	9,016	72.32
< 20 Years	314	2.52
> 35 Years	3,136	25.16
Education		
Higher education	7,162	17.89
Secondary education	2,231	57.45
Primary education	2,954	23.69
No school	119	0.95
Employment		
Working	6683	53.64
Not Working	5775	46.35
Parity		
Primipara	7,695	31.27
Multipara	3,899	61.72
Grande multipare	872	6.99
ANC Quantity		
Good (≥ 4 times)	9573	78.07
Less (< 4 times)	2689	21.92
ANC Quality		
Good (10T)	9149,	74 88
Less (< 10T)	3069	25.11
ANC examiner		
Health workers	11 953	96.25
Non health workers	465	3.74
Residential		
Urban	6,301	50.55
Rural	6,165	49.45
Socio-Economic Status		
Very Rich	2,177	17.46
Rich	2,322	18.62
Medium	2,383	19.12
Poor	2,481	19.90
Very Poor	3,103	24.89

Tab. III. Correlation between the characteristics of pregnant women with Consumption of Iron Tablets in Indonesia.

Characteristics	Consumption of iron tablets				Total		p-value
	Recommendation (≥ 90 tablet)		Not Recommendation (< 90 tablet)				
	n	%	N	%	n	%	
Age							
20-35 Years	124	2.05	190	2.96	314	2.52	
<20 Years	4,380	72.49	4,636	72.17	9,016	72.32	0.005*
>35 Years	1,538	25.46	1,598	24.87	3,136	25.16	
Education							
Higher education	1,208	19.99	1,023	15.92	2,231	17.70	
Secondary education	3,525	58.34	3,637	56.62	7,162	57.45	
Primary education	1,277	21.14	1,677	26.11	2,954	23.70	0.000*
No school	32	0.53	87	1.35	119	0.95	
Employment							
Working	3,284	54.37	3,399	52.96	6,683	53.64	0.119*
Not Working	2,756	45.63	3,019	47.04	5,775	46.36	
Parity							
Primipara	3,756	62.16	3,939	61.32	7,695	61.73	
Multipara	1,958	32.41	1,941	30.21	3,899	31.28	0.000*
Grande multipare	328	5.43	544	8.47	872	6.99	
ANC Quantity							
Good (≥ 4 times)	5,161	85.86	4,412	70.58	9,573	78.07	0.000*
Poor (< 4 times)	850	14.14	1,839	29.42	2,689	21.93	
ANC Quality							
Good(10T)	4,817	81.19	4,332	68.93	9,149	74.88	0.000*
Poor (< 10T)	1,116	18.81	1,953	31.07	3,069	25.12	
ANC examiner							
Health workers	5,898	97.75	6,055	94.85	11,953	96.26	0.000*
Non health workers	136	2.25	329	5.15	465	3.74	
Residential							
Urban	3,476	57.53	2,825 3,599	43.98	6,301	50.55	0.000*
Rural	2,566	42.47		56.02	6,165	49.45	
Socio-Economic Status							
Very Rich	1,376	22.77		12.47	2,177	17.46	
Rich	1,270	21.02	801	16.38	2,322	18.63	
Medium	1,204	19.93	1,052 1,179	18.35	2,383	19.12	0.000*
Poor	1,070	17.71	1,411 1,981	21.96	2,481	19.90	
Very Poor	1,122	18.57		30.84	3,103	24.89	

*Multivariate Candidates (p ≤ 0.25).

Tab. IV. Determinants of Non-compliance with the Consumption of Iron Tablets in Pregnant Women in Indonesia.

Variable	B	p value	OR (95% CI)
Quantity of ANC			
Good			1
Poor	0.735	0.000	2.085 (1.897-2.292)
Quality of ANC			
Good			1
Poor	0.504	0.000	1.655 (1.515-1.807)
ANC examiner			
Health workers			1
Non health workers	0.597	0.000	1.816 (1.467-2.248)
Residential			
Urban			1
Rural	0.233	0.000	1.262 (1.162-1.371)
Socio-Economic Status			
Very Rich			1
Rich	0.306	0.000	1.358 (1.201-1.535)
Medium	0.377	0.000	1.459 (1.289-1.651)
Poor	0.578	0.000	1.783 (1.571-2.023)
Very Poor	0.713	0.000	2.041 (1.792-2.324)
Constant	-0.788		

Overall Percentage = 60.9%

first trimester, once in the second trimester, and twice in the third trimester), more than half (59.8%) had good ANC quality, almost all (96.3%) Pregnant women had their pregnancy checked by health workers, about 50.55% of Pregnant women in Indonesia lived in urban areas, and their socioeconomic status most are very poor at 24.89%.

Table III shows the proportion of consumption that is not according to the recommendation is higher in pregnant women aged 20-35 years (72.17%) followed by pregnant women aged more than 30 years (24.87%), working pregnant women (52.96%), multiparity(61.32%), good ANC quantity (70.58%) and good ANC quality (68.93%), pregnant women living in rural areas (56.02%), social very poor economy (24.89%), poor (19.90%). The lower the socioeconomic status of the family, the higher the proportion of pregnant women who do not comply with consumption of iron tablets. The results of the bivariate analysis in Table III show all variables as candidates for analysis by multivariate logistic regression test (value *p ≤ 0.25)*.

Table IV shows the final model of the multivariate logistic regression analysis. Factors related to non-compliance with Iron Tablet consumption are ANC quantity and ANC quality are not good, antenatal care workers are not health workers, residence in rural areas, and low socioeconomic status. Pregnant women with poor ANC quantity are at risk of 2.1 times (95% CI: 1.897-2.292) to consume Iron Tablet not according to recommendations compared to Pregnant women with good ANC quantity. Likewise, Pregnant women with poor ANC quality are at risk of 1.7 times (95% CI: 1.515-1.807) to consume Iron Tablet not according to recommendations compared to pregnant women with good ANC quality. Pregnant women who did not check their pregnancy with health workers had a risk of 1.8 times (95% CI: 1.467-2.248) to consume Iron Tablet not according to the recommendations compared to pregnant women who checked their pregnancies with health workers. Meanwhile, pregnant women who live in rural areas are at risk of 1.3 times (95% CI: 1.162-1.371) for consumption of iron tablets not according to recommendations compared to Pregnant women who live in urban areas. The results also show that the poorer the mother, the higher the risk of consumption of iron tablets not according to recommendations. Pregnant women with very poor socioeconomic status are at risk of 2 times (95% CI 1.792-2.324), Pregnant women with very poor socio-economic status are at 1.8 times (95% CI 1.571-2.203) risk for consuming Iron Tablet not according to recommendations compared to Pregnant women with social status very rich economy.

The final model in table 3 shows that the most dominant factors related to non-compliance with iron intake consumption in pregnant women in Indonesia are the quantity of ANC that is not good and very poor socioeconomic status. Based on the Overall Percentage value of 60.9%, shows that 60.9% non-compliance with iron intake consumption can be explained because the quantity and quality of the ANC is not good,

socioeconomic status is low, check-ups are pregnancy not provided by health personnel, and the mother lives in rural areas. Overall, 60.9% non-compliance with Iron Tablet consumption can be corrected by improving the risk factors in the final model. Based on the final model of multiple logistic regression, the logistic regression equation model is obtained as follows:

Logit P (non-compliance to consumption of Iron tablets) = -0.788 + (0.735*Quantity of ANC is poor) + (0.504*Quality of ANC is poor) + (0.597*Non health workers) + (0.233*Rural) + (0.713*Very poor).

The probability of non-compliance to pregnant women consumption of Iron Tablets based on predictor values is calculated by the following equation:

$$P = \frac{1}{1+e^{-(\alpha+\beta_1 X_1+\beta_2 X_2+\beta_3 X_3+\cdots.kX_k)}}$$

$$P = \frac{1}{1+e^{-(-0.788+0.735+0.504+0.597+0.233+0.713)}}$$

$$P = \frac{1}{1+e^{-(1.994)}} = \mathbf{0.88 = 88\%}$$

The above equation means that pregnant women with poor quantity and quality of ANC, live in rural areas, check pregnancy not with health workers and verypoor socioeconomic status have a probability of consuming Iron supplement tablets not according to recommendations (< 90 tablets) by 88% compared to pregnant women without risk factors.

Discussion

The results of the study found that only 48.47% of pregnant women in Indonesia consumed iron tablets according to the recommendation (≥ 90 tablets). The proportion of non-compliance of pregnant women based on regional regions of Indonesia in consumption of iron tablets, there is a statistically significant difference. This difference in the proportion of consumption of Iron tablets occurs because demographically and geographically, Indonesia's regional characteristics vary. The highest non-compliance with consumption of iron tablets was in the Sulawesi and Sumatra regions, while the proportion of Iron supplement consumption according to the recommendations was highest in the Java-Bali and Kalimantan regions. This coverage is still far from the target set by the Indonesian government in the Health Development Strategic Plan in 2017 of 90%, the 95% target and in 2018 and the 98% target in 2019 [10]. The non-compliance rate for pregnant women's in consumption of iron tablets in Indonesia is higher than in India (36.9%) [17], in Adwa, Tigray Ethiopia (40.9%) [18], in Hawassa, Southern Ethiopia (38.3%) [19], and in Kiambu County, Kenya (32.7%) [20]. However, it is lower than several other studies such as in Gondar, Ethiopia (55.3%) [21], in Debre Markos, Western Ethiopia (55.5%) [22], in Sri Lanka (80.1%) [23], and a study in Iran. West reports

that the compliance to iron supplement consumption in pregnant women is relatively high (71.6%) [24].

The main reasons pregnant women do not comply with consumption of iron tablets are dislike, nausea/vomiting due to pregnancy, boredom, forgetfulness, and side effects of tablets [4]. Findings from a qualitative study revealed that since Iron Tablets were consumption at night, pregnant women forget to consumption of iron tablets during the day because they are busy with various jobs and at night because they are tired and fall asleep. Lack of attention to compliance can also cause pregnant women to forget to consume iron tablets. In addition to forgetting, fear of the side effects of Iron Tablets such as nausea, vomiting, diarrhea, and constipation is also a reason for non-compliance. The fear of side effects was caused by a lack of counseling from health care providers and a decrease in women's knowledge about anemia and iron tablets. Through better education regarding iron tablets, non-compliance due to fear of side effects will be reduced [22]

One effort to overcome the high prevalence of anemia in pregnant women is to provide iron supplements as much as 1 tablet every day for 90 days during pregnancy. Iron tablets are given by health workers to pregnant women who come to check their pregnancy at health service centers such as Community Health Centers, Integrated Service Post or village health workers through ANC *(antenatal care)* [25]. However, there are still problems faced by Pregnant women, namely Pregnant women often forget to consume them, or Pregnant women do not want to consume them because they are bored, do not like the side effects and other reasons. In order to maximize iron absorption, it is recommended to drink with boiled water and vitamins, and reduce the consumption of foods containing substances that can inhibit iron absorption, such as coffee and tea when consumption of Iron Tablets [26].

This study found that pregnant women who had poor Quantity of ANC had 2 times the risk of consuming Iron Tablets that were not as recommended compared to pregnant women who had good ANC visits. This finding is supported by researchinDenbiya District, Ethiopia [27]. ANC visits are an opportunity to improve maternal compliance because there are meetings and discussions between Pregnant women and health workers who provide information regarding the benefits of iron supplements [16].

The quality of the ANC also affects the compliance of pregnant women consumption of iron tablets, Pregnant women with ANC quality who are less at risk 1.7 times to consumption of Iron Tablets that are not as recommended compared to pregnant women with good ANC quality. Each element of antenatal care must be carried out in full following the minimum service standard of "10 T" [28]. One of the important activities during ANC is giving Iron supplement tablets and counseling. Research in Addis Ababa, Ethiopia revealed effective counseling during ANC visits was the main reason for good compliance to consumption of Iron Tablets [29].

This study also revealed that pregnant women who did not check their pregnancy with health workers had a risk of 1.8 times to consume Iron Tablet not according to the recommendations compared to pregnant women who had their pregnancy checked by health workers. In a study in Tamil India, pregnant women have a positive perception of the services provided by health workers so that satisfaction with health services can affect compliance to iron supplement consumption [30]. The behavior of health workers is able to provide optimal counseling, especially about the importance of consuming of iron supplements for pregnant women to maintain the health of the mother and fetus. In addition, the attention given by health workers such as providing services with a smile, as well as providing feedback on previous visits can increase satisfaction with the services provided so that it is expected that pregnant women's compliance in consumption of iron tablets can be improved [31].

Pregnant women who live in rural areas are at 1.3 times risk of consumption of iron tablets not according to recommendations compared to pregnant women who live in urban areas. This study is in line with research in Gondar Ethiopia, pregnant women who live in urban areas have the privilege of supporting factors compared to pregnant women who live in rural areas, namely having better access to health facilities [21]. However, in this study, maternal age, education, occupation and parity were not statistically significant with compliance to blood-supplementing tablet consumption in pregnant women in Indonesia.

Pregnant women with very poor socioeconomic status are at risk of 2 times consumption of iron tablets not according to recommendations compared to pregnant women with very rich socioeconomic status. This is in line with research in Kiambu, Kenya which states that socioeconomic factors, especially high income, have an effect on good compliance in consuming of iron tablets [20]. Income affects family socioeconomic, low family income tends to influence pregnant women to disobey the consumption of Iron Tablets compared to families with higher incomes [32]. Low family income causes a decrease in daily food needs [33]. Macronutrient deficiencies are more commonly caused by poor dietary intake, but in particular deficiencies of iron, calcium, folate, zinc, thiamin, riboflavin, and vitamins A, D, B6, and B12 are very common and of concern among women of childbearing age, the cause is low income levels and lack of education about healthy practices such as healthy eating patterns [34]. This is different from the study in Lucknow, India which stated that socioeconomic status had no effect on the intake of iron tablets, but in this study explaining social background needs special attention. Often the social environment and cultural constraints become obstacles in finding the right health care not only for the consumption of Iron Tablets but also for improving the health status of the mother so that the root causes of economic problems must be compliance [17].

Conclusion

The prevalence of compliance to the consumption of Iron Tablets in pregnant women in Indonesia is mostly not according to recommendations (48.47%). ANC quantity, ANC quality, antenatal care workers, place of residence, and socioeconomic status were statistically significant with compliance to blood-supplementing tablet consumption in pregnant women in Indonesia. The most dominant factor related to compliance is the quantity of ANC. Therefore, it is important to bring nutritionists at ANC activities to educate pregnant women about the benefits, side effects, and ways of consumption of iron tablets, reactivate supervisors for consumption of iron tablets, increase access to health services in rural areas, and organize free health care programs for the poor.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

S.N.: conceived of the presented idea, collect the data, perfomed the analysis, conceived and designed the analysis, contributed data or analysis tools. D.S.: verified the analytical methods, contributed to the interpretation of the results, designed the model and the computational framework. All Authors discussed the resulst and contributed to the final manuscript.

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The management of healthcare-related infections through lean methodology: systematic review and meta-analysis of observational studies

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Keywords

Summary

Introduction. *Lean is largely applied to the health sector and on the healthcare-associated infections (HAI). However, a few results on the improvement of the outcome have been reported in literature. The purpose of this study is to analyze if the lean application can reduce the HAI rate.*

Methods. *A comprehensive search was performed on PubMed/ Medline, Scopus, CINAHL, Cochrane, Embase, and Google Scholar databases using various combinations of the following keywords: "lean" and "infection". Inclusion criteria were: 1) research articles with quantitative data and relevant information on lean methodology and its impact on healthcare infections; 2) prospective studies. The risk of bias and the study quality was independently assessed by two researchers using the "The*

National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no control group". The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines has been used. 22 studies were included in the present meta-analysis.

Results. *Lean application demonstrated a significant protective role on healthcare-associated infections rate (RR 0.50; 95% C.I.: 0.38-0.66) with significant impact on central line-associated bloodstream infections (CLABSIs) (RR 0.47; 95% C.I.: 0.28-0.82).*

Conclusions. *Lean has a positive impact on the decreasing of HAIs and on the improvement of compliance and satisfaction of the staff.*

Introduction

Lean has been defined "management practice based on the philosophy of continuously improving processes by either increasing customer value or reducing non-value adding activities (muda), process variation (mura), and poor work conditions (muri)" [1]. Ohno identified seven kinds of muda categorized in transportation, inventory, motion, waiting, overproduction, overprocessing and defects [2]. These muda are present also in the healthcare sector [3]. Subsequently, Lean management has been exported to this sector [4, 5]. This application has been described in so many different ways such as strategy, philosophy or way of working [6] and several efficiency results (i.e. time saving or cost reduction) have been achieved over time [7-11]. However, few results on the improvement of the outcome have been published [12]. Although, a protocol for a Cochrane Review on the effect of lean on the patient outcomes has been released [13], the specific impact of Lean application on healthcare-associated infections (HAIs) has not still extensively investigated.

Lean and its variants, such as Six Sigma, can be applied to several aspects of health care including finance,

inventory management, information processing, outpatient clinics, and inpatient setting [14-21].

HAIs are recognized worldwide as an important public health problem, and they are of increasing interest to politicians, patients, and the public [22]. Up to 2,609,911 new cases of HAIs occur every year in the European Union and European Economic Area (EU/EEA) [22]. Many research studies report that in Europe hospital-wide prevalence rates of HAIs range from 4.6% to 9.3%. HAIs have impact on critically ill patients with around 0.5 million episodes of HAIs being diagnosed every year in intensive care units (ICUs) alone, including central line-associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), and ventilator-associated pneumonia (VAP) [23].

The problem of nosocomial infection is increased by the spread of multi-resistant microorganisms [24-30]. Since the 1970s, the selective pressure exerted by antibiotics has given rise to bacterial species that are increasingly resistant, and the last 20 years have seen a dramatic rise in the number of multi-resistant pathogenic strains [31]; the attributable deaths in the EU due to antimicrobial resistant microorganisms were estimated to be 33,110 per year.

At present, monitoring and preventing HAIs is a priority for the healthcare sector and reducing the incidence of HAIs is used as an indicator of the quality of service provided.

Several causes of HAIs have been identified [32] such as the lack of standardized [33-35] or inadequate sanitation procedures that can contribute to the spread of cross-infections [36]. Some scholars estimate that 20-30% of HAIs are avoidable through an extensive infection prevention and control program [37-38].

Lean and six sigma supported by change management are important tools, renamed Robust Process Improvement (RPI), to address those problems by the Joint Commission Center for Transforming Healthcare [39]. In fact, the Joint Commission reported one example of reduction or Surgical Site Infection through RPI [39]. In 2012 a review of the literature focusing on the quality improvement in the surgical healthcare showed how different tools (lean, six sigma and statistical process control or PDCA) can decrease the infection rate [40]. Several lean applications have been described over the years with the purpose of improving healthcare quality [4], nonetheless, to the best of our knowledge, no systematic reviews and meta-analyses have been specifically focused on the lean application for reduction of HAIs.

The aim of this systematic review and meta-analysis of prospective studies is to provide high-level evidence about the lean application for HAIs reduction. More specifically, the purpose of this study is to analyze if the lean application can reduce the healthcare-associated infections rate.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [41] have been used as a guide to ensure that the current standards for meta-analysis methodology were met.

A comprehensive search on PubMed/Medline, Scopus, CINAHL, Cochrane, Embase, and Google Scholar databases was performed using various combinations of the following keywords: "lean" and "infection" from inception up to December 2021 using Medical Subject Headings (MeSH) terms as vocabulary.

Inclusion criteria were: 1) research articles with quantitative data and relevant information on lean methodology and its impact on healthcare infections 2) prospective design studies. Exclusion criteria were: 1) articles not strictly related to the research query; 2) items without enough information on the sample size or on the population; 3) research works not matching the PICOS criteria (Tab. I); all those articles were therefore excluded. No time filter or language filter was applied. Two authors were involved during the screening of the literature. One of them was an industrial engineer and a black belt in lean and six sigma while the other one was a biologist with a postgraduate course on Systematic review and meta-analysis according to the Cochrane methodology. A complete consensus was achieved through discussion for the texts included in this study.

Articles were firstly selected based on title and abstract. The full text of relevant research was then acquired and assessed. Each reference of the selected articles was checked in order not to miss any relevant article. The authors independently read all the papers and they implemented a database for the meta-analysis including the surname of the first author, the year and country of publication, the site of infection and the pre- and post-intervention outcome measures. Studies have been classified depending on the used method within the following six categories: "LEAN", "LEAN/PDSA (Plan, Do, Study, Act)", "LEAN/TPS (Toyota Production System)", "LSS (Lean Six Sigma)", "RPI (Robust Process Improvement)" and "TPS". "LEAN/TPS" included all the paper where lean and TPS were used as synonymous. Any disagreement was solved by meeting consensus.

The following subgroups of HAIs have been identified among the included studies: central line associated

Tab. I. Search strategy.

Search strategy	Details
Search string	(Lean OR Lean Six Sigma OR Toyota Production System) AND (hospital infection OR infection OR Healthcare Associated Infection)
Databases	PubMed/MEDLINE, Scopus, Cochrane and Google Scholar
Inclusion criteria	P (patients/population): hospital patients I (intervention/exposure): Lean C (comparison/comparators): pre and post lean application O (outcome): Primary outcome: infection rate; Secondary outcome: healthcare workers satisfaction, healthcare workers compliance to procedures, hand hygiene compliance, unexpected death S (Study design): prospective study/quasi-experimental study
Exclusion criteria	Articles with insufficient details. Study design: editorial, commentaries, expert opinions, letters to editor, abstract
Time filter	None (from inception)
Language filter	None (any language)

blood stream infections (CLABSI), surgical site infections (SSI), Methicillin-resistant *Staphylococcus aureus* (MRSA) infections, *Clostridiodes difficilis* (CD) infections, Ventilator-associated pneumonia (VAP), and catheter associated urinary tract infections (CAUTI).

The infection rate before and after lean application was considered as the effect size (ES) of primary outcome measure. The ES of the secondary outcome measures was considered as the percentage of satisfied healthcare workers, the healthcare workers' compliance to procedures, the hand hygiene compliance, and the unexpected deaths.

A meta-regression was conducted to verify the effect of different infection sub-categories on relative risk (RR). As no significant impact was detected, all the infection categories were considered for primary analysis followed by a secondary sub-group (CLABSI) analysis.

The risk of bias and the study quality was independently assessed by two researchers using the "The National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no control group" (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) [42]. Results were matched and disagreements were solved by meeting consensus. Fourteen studies were classified as "good" [43-47, 49, 50, 52, 54-57, 60, 61], 6 as "fair" [39, 48, 51, 53, 58, 59] and 2 as "poor" [62, 63].

Statistical heterogeneity was evaluated with I2 statistics and Heterogeneity chi-square test. Heterogeneity was supposed to be significant with P values (χ2) < 0.1. The values of 25, 50 and 75% in the I2 test corresponded to low, moderate and high levels of heterogeneity, respectively. In case of moderate or high heterogeneity among the studies, a random-effects model, using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the Mantel-Haenszel model, was used for the meta-analysis. The RR was calculated as effect estimates, with their 95% confidence intervals (CIs). The RR of the meta-analyses were supposed to be significant if the confidence intervals

did not enclose the value "1". If the confidence interval enclosed the value "1", the absence of an association between exposure and disease cannot be excluded. A smaller confidence interval than value of the individual studies indicated less inaccuracy.

The meta-analysis was performed by means of the STATA SE14® (StataCorp LP, College Station, TX, USA) software and the funnel plot was used to assess the risk of bias. If asymmetry was detected by visual assessment, exploratory analyses using trim and/or fill analysis were performed with investigating and adjusting purposes. The probability of publication bias was tested by means of Egger's linear regression and a value of p < 0.05 was considered as indicative of publication bias. Further stratification was performed with respect to study quality to identify sources of variation. Finally, the stability of the pooled estimate regarding each study was assessed in the setting of sensitivity analyses with exclusion of individual studies from the analysis.

Results

Concerning the systematic review, our initial query resulted in 648 hits (specifically, 600 articles from PubMed/MEDLINE and Scopus, and 48 from other sources); after removal of duplicated items, the resulting list comprised 615 non-redundant articles. Forty-six studies were retained in the qualitative synthesis, and 22 were finally considered in our systematic review and meta-analysis (544 articles were discarded as not being directly pertinent to the topic under investigation and 25 as not meeting the inclusion criteria). Six studies reported more data inherent to infections and were all considered for the meta-analysis. Further details are reported in Figure 1.

The full list of studies included, and their main characteristics are shown in Table II.

Tab. II. List and features of studies included.

First author (year)	Country	Method	Outcome	Process	Pre	Post
Spear (2005)	USA	TPS	CLABSI	1 CLABSI infections review of process in a group of hospitals.	4.2/1,000 central line days	1.9/1,000 central line days
Shannon (2006)	USA	TPS/Lean	HAI CLABSI Mortality	2 CLABSI infections review of process in 2 ICUs	21.1/1,000 pt days 10.5/1,000 central line days 51%	3.33/1,000 pt days 1.2/1,000 central line days 16%
Shepler (2006)	USA	Lean	Satisfaction	3 foot traffic in OR	65%	71%
Muder (2008)	USA	TPS	MRSA: ICU Surgical Units	4 infection control in ICU and surgical unit of an hospital	5.45/1,000 pt days 1.56/1,000 pt days	1.35/1,000 pt days 0.63/1,000 pt days

Burkitt (2009)	USA	TPS/Lean	Compliance	5 reduce MRSA infection on a surgical unit	26%	44%
Carboneau (2010)	USA	LSS	Hand Hygiene	6 increase hand hygiene compliance AND reduce MRSA infections	65%	82%
MacRedmond (2010)	Canada	Lean/PDSA	Mortality Compliance: -identification of potential septic pt -specificity of assessment	7 management protocol for sepsis in an hospital (ED+ICU)	51.4% 75% 91%	27% 92.3% 90%
McCulloch (2010)	UK	TPS/Lean	Hand Hygiene Compliance: -Administration -Correct use of protocol -Team Communication -Vital signs monitoring and recording -Pt without a drug prescription error -Completion of fluid balance	8 Patient safety protocol compliance in an emergency general surgery ward of an hospital	23% 35% 46% 57% 68% 47% 89%	31% 87% 79% 94% 99% 60% 90%
Ellingson (2011)	USA	TPS	MRSA: -Non intensive care surgical unit -Surgical ICU -Remaining acute care units -Hospital wide	9 reduce MRSA in an hospital through prevention of them	2.28/1,000 pt days 3.73/1,000 pt days 2.33/1,000 pt days 2.40/1,000 pt days	1.48/1,000 pt days 2.17/1,000 pt days 1.39/1,000 pt days 1.88/1,000 pt days
Chassin (2013)	USA	LSS/Change Management	CD SSI Mortality	10 reduce HAIs	8.98/10,000 pt days 15.80% 16.44%	7.69/10,000 pt days 10.70% 12.83%
Cima (2013)	USA	LSS	SSI	11 reduce SSI in a tertiary care medical center	9.8%	4%
Dickson (2013)	USA	LSS	SSI	12 reduce SSI in a community hospital	4.07%	1.93%
Martin (2013)	USA	TPS/Lean	CLABSI (travelling off the ICU) CLABSI (rates) Compliance: -Clean medication admin -Clean cart touches -Clean airway procedures	13 reduction of CLABSI for patient travelling of ICU	14.1/1,000 pt days 3.5/1,000 central line days 23.2% 41.8% 14.6%	9.7/1,000 pt days 2.2/1,000 central line days 93.0% 92.3% 91.6%
Chassin (2015)	USA	LSS/Change Management	Hand Hygiene	14 improve hand hygiene in 8 hospitals	48%	81%
O'Reilly (2016)	USA	Lean	Compliance Satisfaction (1/2) Satisfaction (2/2)	15 improve hand hygiene in ICU	8% 34% 49%	70% 47% 70%

Sirvent (2016)	EU	Lean	VAP CAUTI CLABSI Mortality	16 improve flow of critical patients in ICU	7.2/1,000 ventilator days 4.2/1,000 days of catheter 0.95/1,000 central line days 18%	5.2/1,000 ventilator days 4.3/1,000 days of catheter 0.54/1,000 central line days 21%
Montella (2017)	EU	LSS	HAI (Surgical Dpt)	17 reduce HAI in surgery departments	0,37%	0,21%
Horng (2018)	USA	Lean	Mortality	18 optimize timely administration of antibiotics for patients with sepsis	42,6%	50,0%
Improta (2018)	EU	LSS	HAI (Medicine Dpt)	19 reduce HAI in medicine areas	0,36%	0,19%
Ferrari (2019)	USA	Lean/EBP	CLABSI	20 reduce CLABSI (8 procedures in one hospital)	1.96/1,000 central line days	1.02/1,000 central line days
Russell (2019)	USA	Lean/PDSA	CLABSI Compliance	21 reduce CLABSI in ICU	4.2/1,000 central line days 25%	1.8/1,000 central line days 67%
Wolak (2019)	USA	Lean	CAUTI	22 reduce CAUTI	2.47/1,000 days of catheter	1.46/1,000 days of catheter

TPS: Toyota Production System; LSS: Lean Six Sigma; EBP: Evidence Based Practice; PDSA: Plan, Do, Study, Act; HAI: Hospital-acquired infection; CLABSI: central line associated blood stream infections; CAUTI: catheter-associated urinary tract infections; MRSA: methicillin resistant S. aureus; CD: C. difficile infections; SSI: surgical site infections; VAP: ventilator-associated pneumonia.

Fig. 1. PRISMA Flowchart.
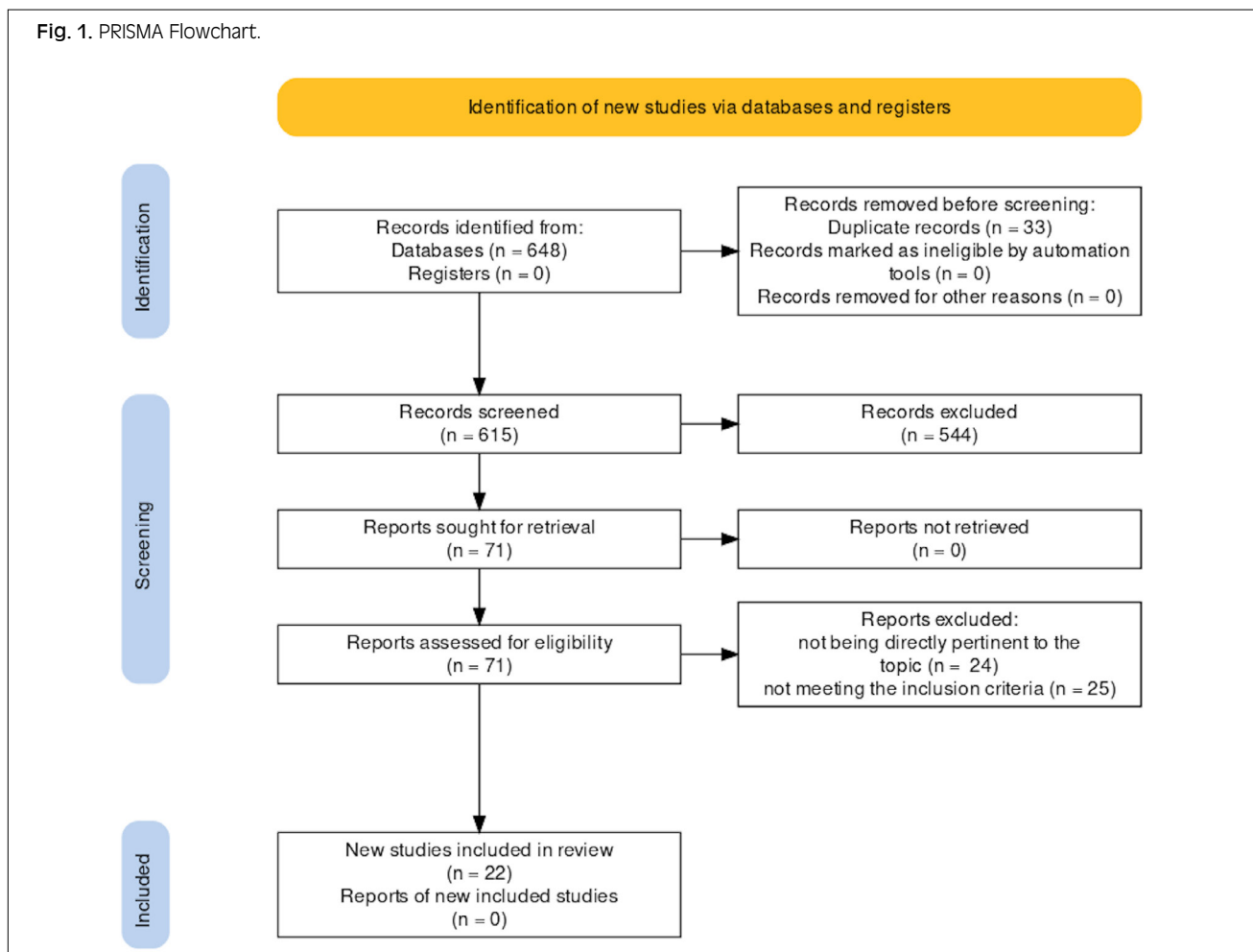
Tab. III. RR and 95% CI for all meta-analyses carried out.

Outcome	HAI subgroup	RR [IC95%] N	p
Healthcare associated infection	HAI (no CLABSI)	0.51 [0.36-0.71] 16	<0.001
	CLABSI	0.47 [0.28-0.82] 7	<0.01
	All	0.50 [0.38-0.66] 23	<0.001
Unexpected death		0.71 [0.42-1.18] 5	n.s.
Healthcare workers satisfaction		1.24 [1.08-1.42] 3	<0.001
Hand hygiene and all compliance	Hand hygiene compliance	1.42 [1.15-1.76] 3	<0.01
	Compliance (no hand hygiene)	1.98 [1.50-2.63] 14	<0.001
	All	1.86 [1.47-2.34] 17	<0.001

Three studies were performed in European countries, 1 in UK and the others in North America (1 in Canada and 17 in USA).

Among 22 studies finally included for meta-analysis fourteen studies measured the HAI as primary outcome measure and 8 studies the healthcare worker compliance. Five studies included relevant data on unexpected mortality and 2 studies on healthcare workers satisfaction. Meta-analysis on 14 prospective studies measuring the reduction of healthcare-associated infections rate showed that lean approaches have a significant protective role (RR 0.50; 95% C.I.: 0.38-0.66). Moreover, meta-analysis showed that lean application significantly decreased incidence of CLABSI (RR 0.47; 95% C.I.: 0.28-0.82). The results showed a positive effect of lean application on healthcare worker satisfaction and compliance, but no significant decrease of mortality has been reported (Tab. III).

The adjusted rank correction test (Begger test) and the regression asymmetry test (Egger test) were used to evaluate the risk of bias. The studies evaluating the compliance had high risk of biases (p < 0.001).

A stratified meta-analysis for different lean methods has been conducted to assess for the impact of each method on the outcome measure (Tab. IV).

Tab. IV. RR and 95% CI of all outcome measures stratified for each lean method.

	Healthcare associated infection	Unexpected death	Healthcare workers satisfaction	Compliance (without hand hygiene)	Hand hygiene compliance
Methods					
LEAN	0.80 [0.36-1.74] 4	1.17 [0.66-2.05] 1	1.24 [1.08-1.42]** 3	8.75 [4.45-17.22] 1	-
LEAN/ PDSA	0.50 [0.09-2.72] 1	0.53 [0.36-0.77] 1	-	1.34 [0.92-1.94] 3	-
LEAN/ TPS	0.30 [0.11-0.86]** 4	0.31 [0.19-0.51] 1		1.99 [1.43-2.76]*** 10	1.35 [0.85-2.14] 1
LSS	0.46 [0.23-0.93]* 5	1.17 [0.77-1.79] 1		-	1.26 [1.06-1.50] 1
RPI	0.75 [0.43-1.34] 2	0.81 [0.41-1.60] 1		-	1.69 [1.35-2.11] 1
TPS	0.49 [0.23-1.07] 7	-	-	-	-
Overall	0.55 [0.41-0.74]*** 23	0.71 [0.42-1.17] 5	1.24 [1.08-1.42]** 3	1.98 [1.50-2.63]*** 14	1.42 [1.15-1.77]*** 3

* p<0.05; ** p<0.01; *** p<0.001

Fig. 2. Forest plot of Impact of different Lean methodology on HAI.
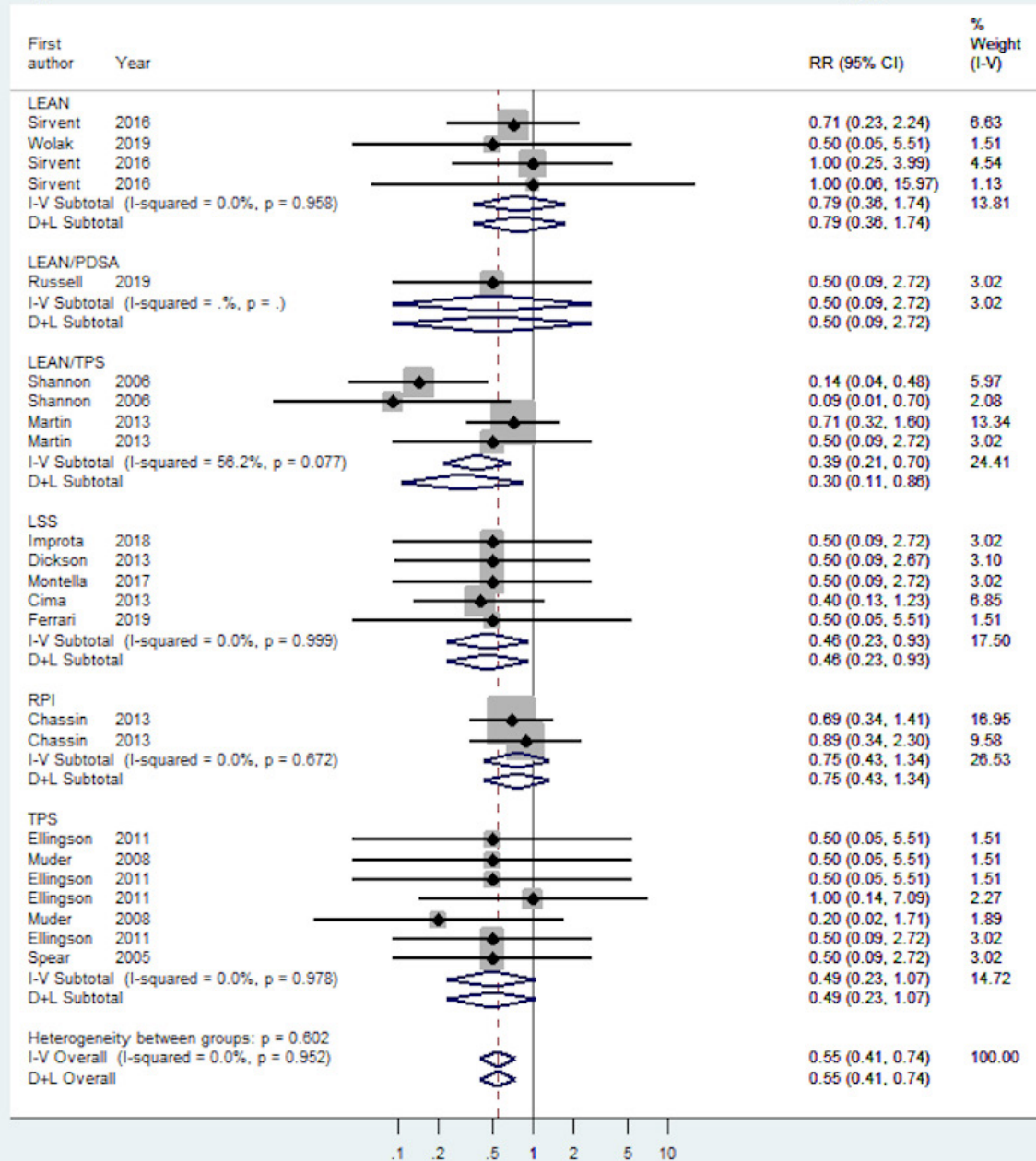
Healthcare associated infections

The meta-analysis showed that application of LEAN/TPS (RR 0.30; 95% C.I.: 0.11-0.86) and LSS (RR 0.46; 95% C.I.: 0.23-0.93) had significant impact on HAIs. The application of LEAN, LEAN/PDSA, RPI and TPS showed no significant impact on HAIs (Fig. 2).

More than 30% of included studies focused on sub-group of CLABSI with overall significant data for all applied methods (RR 0.54; 95% C.I.: 0.31-0.95) (Fig. 3). However, no significant data have been obtained with analysis of each method applied, due to few studies available for each method. Data on other HAIs confirmed that LEAN/TPS and LSS had significant results on other HAIs (Tab. V).

Tab. V. RR and 95% CI for HAI stratified for LEAN methods.

Healthcare Associated Infection		
	Other HAIS	Only CLABSI
Methods		
LEAN	0.77 [0.34-1.77] 3	1.00 [0.06-15.96] 1
LEAN/PDSA	-	0.50 [0.09-2.72] 1
LEAN/TPS	0.14 [0.04-0.47] 1	0.53 [0.23-1.06] 3
LSS	0.45 [0.22-0.95]* 4	0.50 [0.04-5.51] 1
RPI	0.75 [0.43-1.34] 2	-
TPS	0.49 [0.21-1.17] 6	0.50 [0.09-2.72] 1
Overall	0.55 [0.39-0.78]** 16	0.54 [0.31-0.95]* 7

* p<0.05; ** p<0.01

Unexpected deaths

Only one study demonstrated that the application of LEAN/PDSA had significant influence on unexpected deaths (RR 0.53; 95% C.I.: 0.36-0.77). Another study showed that LEAN/TPS significantly decreased the unexpected deaths (RR 0.31; 95% C.I.: 0.19-0.51).

Healthcare workers satisfaction

All studies evaluated the LEAN application impact on healthcare workers satisfaction with significant results (RR 1.24; 95% C.I.: 1.08-1.42).

Fig. 3. Forest plot of Impact of different Lean methodology on HAI (without CLABSI).
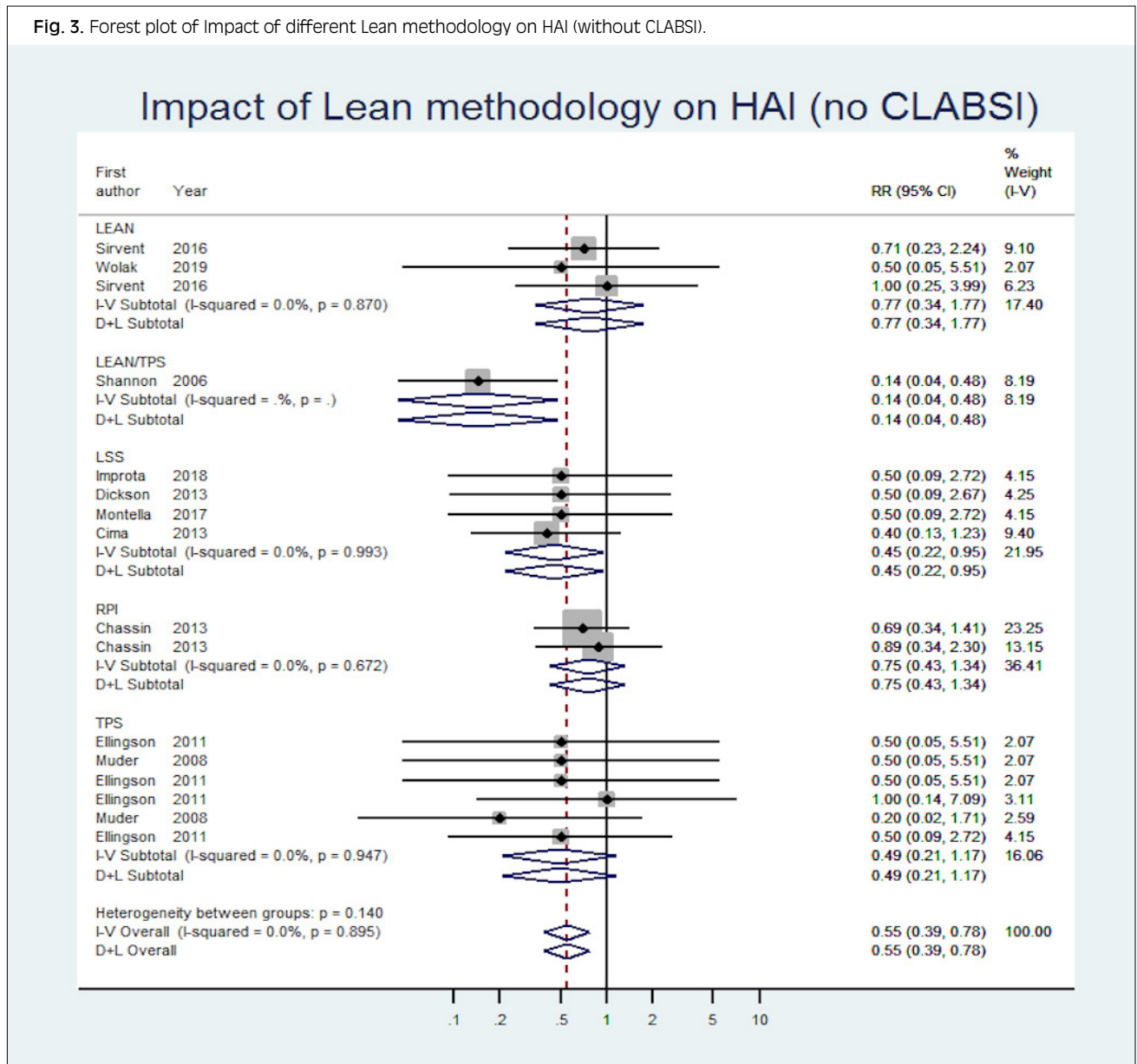
Compliance

Only one study measured the compliance with application of the LEAN method with a significant influence (RR 8.75; 95% C.I.: 4.45-17.22).

Three studies, reporting a total of ten outcomes, used the lean and the TPS approaches and measured the pre- and post-intervention compliance. The stratified analysis showed that "LEAN/TPS" significantly increased the compliance of healthcare workers (RR 1.99; 95% C.I.:1.43-2.76). Nonetheless, two studies including three outcomes used the LEAN and PDSA. The application of "LEAN/PDSA" method showed no significant influence on compliance of healthcare workers.

Hand hygiene compliance

Only one study measured the hand hygiene compliance with application of the LEAN/TPS, one study measured the hand hygiene compliance with application of the LSS and one with application of RPI.

The overall analysis highlighted a significant correlation between LEAN (all methodologies) and hand hygiene compliance (Tab. IV).

Discussion

The most important finding of this study is the significant protective impact of lean strategies on HAIs, compliance and staff satisfaction.

Healthcare associated infections are the most common adverse events that afflict millions of patients annually around the world [23]. The reduction of HAIs is considered a quality indicator of the healthcare provided [38]. Over the years different strategies and preventions measures have been applied against infections [40].

Several studies described the lean approach as an effective method to prevent infections, however literature is surprisingly lacking quantitative and measurable results on outcome measures. Johnson et al [64] proposed an example of lean method to reduce the readmission for patients with community acquired pneumonia without providing data of outcome. Simons et al [65] proposed the lean method to decrease the SSI rate through the reduction of the door movement. Nonetheless authors measured only the number of door movement without assess the SSI rate in their research.

To the best of our knowledge, this is the first systematic review and meta-analysis of prospective studies focused on lean application and their relative impact on HAIs.

Due to lack of high-quality evidence data Vest et al [66] raised doubts about the efficacy of the application of lean method on several clinical outcomes. Moraros et al [67] in a systematic review of the literature reported conflicting results on reduction of MRSA infection and lean application with significant data in only three out of twenty-two included studies.

In the present meta-analysis, the overall lean application demonstrated a significant impact on HAIs reduction. The subgroup analysis showed that LEAN/TPS and LSS had significant impact on HAIs reduction on nine studies. Moreover, the lean application showed significant impact on CLABSI and all subcategories of HAIs.

There is uncertain evidence of statistical reduction of mortality with the lean application. Mason et al [68] reported only one study with significant reduction of mortality in patients with proximal femoral fractures with lean application. This finding could be explained considering the lack of data of other factors influencing death. In the present meta-analysis, the lean application seems to have a protective role on unexpected deaths although with inconclusive data. Only two studies showed a significant reduction of mortality with "LEAN/ PDSA" and "LEAN/TPS" methods. Certainly, further studies are required to definitively ascertain this aspect.

Limitation

This study presents some limitations: there are several independent factors influencing the healthcare-associated infections rate that were not measured in the included studies. Patients and pathogens features were not detailed, vaguely reported and precluded a detailed analysis of potential confounding factors. Data of infection reduction were calculated measuring the infection rate before and after a period of Lean application in the same hospital ward and assume that the characteristics of patients don't substantially change. Nevertheless, no detailed population analysis before and after the intervention has been reported. Further potential weakness of this research is the limited number of available articles as consequence of novelty of the research area. Finally, there was high heterogeneity of HAIs spectrum among the published studies.

Conclusions

HAIs are a plague for the healthcare sector. Lean approach seems to be an important method to decrease infection rate and to achieve improvement in compliance and staff satisfaction.

Lean allows to implement the risk management of HAIs, identifying the causes that can determine the occurrence, eliminating them. Moreover it facilitate implementation of infection control practices, including the use of active surveillance cultures and contact precautions.

As Murder et al. underlined, strategies designed to engage frontline workers in changing institutional culture and the work environment could be critical to the success of programs preventing healthcare associated infections [45].

Acknowledgments

Conflicts of interest

The authors declare no conflict of interest.

AuthorS' contributions

Conceptualization, M.S., C.P., and M.L.C.; methodology, M.S., C.P. and N.L.B.; software, E.S., G.O. and C.D.; formal analysis, M.S. and N.L.B.; investigation, M.S., C.P. and M.L.C.; data curation, A.M.S., E.S. and G.O.; writing-original draft preparation, M.S., C.P. and M.L.C.; writing-review and editing, M.S., C.P., A.M.S., E.S., G.O., C.D., M.A.-M., N.L.B., and M.L.C.; project administration, M.S. and M.L.C.. All authors have read and agreed to the published version of the manuscript.

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The history of vaccinology and hygiene through Achille Sclavo and the cultural patrimony conserved in the archives and museums: the key role of medical museology

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Keywords

History of public health • Archives and museums • History of vaccines and vaccinations • Medical museology • A. Sclavo • Cultural heritage

Summary

Over the centuries, the oldest universities have amassed an extraordinary patrimony of material and immaterial cultural assets, which have been created or acquired for the purposes of research or teaching. Now on display in museums, they testify to the evolution of knowledge and its diversification in various disciplines. In order to safeguard, conserve and study this precious heritage, we need to implement a cultural project that activates that "process of awareness" on which cataloging is based. This is a "reasoned awareness" that enables an object to be framed within a system of scientific knowledge and historical-critical relationships, which are essential to its conservation and, consequently, to its public exploitation. Through this process, we can uncover the history of an object, its characteristics and its uniqueness. This is the case, for example, of an optical microscope on display in the Museo di Strumentaria medica (Medical Equipment Museum), which is part of the Museum System of the University of Siena.

Background

Achille Sclavo (1861-1930) graduated in medicine at the University of Turin in 1886, and belonged to the second generation of Italian hygienists. In 1887, he was called by his mentor Luigi Pagliani (1847-1932) to the General Directorate of Health (Direzione Generale di Sanità), as a member of the work-group founded by prime Minister Crispi to reorganize national healthcare policy [1].

He was therefore able to acquire great experience in the fields of Hygiene and Public Health through his collaboration with Pagliani himself, Pietro Canalis (1856-1939) and Alfonso di Vestea (1854-1938).

At the beginning of the 1890s, following his promotion to Director of the Bacteriology Laboratory and his appointment as a teacher at the Upper School of Hygiene (Scuola Superiore di Igiene), Sclavo undertook original studies on anti-diphtheria and anti-anthrax sera.

He maintained and broadened this research activity when, in the academic year 1896-1897, he was appointed to teach Hygiene at the University of Siena, where, in 1898, he became Extraordinary Professor of Hygiene and Director of the Laboratory of Hygiene.

The microscope used by Achille Sclavo to study anthrax

The microscope used by Achille Sclavo to study anthrax (Fig. 1), was made by the Fratelli Koristka company (1900), it comes from the Laboratory of Hygiene of University of Siena and it is now preserved in the Medical Equipment Museum of the University, of course.

Its first inventory tag (IG4) indicates that it came from the *Regio Istituto di Igiene e Batteriologia* (Royal Institute of Hygiene and Bacteriology) of the University of Siena; this provenance is confirmed by the new and still existing inventory tag numbered 116 of the same Institute.

The *Fratelli Koristka* company was founded in Milan in 1881 by Franz Koristka (1851-1933), an Italian optician and entrepreneur of Czech origin. It soon became the most important manufacturer of microscopes and one of the few precision industries in Italy at the time, with clients even in America. Thanks to his personal friendship with the physicist and research director at Zeiss Ernst Abbe (1840-1905), Franz Koristka was able to build microscopes and photographic lenses under Zeiss patents [2].

The microscope is equipped with a wooden case, which houses the containers of its three eyepieces; together

Fig. 1. Microscope Koristka Brothers used by Achille Sclavo (*Medical Equipment Museum, Museum System of the University of Siena*).

with a range of technical information, it also bears the name of its owner: Achille Sclavo.

Thus, as indicated by the note that accompanies the instrument and which attests to its use by the great hygienist, we can affirm that this microscope was used in the studies that led to the discovery of Sclavo's anti-anthrax serum.

Anthrax is a zoonosis that chiefly affects cattle and sheep, and more rarely horses and goats. It can sometimes be transmitted to humans [3].

It is caused by *Bacillus anthracis*, which was discovered in 1877 by Robert Koch, who was the first to demonstrate the causal link between this microorganism and the disease; the demonstration by Robert Koch of *Bacillus anthracis* as the cause of anthrax was a cornerstone of proving the germ theory of disease [4].

In humans, the disease may develop in three different forms:
- *cutaneous (*by far the most frequent);
- *respiratory;*
- *gastrointestinal.*

The infection can be cured by means of antibiotics, but in order to be efficacious, the treatment must be initiated immediately after contagion.

In those days, however, there were no elective drugs for the treatment of this disease, which was a very common professional infectious disease among shepherds, farmers and, especially, tanners. Moreover, being a veterinary disease, anthrax had a heavy economic impact on cattle and sheep farming. Sclavo therefore decided to channel his efforts into the search for a serum that

could efficaciously cure this disease. Indeed, instead of using the vaccine that Louis Pasteur had proposed on the basis of his studies on the techniques of attenuating the virulence of germs in culture, Sclavo designed a new method of eliciting immunity to anthrax in humans and animals; this method utilized serum obtained from anthrax-infected sheep, which he then tested on rabbits in order to ascertain its preventive and curative properties [5].

Sclavo devoted many of his writings to this subject, from the first "*On the preparation of anti-anthrax serum*" (1895) [6], the year in which he officially communicated the first results of his research into the preparation of a hyperimmune serum against anthrax, to the last, when he was still working at the General Directorate of Health of the Ministry of the Interior, entitled "Concerning some properties of anti-anthrax serum*"* (1906), co-authored by his pupil Donato Ottolenghi [7].

Through these publications, Sclavo explained the mechanism of the immune reaction in anthrax-infected animals treated with his serum, and demonstrated that this serum could be used not only in humans but also in veterinary practice. Moreover, he ascertained that the donkey was the best serum-producing animal in terms of both quantity and quality.

In 1898, by immunizing two donkeys, he obtained a serum that displayed life-saving efficacy.

From the end of the 19th century onwards, much of Sclavo's research focused on finding the best animals to select as producers of highly efficacious sera. This research also included, for example, the somewhat unusual use of serum from the female deer (*cervus elaphus*) against anthrax [8].

The photographic archive of the Medical Equipment Museum houses a series of early 20th century photographs showing some of the serum-producing animals used by Achille Sclavo in his research. Among them are Eurialo and Niso, the first two donkeys used by Sclavo for the preparation of his anti-anthrax serum.

The *Riberi prize* and the foundation and development of the Tuscan Serotherapy and Vaccinology Institute

In 1903, in recognition of his studies, Sclavo was awarded the "Riberi" Prize by the Turin Academy of Medicine. With the money he received, and a portion of his wife's inheritance, he bought a small country villa just outside Siena. In the 1825 land register of the Grand Duchy, this property appears as the "Villetta dell'Ebreo", very probably in a reference to a former owner.

It was on this property that the "Sclavo Institute" was founded in 1904. Subsequently, it was renamed as the "Tuscan Serotherapy Institute" (Istituto Sieroterapico Toscano), which was founded jointly by Sclavo and his hygienist colleague Ivo Bandi (1867-1926) "for the preparation of sera, vaccines, viruses, similar products and other therapeutic and prophylactic materials" [9]. However, Bandi split from Sclavo in 1908 to found

his own institute, named "Italian Serovaccinotherapy Institute" (Istituto Sierovaccinoterapico Italiano), in Naples a few years later (1914).

Following the introduction of vaccine production, the *Sienese Institute* was later enlarged and it took the name of "Tuscan Serotherapy and Vaccinology Institute" (Istituto Sieroterapico e Vaccinogeno Toscano, ISVT).

Thus, Sclavo embarked upon a new career as an entrepreneur – in much the same way as other colleagues, including Serafino Belfanti (1860-1939), the founder of the Milanese Serotherapy Institute (Istituto Sieroterapico Milanese).

Sclavo realized that he needed to have a production center where he could manufacture his anti-anthrax serum on a large scale, thereby contributing to public health policies aimed at avoiding or preventing the spread of infectious diseases in Italy.

We are able to reconstruct the history of the Institute and the decisions taken by Sclavo with regard to his research and the development of the Institute itself partly on the basis of the written and photographic documentation that was saved by the company's employees when the company was sold in the 1980s. Despite the divisions and losses suffered over the years and the changes of ownership, this documentation constitutes one of the few company archives that have been preserved in Italy. The University of Siena has reorganized and inventoried this documentation [10], thereby rendering it accessible to the public.

The first great expansion of the Institute founded by Sclavo took place not only as a result of the advances made in microbiology, but also because of the increased demand for the products needed to vaccinate military personnel. Indeed, during the First World War, the soldiers at the front had to be immunized against numerous infectious diseases [11, 12, 13, 14, 15].

In this way, as Sclavo himself had intended, a privileged link was forged with the State, which became the Institute's chief interlocutor and client. Bacterial sera and vaccines, especially against typhus and cholera, were particularly required for the Armed Forces. The war therefore became a fundamental testing ground for the Italian pharmaceuticals industry.

Subsequently, at the end of the war, attention turned to the needs of the civilian population, which, exhausted and undernourished, fell victim to epidemics, the most disastrous of which being the tragic pandemic of so-called Spanish Flu [16].

At the time of its foundation, the Tuscan Serotherapy and Vaccinology Institute was a sort of "farm with scientific objectives" [17], its laboratories consisting simply of rooms endowed with the primitive equipment available at the time. Nevertheless, it achieved great results.

Among the products marketed by the ISVT at that time were anti-anthrax serum, antidiphtheria serum, antityphoid vaccine and anti-anthrax vaccine, as testified by a document dated 25 May 1907 in the historical archive of the Institute, which enables us to precisely reconstruct the list of products available [18].

Sclavo's specialities and the popularization of scientific knowledge

Analysis of the archival documents and the equipment conserved by the Gruppo Anziani Sclavo (Sclavo Group of Elders) and the University Medical Equipment Museum, equipment, pharmaceutical products, and descriptive and advertising material also enables us to reconstruct the production of other specialties manufactured by the Institute – what would now be called "over-the-counter products".

The very first of these products to be marketed was "Sclavo Jodogelatina". "Discovered and introduced into therapy by Prof. Sclavo, it is a special combination in which iodine is incorporated into the molecule of gelatine"; it had numerous therapeutic indications: "scrofula, rickets, arteriosclerosis, organic decay, chronic forms of malaria, tubercular forms, goiter, syphilis, gout", as claimed by advertising material of the time (from 1910 onwards) [19].

Unlike the Institute's sera and vaccines, which required only the distribution of information to doctors, without the need for advertising, the specialties that Sclavo marketed had to be publicized, just like any other industrial product. This was chiefly due to the fact that they promised benefits that had not always been ascertained through research and experimentation. Moreover, it reflects the phenomenon of the popularization of scientific knowledge, which emerged at the end of the 19th century and at the beginning of the 20th. Thus, appropriately simplified medical information was circulated among the people, who were able to receive news of the most recent discoveries in pharmaceutical chemistry and of their application in the field of healthcare.

Another area of pharmacology dealt with by Sclavo was that of opotherapy products, i.e. extracts of animal organs for the treatment of endocrine diseases, e.g. the *Simiormina* (hormones of monkeys, testicles, thyroid, pituitary gland, adrenal glands) (Fig. 2).

To pursue this new line of research, he founded the National Opotherapy Institute (Istituto Opoterapico

Fig. 2. Advertising postcard Simiormina Sclavo 1927 (Elderly Group Archive, Sclavo, Siena).

Nazionale "Pisa"), together with other partners, in Pisa in 1916.

With regard to publicity, intense advertising campaigns were conducted in newspapers and magazines, as in the case of Sclavo Jodogelatina, for example.

In 1911, the newspaper *"Il Ponte di Pisa" wrote "Jodogelatina, discovered by Prof. Sclavo and introduced by him into medical practice, advantageously substitutes all other iodine preparations"* [20]. Advertising posters in the *Art Nouveau* style began to appear in pharmacy windows and city streets, inviting consumers to purchase creams, pastilles and elixirs, which were rendered all the more attractive by fantastic figures such as angels, dragons and snakes

In 1914, the Tuscan Serotherapy and Vaccinology Institute entrusted the graphic design of the advertisements for Sclavo Jodogelatina to Carlo Biscaretti di Ruffia (1879-1959), one of the most famous technical and advertising designers of the day.

A roaring dragon vividly evoked the regenerating power of Jodogelatina. The same mythical theme of the Dragon appeared in 1928 in the advertisements for *Adrenofer* (Fig. 3), again designed by Biscaretti, who inserted an additional element: the *Torre del Mangia,* which towers above the Campo di Siena, one of the most famous piazzas in the world. Two dragons are twisted around the tower; one holds in its mouth a vial of the potent preparation of "iron, manganese and total extract

Fig. 3. Advertising postcard Adrenofer Sclavo 1911 (*Elderly Group Archive, Sclavo, Siena*).

of adrenal capsules" [19], while a drop of the same preparation drips onto the snout of the other.

Over the years, Adrenofer was advertised in various ways, starting with a postcard (1911) in *Art Nouveau* style featuring an elegant lady dressed in red with a garland of roses in her arms, against a backdrop of the Campo di Siena and the Palazzo Pubblico. After the Second World War, the advertising of Adrenofer was entrusted to Giancarlo Rossetti, the founder of Studio Stile (1920-1994) in Milan.

The creation of a single graphic layout for the Sclavo products

Not only the postcards and advertising posters have been conserved, but also, in many cases, the original drafts, such as those by Rossetti. Together, these constitute a patrimony of cultural assets that enables us to reconstruct not only the production of the Tuscan Serotherapy and Vaccinology Institute, but also the communication strategies that it implemented during the course of the 20th century. In this regard, we should also take into account the history of the "image-building" of the Sclavo Institute, which saw a turning point after the death of its founder in 1930.

A few years later, in 1935, Dario Neri (1895-1958) was appointed proxy for the Sclavo heirs. The husband of Achille Sclavo's youngest daughter, Neri introduced into the Institute a new idea of work organization and, possessing the artistic sensitivity of the painter and xylographer, worked to create a new and strong image. His main objective was to create a single and easily recognizable graphic layout for the whole range of production. He used two colors, green and white, and a logo consisting of an arrow broken by another arrow, surmounted by the motto "Contraria" ("contrary"), which had previously been chosen by Achille Sclavo himself [10].

Realistically Sclavo intended to insert the research carried out in his Institute in the tradition of classical medicine, taking up the Hippocratic principle "*contraria contrariis curentur*" (the opposites are cured with the opposites) and opposing the theory "*similia similibus curantur*" (the likes are cured with the similar) typical of the homeopathic approach of Christian Friedrich Samuel Hahnemann (1755-1843).

According to Achille Sclavo and Dario Neri the logo *"Contraria"* (in Latin means *"antagonist")* perfectly summed up the vaccination action: the 'good' arrow breaks the 'evil' one (same but opposite).

Contraria logo featured not only on the packages of the Institute's products, but also, and especially, on its advertising material, thereby creating an incisive image that was based on the Institute's prestigious past and the figure of Sclavo. They also conveyed an important message for the subsequent years and for the study of new immunological methods, which saw the Institute at the forefront of this sector at the international level in the middle of the 20th century.

Conclusions

Much work has been done by the Sclavo Group of Elders and by the University of Siena through its Museum System of conservation, inventorying and study, not only of archival documents but also of the instrumentation that Sclavo routinely used and of the descriptive and advertising material produced by his Institute over the years. This work has proved indispensable to the exploitation of the entire patrimony of the great hygienist. Indeed, cultural assets can be displayed in a museum only after the meticulous process of investigation and study described above.

In this work of organizing the material remains of the history of such an important Italian Institute of serotherapy and vaccinology – which, among others, was chosen in the late 1950s by Albert Sabin for the production of his anti-polio vaccine [21] – great efforts have been required in order to a fill in the evident gaps that point to other documents and objects that have been lost or located elsewhere, and to correctly interpret the stories that the available testimony can "narrate".

The future challenge lies in exploiting this patrimony in such a way that it can be publicly displayed, while at the same time ensuring that it is properly safeguarded. In this way, it will continue to "tell its story" to future generations and to illustrate the value of one of Italy's great hygienists.

The objective is to ensure that, thanks to this historical testimony, Sclavo's enormous scientific value will be brought to the attention of all in a museum setting where these cultural assets can become an effective means of communication with the public – a sort of open "window" on the history of hygiene and public health, to which Achille Sclavo contributed so much.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

DO and MM designed the study, conceived and drafted the manuscript; the authors revised the manuscript, performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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HISTORY OF MEDICINE AND ETHICS

The mediating effects of barriers to vaccination on the relationship between race/ethnicity and influenza vaccination status in a rural Southeastern Louisiana medical center

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Keywords

Influenza • Influenza vaccination • Adult vaccination • Disparities • Vaccination barriers • Mediation analysis

Summary

Introduction. *Persistent disparities in influenza vaccination rates exist between racial/ethnic minorities and Whites. The mechanisms that define this relationship are under-researched.*
Methods. *Surveys assessing barriers to vaccination were administered to outpatients in a rural medical center in Southeastern Louisiana. Survey responses were matched to patient medical records. Likert-style statements were used to measure barriers to vaccination. A mediation analysis assessing the relationship between race and influenza vaccination mediated by vaccination barriers was conducted.*
Results. *The self-reported influenza vaccination rate in those surveyed was 40.4%. Whites (45.5%) were more likely than racial/ethnic minorities (36.3%) to report receipt of an influenza vaccination (p = 0.02). Racial/ethnic minorities reported*

significantly higher vaccination barrier scores (p < 0.01). The relationship between race/ethnicity and vaccination was mediated by vaccination barriers, when controlling for provider recommendation and having at least one comorbid medical condition (natural indirect effect [NIE] p-value = 0.02, proportion mediated = 0.71).
Conclusions. *Barriers to vaccination mediates the relationship between race/ethnicity and vaccination status. Providers should focus on minimizing fears that the vaccine will cause illness and emphasize that the vaccine is safe and effective at preventing severe influenza-associated illness. Additional efforts should be made to improve accessibility of the influenza vaccine, including addressing costs of vaccination and expanding the number and types of settings where the vaccine is offered.*

Introduction

The influenza virus infects 5-20% of the United States (US) population, resulting in an estimated 200,000 hospitalizations and between 3,000 and 49,000 deaths each influenza season [1-3]. Receiving the annual influenza vaccine offers significant protection against severe sequelae of influenza infection. Influenza vaccination prevented an estimated 1.6-6.7 million illnesses, 790,000-3.1 million outpatient medical visits, 39,000-87,000 hospitalizations, and 3,000-10,000 respiratory and circulatory deaths from the 2010-11 through the 2015-16 influenza seasons in the US alone [4]. However, despite the tremendous health burden caused by seasonal influenza and the large health and economic burden that could be mitigated by annual vaccination, vaccination rates have remained low in the general population, with annual influenza vaccination uptake among US adults fluctuating between 38.8-43.6% from the 2009-10 through the 2016-17 influenza seasons [5].
When rates of annual influenza vaccination are stratified by race/ethnicity, it becomes clear that racial/

ethnic disparities are consistently present in influenza vaccination. White adults aged 18 years and older (45.9% vaccination uptake) were more likely than non-Hispanic Black adults (37.4%) and Hispanics (36.9%) to receive the influenza vaccination during the 2016-17 influenza season [5]. Similar differences in influenza vaccination among different races have been documented in previous flu seasons [6-9].
There are many factors that contribute to the persistent racial/ethnic disparities in influenza vaccination. Potential barriers to influenza vaccination fall into one of three categories: (1) demographic, socioeconomic, and health-related factors, (2) negative attitudes and beliefs toward vaccination, and (3) healthcare access barriers to vaccination [10-16].
Various demographic, socioeconomic and health-related factors have been identified in the literature as potentially influential on vaccination status, including education status, employment, income, age, insurance status, having regular preventive care, having medical conditions that increase the risk of influenza-associated morbidity and mortality, receiving a provider recommendation, and others [10-14, 17-21].

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THE MEDIATING EFFECTS OF BARRIERS TO VACCINATION ON THE RELATIONSHIP BETWE-
EN RACE/ETHNICITY AND INFLUENZA VACCINATION STATUS IN A RURAL SOUTHEA-
STERN LOUISIANA MEDICAL CENTER

Negative attitudes and beliefs include a misunderstanding of the importance of the influenza vaccine, an underestimation of personal risk, doubts about the vaccine efficacy, the belief that the influenza vaccine will cause influenza-associated illness or that the influenza vaccine is unsafe, among others [12, 16, 22]. These beliefs have been demonstrated in higher proportions in racial/ethnic minorities [12, 16, 22].

Healthcare access refers to the ability of the patient to obtain an influenza vaccine, including the ability to afford the influenza vaccine and the ability to reach a location offering the influenza vaccine (16). Racial/ethnic minorities remain disproportionately under or uninsured [23]. The lack of insurance increases the out of pocket cost of immunizations, potentially reducing vaccination uptake among racial/ethnic minorities [24]. Additionally, some individuals may find it difficult to get to locations that offer immunizations. This would present another barrier to vaccination, particularly among persons who live in rural areas [16].

Each of these factors has been studied independently. However, the underlying mechanisms that relate these factors are under-researched [25-27]. This study attempts to account for the multifactorial and complex relationship between these differing factors in an attempt to explain the mechanisms by which an individual's influenza vaccination behavior is defined. Specifically, we propose that negative attitudes and beliefs toward and healthcare access barriers to influenza vaccination mediate the relationship between race/ethnicity and influenza vaccination.

As such, this study has two objectives. First, we will establish that disparities in influenza exist in our patient population. Second, we will assess the mediating effects of negative attitudes and beliefs toward and healthcare access barriers to influenza vaccination on the relationship between race/ethnicity and influenza vaccination.

Methods

STUDY DESIGN AND SETTING

This study combined a cross-sectional survey with retrospective data linkage through the Louisiana State University Health Care Services Division (HCSD) Epic electronic health record (EHR) database. This study was conducted among a convenience sample of patients aged 18 years and older seeking care at Lallie Kemp Regional Medical Center (LKRMC) outpatient clinics between May 23rd, 2017 and September 1st, 2017. LKRMC is a federally designated critical access hospital, with a maximum capacity of 25 acute care beds. It is located in Independence, LA (2018 population: 1,902) and serves a rural population that is primarily racial/ethnic minority and low-income (28). LKRMC provides 24-hour emergency care and is available to anyone, regardless of an individual's ability to pay. LKRMC has approximately 35,000 visits per year in designated outpatient clinics.

SURVEY DEVELOPMENT

The survey used in this study was designed to capture information regarding attitudes and beliefs with respect to the annual influenza vaccine and healthcare access barriers to the receipt of the influenza vaccine. More specifically, the survey was designed to examine the barriers, both of perception and reality, to the receipt of the influenza vaccination. These potential barriers to vaccination were identified through a search of the literature surrounding influenza vaccination and converted into 5-item Likert-style statements assessing how strongly each individual experienced barriers to vaccination [10, 12, 15-22, 26, 29-35].

The initial questionnaire was screened by HCSD physicians and Louisiana State University Health Science Center (LSUHSC) investigators to ensure that the question construct accurately reflected the vaccination barrier it was designed to represent, that the questions would be easily understood by patients seeking care at LKRMC, and that the questionnaire would be of an appropriate length to incorporate into the clinic flow at LKRMC. An initial pilot of the questionnaire was then implemented in LKRMC outpatient clinics. Twenty patients were surveyed and asked questions to ascertain whether the Likert measures accurately measured barriers to influenza vaccination. As a result of the pilot questionnaire, the 5-item Likert scale was collapsed to a 3-item Likert scale and the wording of several statements was adjusted. The 5-item statements were confusing to the patients and several of the questions required more specificity.

The final ten 3-item Likert statements (Tab. I) allowed responses of "disagree," "no opinion," and "agree" and eliminated possible "strongly disagree" and "strongly agree" responses. Three of the final statements, "the flu shot is too expensive," "it is too much effort to get the flu shot," and "it is difficult to get to a location that offers the flu shot" related specifically to healthcare access barriers to influenza vaccination. Seven of the final statements, "your personal or religious beliefs prevent

Tab. I. Likert statements used in the questionnaire administered among outpatients in Lallie Kemp Regional Medical Center from May 2017-September 2017.

Healthcare Access Barriers
The flu shot is too expensive
It is too much effort to get the flu shot
It is difficult to get to a location that offers the flu shot
Attitudes and Beliefs
Your personal or religious beliefs prevent you from receiving the flu shot
The flu shot is safe*
The flu shot works*
You are unlikely to get the flu even if you do not get a flu shot
If you already had the flu, you do not need to get a flu shot
The flu shot will give you the flu
You need to get the flu shot every year to prevent the flu*

*Reverse coded

you from receiving the flu shot," "the flu shot is safe," "the flu shot works," "you are unlikely to get the flu even if you do not get a flu shot," "if you already had the flu shot you do not need to get a flu shot," "the flu shot will give you the flu," and you need to get the flu shot every year to prevent the flu," related specifically to attitudes and beliefs regarding the flu shot.

The final questionnaire was screened by HCSD physicians and LSUHSC investigators and re-piloted among twenty patients seeking care at LKRMC. Based on the feedback of investigators, physicians, and patients, the second version of the survey was accepted and used as the survey for the study.

In addition to the assessment of vaccination barriers, information regarding patient influenza vaccination status, socioeconomic indicators, including income and employment, and health-related factors such as primary care access and receipt of a provider recommendation, were also collected using the patient survey. Surveys were linked to patient's medical records using a medical record number (MRN) match. Information regarding patient demographics, including race, age, and sex, insurance status, and comorbid conditions considered to be high risk for influenza-associated morbidity and mortality was captured from the EHR.

DATA COLLECTION

Data collection began on May 23rd, 2017 and extended through September 1st, 2017. Nurses informed patients upon check-in to LKRMC outpatient clinics that members of the LSUHSC staff would be contacting them at some point during their visit to complete a brief survey. Patients were recruited after the LKRMC medical assistants took the patient's vital signs, but before they were called into a patient room by a nurse. This was identified as the point in the patient visit where a survey would be able to be completed without disrupting the clinic workflow at LKRMC. Patients were asked to sign an informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization forms, allowing investigators to record survey responses, access medical records, and use that information for analysis and publication.

LSUHSC investigators administered surveys orally and in-person to patients. This process alleviated concerns of illiteracy and misclassified or incomplete answers. Upon check-in to the outpatient clinics, each patient was given an identification bracelet which contained their MRN. LSUHSC investigators used these bracelets to gather the patient MRN, which was recorded into a Research Electronic Data Capture (REDCap) database, a secure online web application for building surveys and managing databases [36]. To ensure accuracy, investigators were required to enter the MRN twice. Matching MRNs allowed investigators to proceed with the interview, while inconsistent MRNs forced investigators to reenter the MRN. Patients were provided with a card detailing the available responses for visual representation of the questions. All responses were given verbally by patients

and entered by LSUHSC investigators into the study database.

Upon completion of data collection, a dataset containing all survey responses, patient information, and unique MRNs was sent to HCSD for linkage with information of interest abstracted from patient EHR records. Data regarding age, height, weight, gender, pregnancy status, race, chronic conditions that increase the risk of influenza-associated morbidity and mortality, (asthma, diabetes, HIV/AIDS, chronic obstructive pulmonary disorder (COPD), heart disease, blood disorders, kidney disease, liver disease), and insurance status were requested for linkage. After this linkage was completed, the dataset was stripped of identifying information, including the MRN, and returned to LSUHSC investigators for analysis. In doing so, investigators minimized the risk of identification through medical information.

VARIABLES

The primary outcome of interest was influenza vaccination status during the 2016-17 influenza season. Information regarding the outcome was collected from self-reported responses. Participants were asked whether they received their flu shot during last year's flu season and were allowed to respond "yes," "no," or "don't remember." Those who replied, "don't remember" (n = 9) were excluded from analysis. Self-reported responses were used because patient medical records only captured influenza vaccination administered within LKRMC and did not account for vaccinations administered at other locations such as workplaces, stores, or retail pharmacies.

The exposure of interest for the study was race/ethnicity. The patient population of LKRMC is comprised primarily of Black and White patients, including few Hispanics and other races and ethnicities, which mirrors the general demographic composition of Louisiana. Therefore, race/ethnicity was dichotomized into a White and racial/ethnic minority (non-White race or Hispanic ethnicity) categories.

The mediator of interest was barriers to vaccination. Barriers to vaccination is a composite continuous variable formed from the 3-item Likert-style statements regarding attitudes and beliefs toward and healthcare access barriers to influenza vaccination. Responses were coded 1-3, with higher numbers indicating increased barriers to vaccination. The coded responses were summed, creating a scale ranging from 10-30, with higher numbers representing increased barriers. Seven of the statements tracked factors that inhibit influenza vaccination and were coded with disagree= 1, no opinion = 2, and agree = 3, while the remaining three (the flu shot is safe, the flu shot works, and you need to get the flu shot every year to prevent the flu) tracked factors that promote influenza vaccination and were reverse coded with agree = 1, no opinion = 2, and disagree = 3. A small portion of the study population had missing values for one (n = 10) or two (n = 1) of the Likert statements. In this case, available responses were summed, divided by the number of available questions, and then rounded

to the nearest whole number. This whole number was then inserted for the missing value.

Potential confounders were captured using both the survey tool and medical records and fell into three categories, demographics, socioeconomic indicators and health-related factors. Demographic variables included age and sex. Age was categorized based on age groups used by the Centers for Disease Control and Prevention (CDC) to report influenza-associated data, those aged 18-49 years, aged 50-64 years, and aged 65 years and older. Sex was categorized as male or female.

Socioeconomic variables included employment, education, and income. Employment was categorized as full/part time, retired, and disabled, unemployed, student, or other. Education was categorized as did not graduate high school, high school graduate/GED recipient, or attended/graduated college.

Health indicators included insurance status, having one or more comorbid conditions considered to be at high risk for influenza-associated morbidity and mortality, having regular preventive care, and receipt of a recommendation to receive the influenza vaccination from a provider. Insurance status was categorized as insured and uninsured. Conditions at elevated risk for influenza-associated morbidity and mortality available in the Epic database were asthma, diabetes, HIV/AIDS, chronic obstructive pulmonary disorder (COPD), heart disease, blood disorders, kidney disease, liver disease [36]. Those with at least one of these conditions in their medical records were considered to have at least one comorbid condition. To classify regular preventive care, patients were asked if they had somewhere they typically receive preventive care services. If a patient stated that they did have a place where they received preventive care services, they were considered to have access to regular preventive care. To assess provider recommendation, patients were asked whether they had received a recommendation to receive the influenza vaccination from a provider during the previous year's influenza season. If the participant replied that they received a recommendation from a provider, then they were considered to have received a provider recommendation. If the participant replied that they did not receive a recommendation, did not see a doctor during that time, or did not remember, then they were considered to not have received a recommendation from a provider, resulting in a dichotomous categorical variable.

STATISTICAL ANALYSIS

Unadjusted relationships between potential confounders, the mediator, and vaccination status were examined using chi-squared tests for categorical variables and t-tests for continuous variables. Barriers to vaccination, the potential mediator of interest, was assessed in a unadjusted model analyzing the relationship between race/ethnicity and vaccination status using the SAS macro established by Valeri and VanderWeele [38].

A full model with all confounders, the mediator, the exposure, and the outcome was created to assess effects of barriers to vaccination on the relationship between race/ethnicity and influenza vaccination status. Exposure-mediator interaction was tested. No interaction was identified. Initially, a log-linear model was attempted. However, the log-linear model failed to converge. Therefore, a Poisson model with more robust standard error was substituted. Backwards elimination was used to establish a final model by eliminating confounders that did not demonstrate significance in the model (p≤0.05) one-by-one until all remaining factors were significant. The final model ultimately included provider recommendation and the presence of at least one comorbid condition (as confounders), race/ethnicity (exposure), vaccination status (outcome), and barriers to vaccination (mediator). Parameter estimates for the unadjusted and adjusted models were obtained.

Results

A total of 703 individuals were approached in LKRMC outpatient clinics, of whom 623 were consented and completed interviews. Five of those who completed interviews were excluded because they were not found in the Epic database (n = 2) or they were called into their appointment prior to completion of the interview (n = 3). Nine individuals who reported not remembering their vaccination status were also excluded. This left a final sample of 609, yielding a final response rate of (86.6%). 40.4% of the final sample had received an influenza vaccination (Tab. II). White patients (45.5%) were more likely than racial/ethnic minority patients (36.3%) to have received an influenza vaccination (p = 0.02). Those of older age groups (p < 0.01), who were employed full or part time or retired (p = 0.01), and had incomes above the Louisiana poverty level (p = 0.03) were all more likely to receive influenza vaccination than their respective reference groups. Those who received a doctor's recommendation (p < 0.01), had access to preventive care (p < 0.01), and who reported having at least one comorbid condition were more likely to receive the influenza vaccination than those without (p < 0.01). Other factors showed no unadjusted association with influenza vaccination status.

The mean vaccination barrier score in the population was 15.2 (SD = 3.6) (Tab. III). Those who were unvaccinated (mean = 16.7, SD = 3.3) reported significantly higher barriers to vaccination than those who were vaccinated (mean = 12.8, SD = 2.7) (p < 0.01). Additionally, racial/ethnic minorities (mean = 15.5, SD = 3.5) reported higher levels of barriers to vaccination than Whites (mean = 14.8, SD = 3.6) (p = 0.01).

The unadjusted model assessing the mediating effects of barriers to vaccination demonstrated significant mediation of the relationship between race/ethnicity and vaccination status (NIE p-value = 0.01, proportion mediated = 0.69) (Tab. IV). In the final, adjusted model

Tab. II. Characteristics of the patients seeking care at Lallie Kemp Regional Medical Center by influenza vaccination status, May 2017- September 2017 (n = 609).

Patient Characteristics	Study Sample n = 609 (%)	Unvaccinated n = 363 (%)	Vaccinated n = 246 (%)	P-Value*
Outcome				
Vaccination Status				
Vaccinated	246 (40.4)	N/A	N/A	N/A
Unvaccinated	363 (59.6)			
Demographics				
Race				
White	266 (43.8)	145 (54.5)	121 (45.5)	**0.02**
Racial/Ethnic Minority	342 (56.2)	218 (63.7)	124 (36.3)	
Age				
Aged 18-49 Years	219 (36.0)	157 (71.7)	62 (28.3)	**< 0.01**
Aged 50-64 Years	279 (45.8)	153 (54.8)	126 (45.2)	
Aged 65 Years and Older	111 (18.2)	53 (47.8)	58 (52.2)	
Sex				
Male	226 (37.2)	146 (64.6)	80 (35.4)	0.06
Female	382 (62.8)	217 (56.8)	165 (43.2)	
Socioeconomic Indicators				
Education				
Did not Graduate High School	173 (28.4)	99 (57.2)	74 (42.8)	0.75
High School Graduate	265 (43.5)	160 (60.4)	105 (39.6)	
Attended/Graduated College	171 (28.1)	104 (60.8)	67 (39.2)	
Employment				
Full/Part Time	228 (37.5)	154 (67.5)	74 (32.5)	**0.01**
Retired	96 (15.8)	53 (55.2)	43 (44.8)	
Unemployed/Disabled/Student/Other	284 (46.7)	155 (54.6)	129 (45.4)	
Income				
Above Poverty Level	127 (21.0)	86 (67.7)	41 (32.3)	**0.03**
Below Poverty Level	478 (79.0)	274 (57.3)	204 (42.7)	
Health-Related Factors				
Insurance				
Insured	492 (80.9)	285 (57.9)	207 (42.1)	0.06
Uninsured	116 (19.1)	78 (67.2)	38 (32.8)	
Doctor's Recommendation				
Recommended Vaccine	368 (60.7)	163 (44.3)	205 (55.7)	**< 0.01**
Not Recommended Vaccine	238 (39.3)	197 (82.8)	41 (17.2)	
Preventive Care Access				
Has Preventive Care Access	515 (84.6)	287 (55.7)	228 (44.3)	**<0 .01**
No Preventive Care Access	94 (15.4)	76 (80.9)	18 (19.1)	
Has at Least One Comorbid Condition				
Yes	303 (49.8)	149 (49.2)	154 (50.8)	**< 0.01**
No	306 (50.3)	214 (69.9)	92 (30.1)	

n = population.
Bolded values are significant at p ≤ 0.05.
*p-value calculated using chi-squared tests.

only provider recommendation (p < 0.01) and having at least one comorbid condition (p= 0.04) remained predictors of vaccination status. The relationship between race/ethnicity and influenza vaccination status also proved to be mediated by barriers to vaccination (NIE p-value = 0.02, proportion mediated = 0.71). However, both the direct (p = 0.68) and the total (p = 0.16) effects of the adjusted model were non-significant.

Discussion

The objectives of this study were (1) to evaluate racial/ethnic disparities in influenza vaccination and (2) to assess the mediating effects of barriers to influenza vaccination on the relationship between race/ethnicity and receipt of influenza vaccination. We determined that there was a relationship between race/ethnicity and influenza vaccination status, where racial/ethnic

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THE MEDIATING EFFECTS OF BARRIERS TO VACCINATION ON THE RELATIONSHIP BETWE-
EN RACE/ETHNICITY AND INFLUENZA VACCINATION STATUS IN A RURAL SOUTHEA-
STERN LOUISIANA MEDICAL CENTER

Tab. III. Vaccination barrier score by influenza vaccination status and race/ethnicity among patients seeking care at Lallie Kemp Regional Medi-cal Center, May 2017-September, 2017 (n = 609)

Mediator by Outcome and Exposure	Vaccination Barriers Score (Mean (SD))	P-Value*
Overall	15.2 (3.6)	N/A
Outcome		
Vaccination Status		
Unvaccinated	16.7 (3.3)	**< 0.01**
Vaccinated	12.8 (2.7)	
Exposure		
*Race**		
White	14.8 (3.6)	**0.01**
Racial/Ethnic Minority	15.5 (3.5)	

S= standard deviation.
Bolded values are significant at p≤0.05.
*p-value calculated using t-tests.
**There is one person missing data on race/ethnicity.

Tab. IV. Assessment of the relationship between race/ethnicity and influenza vaccination status, mediated by barriers to vaccination (n = 605*)

Effect	Unadjusted** Model		Adjusted Model***	
	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)
Direct Effect	0.59	0.93 (0.73, 1.20)	0.68	0.95 (0.74, 1.22)
Indirect Effect	**0.01**	0.84 (0.73, 0.96)	**0.02**	0.87 (0.77, 0.98)
Total Effect	0.09	0.78 (0.59, 1.04)	0.16	0.82 (0.62, 1.08)
Proportion Mediated	0.69		0.71	

CI = confidence interval.
Bolded values are significant at p ≤ 0.05.
*Four individuals had missing data (3 on provider recommendation and 1 on race/ethnicity) and were excluded from the adjusted model.
** Unadjusted model assessed an empty model, with only vaccination status (outcome), race/ethnicity (exposure), and barriers to vaccination (mediator).
***Adjusted model includes having at least one comorbid condition (p = 0.04) and doctor's recommendation (p < 0.01).

minorities were more likely to be unvaccinated against influenza. Furthermore, we discovered that this relationship was mediated by barriers to vaccination.

The proportion of adults receiving the influenza vaccination (40.4%) in LKRMC during the 2016-17 influenza season was slightly lower than the national 2016-17 adult influenza vaccination rate in the US (43.3%) [5]. Similar disparities in influenza vaccination existed between samples in LKRMC and national samples used by the Centers for Disease Control and Prevention (CDC) [5-7, 9, 18 39-41]. White adults (45.7%) and racial/ethnic minorities (36.3%) in LKRMC were vaccinated in roughly equal proportions to Whites (45.9%) and Blacks (37.4%)/Hispanics (36.9%) in the national sample [5].

Racial/ethnic minorities typically hold more negative beliefs regarding influenza vaccination, lack trust in the influenza vaccine (i.e., belief that the vaccine will cause illness), misunderstand risks of the influenza virus, believe that seeking the vaccine is inconvenient, and experience barriers such as cost, lack of insurance, and lack of access [12, 16, 18-20, 22, 27, 30, 31. 35, 42, 43]. This held true in this study. Racial/ethnic minorities in the sample were more likely to report higher rates of barriers to vaccination, including negative attitudes and beliefs and healthcare access barriers, than Whites. When the aggregated vaccination barrier score is considered in a mediated model, the direct relationship between race/ethnicity and vaccination status disappears

and is replaced by the indirect relationship mediated by barriers to vaccination. These results suggest complete mediation, where there is an observed indirect effect and no observed direct effect [44]. Complete mediation is the gold standard and reflects strong evidence that the relationship between race/ethnicity and vaccination status is mediated by barriers to vaccination.

The total effect is the sum of the indirect effect and the direct effect and measures the overall effect of the independent variable (race/ethnicity) on the dependent variable (vaccination status) [45]. Traditional mediation analysis, or the "causal steps approach," popularized by Baron and Kenny calls for a significant total effect to consider whether mediation analysis should be used [44]. However, more recent literature suggests that a significant total effect is not required for mediation to be present [45-52]. In fact, in the presence of complete mediation, one may not uncover a significant total effect and still have enough power to detect a significant indirect effect [51]. This anomaly occurs because the power to detect the total effect is dramatically less than the power to detect the indirect effect [51]. In the adjusted model of this study, the total effect does not reach significance, but given the preponderance of recent literature suggesting that a significant total effect is not required, this result does not nullify the mediation of the race/ethnicity-vaccination status relationship by barriers to vaccination.

The final, mediated model also controlled for provider recommendation and having at least one comorbid condition. These factors are consistent predictors of influenza vaccination across studies [17-21]. In fact, there is typically no stronger predictor of influenza vaccination than a provider recommendation [18-21]. Those with comorbid conditions for increased influenza-associated morbidity and mortality are more likely to be in care and are likely to be a focal point for provider vaccination efforts given their risk status. These factors likely contribute to the increased likelihood of vaccination for those with comorbid conditions. Provider recommendation and having at least one comorbid condition are also potentially associated with race/ethnicity. It has been suggested that providers may recommend the influenza vaccination with varying frequency based on race/ethnicity [13, 16, 34]. Additionally, one study has shown that Whites with comorbid conditions for increased influenza-associated morbidity and mortality were more likely than Blacks with the same conditions to receive an influenza vaccination [17]. As such, it follows that these factors would prove to confound the relationship between race/ethnicity and influenza vaccination status.

LIMITATIONS

The data used in this study are cross-sectional, making causal inference impossible. There are several studies that have shown that substantial bias can results from the use of cross-sectional data in mediation analysis [53-55]. However, many of these concerns arise as a result of interpreting cross-sectional results as temporal or causal [56]. The results presented in this study are atemporal, indicating that longitudinal observation is not necessary to quantify their effects. Additionally, we make no claims that the proposed mediation model represents a causal mechanism. Instead, identify that race/ethnicity is atemporally associated with influenza vaccination and that this association is mediated by barriers to vaccination.

Surveys were administered in hospital outpatient clinics, potentially introducing selection bias into the study. Those in outpatient clinics are more likely to have access to care than those in the general public. Increased access to care can lead to more points of contact between patient and provider and an increased likelihood of a provider recommendation. This may increase the likelihood of influenza vaccination and decrease the likelihood of negative attitudes and beliefs regarding the influenza vaccination and indicate a decreased degree of healthcare access barriers to influenza vaccination. The resulting bias would likely be towards the null as the rate of vaccination would be artificially increased and the vaccination barrier score would be artificially decreased. The outcome, influenza vaccination, is self-reported. Potential misclassification is introduced due to recall bias and social desirability bias. However, this misclassification is likely non-differential, which only serves to bias the associations towards the null.

Surveys were administered in a single medical center in rural Louisiana. As a result, the population surveyed will not be generalizable to the US population. However, there are likely similarities between this study and other hospitals and clinics in rural America. Influenza vaccination rates among rural racial/ethnic minorities are generally lower than those of rural non-minorities, urban racial/ethnic minorities, and urban non-minorities with regards to influenza vaccination, making this population of particular interest [10].

STRENGTHS

The relationship between race/ethnicity and influenza vaccination is complex and multifaceted. This study accounts for differing racial/ethnic experiences and attitudes regarding influenza vaccination through a mediated model. Additionally, this study was conducted in a rural population. Available literature suggests that rural populations may be less likely to receive influenza vaccination, particularly rural racial/ethnic minorities [10]. Finally, this study ensured internal validity by administering surveys orally and combining survey responses with patient medical records.

Conclusions

The results of this study indicate that the relationship between race/ethnicity and vaccination status is mediated by measured barriers to vaccination, both attitudinal and to healthcare access. This provides valuable information on how to increase vaccination rates among racial/ethnic minorities. Typical efforts made to increase vaccination in medical settings such as standing orders, EHR reminders, and other efforts to increase provider recommendation are proven to be effective, but there is a substantial opportunity to increase vaccine uptake among racial/ethnic minority populations by addressing how providers recommend the influenza vaccine. Providers should focus on minimizing fears that the vaccine will cause influenza and emphasize that the influenza vaccine is not only safe and effective at preventing severe influenza-associated illness, but must be administered every year to provide protection. Additional efforts should be made to improve the accessibility of the influenza vaccination, including addressing costs of vaccines and expanding the number and types of setting where vaccines are available.

There are several opportunities for future research. Now that several aggregated constructs have been established as mediating factors in the race/ethnicity-influenza vaccine uptake relationship in a limited population, these constructs should be tested in larger populations that are more representative of the general US adult population. Additional constructs should also be included in the measurement of barriers to vaccination, including perceived discrimination and patient trust in the provider.

Acknowledgements

Conflicts of Interest

The authors report no conflicts of interest.

Authors' Contributions

Dr. Maloney designed and implemented this study, collected data, performed analyses, and authored the manuscript. Ms. Tietjer designed the REDCap database used in this study and assisted in data collection. Drs. Rung, Straif-Bourgeois, and Peters provided consultation on study design and analysis and edited this manuscript. Dr. Couk aided in implementation in LAK. He coordinated with hospital administration and helped secure necessary approvals. He also edited this manuscript.

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ERRATA CORRIGE

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page E211

Abstract Code: SIT16745-03

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