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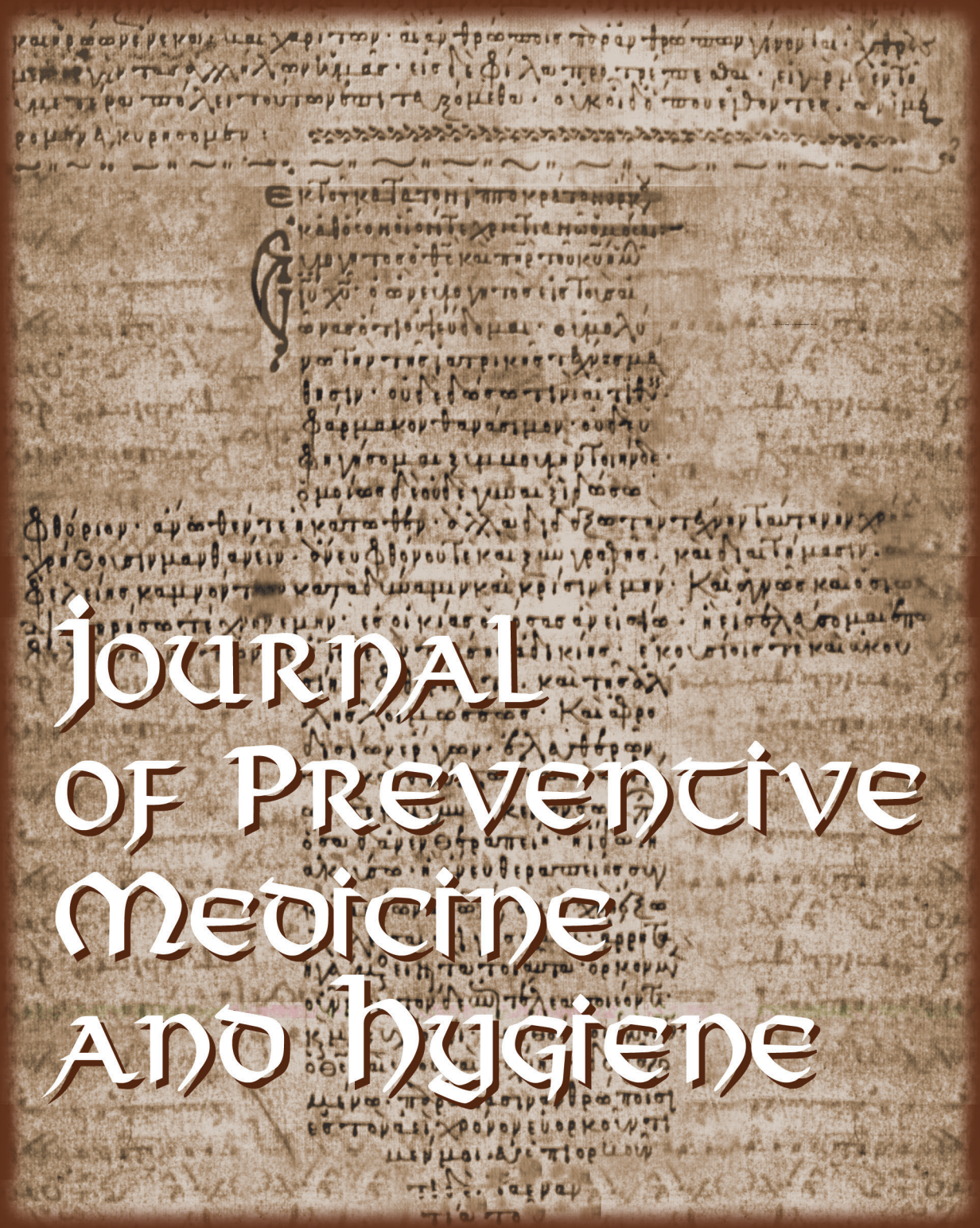

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Contents

EDITORIAL

Exploring the pathway toward the reduction of paediatric seasonal influenza burden: school-based vaccination and surveillance

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Keywords

Influenza • Children • School-based interventions • Universal childhood influenza vaccination • Saliva-based surveillance

Dear Editor,

Influenza is a highly contagious infectious disease and a major health problem in the paediatric population, especially in preschool-aged children, who are at increased risk for severe influenza-related illness and complications [1]. Children have the highest influenza attack rates, up to 30%, especially because of the immaturity of their immune system and the wide attendance of school and other community settings [1, 2]. Indeed, seasonal influenza can spread easily in crowded areas such as schools. Influenza viruses can also be spread by contaminated hands, and children can have poor hygiene habits [1].

Children, especially those in preschool-age, are the primary source of influenza transmission within the community [3, 4]. Indeed, it has been demonstrated that influenza viruses shedding is higher in children compared with adults [1, 5]. Additionally, Ng et al. reported that preschoolers started and kept shedding influenza viruses earlier and for a longer period than adults, because they have low pre-existing influenza-specific immunity [6].

Annually 870,000 children under 5 years of age seek care in emergency settings because of influenza and related conditions worldwide, with an associated hospitalisation rate of 20% [7, 8]. Between 28,000 and 111,500 deaths in such age group are imputable to influenza-related causes, with the majority occurring in children under 4 years of age [3].

Influenza epidemics can result in high levels of work and school absenteeism, leading to significant burden in terms of financial and health outcomes [3]. In particular, childhood seasonal influenza impacts on absenteeism both of sick children and their parents, who often need to miss several working days for taking care of their children [7, 8].

In children with good health, influenza often manifests with non-specific and mild symptoms, which do not require medical care. In these conditions, without proper testing, influenza may be mistaken for other respiratory illnesses and is frequently underestimated. Indeed, during periods of low influenza activity or outside of epidemics situations, the infection of other respiratory viruses can also present as influenza-like illness (ILI), which makes the clinical differentiation of influenza from other pathogens difficult [8]. Hence, assessing the real impact burden of influenza among children is still challenging.

To reduce the burden of influenza infections, vaccination coverage has to be necessarily increased and large-scale surveillance has to be implemented.

Influenza vaccination is the most important public health tool to reduce virus spread and the morbidity and mortality associated with influenza and related complications, particularly for the elderly. When the vaccination is not able to prevent influenza, it has been shown to reduce severity of illness in people who get vaccinated but still get sick. Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Current evidence suggests that universal childhood vaccination is a strategy of paramount importance to reduce the health and economic burden of influenza to the community as a whole, as well as that of other respiratory diseases when other viruses are co-circulating. It has been demonstrated that vaccination against influenza has a direct protective effect on children, reducing hospitalisation and mortality rates, and it also provides indirect protection to close and susceptible contacts [2]. In Japan, it has been demonstrated that vaccination against influenza among school-aged children has an important impact on the elderly [9, 10].

Several seasonal influenza vaccines have been licensed for use worldwide, including the live attenuated influenza vaccine (LAIV), approved for children and adolescents from 24 months up to 49 years of age [11], and the inactivated influenza vaccines, approved for children from six months of age [12].

The WHO recommends vaccinating children aged 6-59 months against influenza [13].

During the COVID-19 pandemic, with the co-circulation of SARS-CoV-2 and influenza viruses, the Strategic Advisory Group of Experts (SAGE) of the World Health Organization (WHO) has recommended reconsidering the prioritisation of high-at-risk groups for influenza vaccination, to limit the impact on the healthcare system and avoid an additional burden on vulnerable populations [14]. Before the COVID-19 pandemic, among the risk groups for priority use of influenza vaccines, only children with underlying medical conditions were included [15]. Starting from 2020, all children aged 6 months to 6 years are considered an additional risk-group for seasonal influenza vaccination [14].

Nevertheless, influenza vaccination coverage remains suboptimal (lower than 75% [16]) in many countries, including Italy, where the coverage ranged from 10.5% in influenza season 1999/2000 to 23.7% in influenza season 2020/2021 [17]. D'Ambrosio et al., described the trend of influenza vaccination uptake in Italy along 11 influenza seasons (2010-2021), reporting a decrease in vaccination coverage in children aged 0-8 years in the period 2010-2020, followed by a significant increase during COVID-19 pandemic, especially in the age group 2-4 years (19%) [2]. This data highlights the need for prioritising strategies to implement influenza vaccination coverage in children to be in line with WHO recommendations [18].

Most paediatric influenza vaccinations are currently administered in primary care offices, hence vaccinating all children during the vaccination season can be challenging. Vaccine administration in alternative settings can be useful to overcome logistical issues, other than for reaching hard-to-reach children and adolescents and increasing families' compliance with the vaccination schedule. Also, alternative delivery options should be considered to improve adherence to vaccination campaigns. The live-attenuated influenza vaccine (LAIV) is needle-free, delivered via nasal spray, and offers protection against influenza A and B viruses. Moreover, LAIV elicits an immune response without replicating efficiently in the lower respiratory tract, reducing the risk of virus transmission [4]. For all these reasons, LAIV represents an attractive choice for mass vaccination campaigns in non-healthcare settings.

Several pilot studies have demonstrated the feasibility and effectiveness of school-based influenza vaccination (SLIV) in increasing vaccination coverage among schoolchildren [4, 19-21]. Especially for very young children, and consequently for their parents, the school represents a familiar and trusted community environment and can help to partially overcome parental hesitancy.

Furthermore, schools could reduce barriers to vaccination compared with primary case offices. It has been demonstrated that influenza vaccine uptake is lower in people, both children and elderly, living in deprived neighbourhoods, probably due to a lack of health knowledge and information and an underestimation of the risk associated with influenza virus infection [22]. Being in direct contact with families, schools could represent a key site to increase accessibility to vaccination, to overcome linguistic barriers, and for bridging the gap between different socioeconomic groups.

During the 2013/2014 influenza season, the United Kingdom started a universal childhood immunisation programme with LAIV in primary school settings (children aged 4-11 years old), achieving a relatively good uptake, ranging from 45.6% to 71.5% in different pilot areas [23, 24]. This campaign was associated with an important decrease in emergency department accesses and hospitalisation for ILIs in children vaccinated at school. Concurrently, the authors observed a reduction of 59% in adult primary care visits for respiratory symptoms, confirming the population impact of childhood vaccination [23, 24].

Similar benefits of SLIV have previously been demonstrated in North America, during the 2005/2006 influenza season, when a large immunisation campaign involving public school children from kindergarten through 12th grade (4-11 years old) was launched [23]. Importantly, it has been demonstrated that this programme, reaching a vaccination coverage of 45%, was associated with a significant reduction in morbidity attributable to influenza.

In Italy, during the 2021/2022 influenza season, when the vaccination was extended to all children aged 6 months to 6 years, a SLIV pilot study was set up in preschools (children aged 2–6 years) in the Milan municipality [25]. The percentage of adherence in the various schools ranged from 11 to 49%, resulting in a relatively good participation in the immunisation campaign, considering possible absences due to COVID-19 pandemic. An increase in childhood vaccination coverage was observed in the same geographical area during the considered influenza season compared to the previous one (from 1.9 to 22.2% in the 2-4 age group, and from 1.4 to 15.5% in the 5-8 age group). Another benefit of this study was the high participation of preschoolers with an immigrant background, most of whom with language difficulties, highlighting that the involvement of cultural mediators and the set-up of a multi-language informative were crucial for rising families' engagement.

Several studies have reported that saliva has high sensitivity and specificity for the detection of influenza and offer a feasible approach for testing ILI particularly in children [26]. Indeed, school has been proven to be also the ideal context for promoting influenza surveillance [21]. Additionally, another aim of this Italian study was to perform an innovative school-centred ILI surveillance by saliva self-sampling. Monitoring school absenteeism has long been proposed as a surveillance tool of influenza, but its potential remains limited [27], especially because surveillance based only on absenteeism does not allow the identification and characterization of the pathogens responsible for respiratory infections. In this sense, virological surveillance allows monitoring influenza viruses circulation and respiratory pathogens differential diagnosis, essential for adequate case management and estimating real-time vaccine effectiveness. Especially in "out-of-

season" periods, investigating not only the presence of influenza viruses, but also other more common paediatric viruses appear of utmost importance, as already suggested by other authors [28]. Importantly, this surveillance system proved to be a valuable tool, at a pandemic time, to screen for COVID-19 and influenza [25].

Additionally, implementing school-based surveillance is crucial since monitoring the school-age population provides enhanced early detection of influenza epidemics [4].

In Hong Kong, Leung et al. conducted a school-based surveillance study using nasopharyngeal swabs, which is the gold standard specimen type for influenza detection but represents a sampling method difficult to perform in the paediatric population. This translates into a reduced number of school-age children included in the surveillance [29]. Virological surveillance could be strengthened using oral fluids self-sampling or sampling under parents' supervision, which might overcome the need for the presence of medical staff, allowing virtually reaching all the school population [25, 30].

In the aforementioned Italian study, saliva-based testing was well accepted by children and their families, being able to collect an adequate amount of saliva for the purposes of molecular detection of respiratory pathogens. For this reason, the study was proposed again during the influenza season 2022/2023 [25].

Building a routinary saliva-based surveillance system could allow conducting future studies on vaccine effectiveness using the case-control test-negative design, and to assess the vaccine protection against the most severe forms of the disease.

To conclude, COVID-19 pandemic taught us that it is possible to screen with alternative biological samples (such as saliva) and to vaccinate in every setting (*e.g.*: in sports halls, in schools). In this paper, we have argued and proposed two possible key strategies to reduce the burden of influenza infections in children: i) increase universal vaccination coverage in children by offering vaccination in schools, and ii) implement large-scale influenza surveillance using an easy and painless collection method of respiratory samples. Indeed, the implementation of influenza vaccination in children through LAIV and SLIV programmes could represent the key strategy to increase vaccine uptake, and consequently to reduce hospitalisation and mortality rates in both children and, indirectly, the whole population.

Surveillance represents an important tool for monitoring influenza viruses circulation profiles and the effectiveness of influenza vaccination. Despite nasopharyngeal swabs are still the gold standard specimen type for respiratory infections detection, saliva has been proven to represent an easy, painless, and non-invasive alternative since the first COVID-19 wave [31]. The less expensive and flexible nature of saliva sampling provides better opportunities to enforce respiratory infection screening and surveillance.

Influenza affects all countries, communities, and individuals, and influenza pandemics represent a serious threat to public health. In countries such as Italy, where vaccinations are mainly provided as part of primary care, the school vaccination campaign can be seen as an important 'catch-up' intervention for those children not adequately reached by the paediatrician/territory. The use of nasal spray influenza vaccine coupled with a saliva-based surveillance for the detection of influenza viruses could represent a relevant approach to reduce the burden of influenza and other respiratory infections, achieving the goals of the WHO's Global Influenza Strategy 2019-2030 [18].

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None.

Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization, AA; Writing-Original Draft Preparation, MG, CF; Writing-Review and Editing, SB, ET, GZ, AA; Supervision, AA. All authors have read and agreed to the published version of the manuscript. These first authors contributed equally to this article: MG and CF. These senior authors contributed equally to this article: GZ and AA.

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EDITORIAL

The Crucial Role of the Project Manager: Comparing Healthcare Experiences

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Keywords

Project management • Healthcare efficiency • Public Health • Resource Optimization

Dear Editor,

In the context where healthcare companies face increasingly complex challenges such as long waiting lists, a shortage of medical staff, overcrowded emergency rooms, and limited bed availability, the role of the project manager emerges as fundamental in determining priorities, organizing work, developing projects, and achieving set objectives. Optimizing time and efficiently managing resources is imperative and a thorough understanding of the medical-healthcare environment proves advantageous for conscious and balanced management of aspects such as budget, medical staff, and supplies [1].

The role of the project manager emerges as fundamental in determining priorities, organizing work, developing projects, and achieving set objectives in the context where healthcare companies face increasingly complex challenges such as long waiting lists, a shortage of medical staff, overcrowded emergency rooms, and limited bed availability [1].

Optimizing time and efficiently managing resources become imperative, and a thorough understanding of the medical-healthcare environment proves advantageous for conscious and balanced management concerning aspects such as budget, medical staff, and supplies. The project manager plays a key role in the internal organization of the healthcare company. The ideal profile for this role could be an external consultant bringing a different perspective or an internal appointee [2].

The project manager can be an internal collaborator acting as an operational arm alongside the medical director. This is the case in the South Tyrol Healthcare Company, where the decision was made to limit the use of external consultants, favoring the implementation of software to manage projects and, importantly, to see them through to completion. Starting from mid-2021 and within a year and a half, this role was reactivated in light of the many imminent challenges: from the migration to a new information system to managing waiting lists, constructing a new clinic, and developing prevention apps. The project manager's role, in addition to demonstrating to healthcare colleagues how their contributions improve operational efficiency, involves understanding the company's methodology and vision, deciding priorities, and building a complex network with external stakeholders.

The organizational culture within the staff and set standards to adhere to can be revitalized.

Concrete examples of success include the Coordination Health Agency of Friuli-Venezia Giulia, which established a centralized and outsourced hub active in the Pordenone inland port. It is an automated regional pharmaceutical warehouse supporting all healthcare companies, meeting patient needs by aggregating requirements and providing innovative drugs ahead of the European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA) timelines. This has made Friuli the national best performer: it takes just 55 days to purchase innovative drugs after AIFA approval and publication in the Official Gazette, a record time compared to Sicily's 81 days in second place [3]. The activities aimed at reaching this outcome began in 2018. The Friuli-Venezia Giulia Region, as part of regional planning in 2022, established the regional innovative drugs fund, which in 2023 reached an investment of 15 million euros – a unique experience for a special statute region that does not access national funds, aiming to support its healthcare companies in spending on innovative drugs classified in classes A and H within the LEA (Essential Levels of Assistance). Overall, almost 20 million euros are spent in this sector [4]. Despite the small population (1.198 million people) and special statute exemptions, management entrusted to an administrative director and a socio-health director has led to excellent results, demonstrating that the model could be replicated in other contexts.

The success of such initiatives, however, largely depends on involving all staff, initially resistant to change. The project manager's task is also to make doctors, healthcare providers, and pharmacists understand how these processes allow them to reclaim their professionalism increasingly. This applies from drug management to emergency room management: emergency room problems are often not its responsibility but are attributed to both territorial health and social-health services and the hospital where the emergency room operates.

This should be the guiding philosophy of healthcare management.

A discharge room was created in a nurse-led ward for patients awaiting at San Matteo Polyclinic in Pavia, Lombardy - Italy. Specifically, a platform was developed to measure handling times and the number of accesses, with results (and information) shared weekly. This reduced the average length of stay, encouraging timely and applicable patient discharge. Simultaneously, a platform was developed by the Territorial Health and Social Company (ASST) of Pavia finalize to monitoring in real-time the availability of healthcare beds in different setting, creating an automated dialogue between structures, including accredited private ones.

In another Italian Region, Marche, specifically at the Madonna del Soccorso Hospital in San Benedetto del Tronto, a similar solution was tested: due to high seasonal access to the emergency room, a "silver code" laboratory was activated for the benefit of the elderly population. This supported the emergency medicine department in managing a population segment that accounts for almost 38% of hospital access. The night shift was also rotated to a single department to free up other specialties to work more during the day. All with the aim of speeding up discharges. For the same reason, a home care nurse was activated directly in the emergency room, even on Saturdays and Sundays. To streamline territorial handling, municipal social workers were also involved.

Not only healthcare pathways need to be reviewed, but also pathways such as those involving analyses. In this case, the project manager can be the same laboratory director facing reorganization from the sample pathway perspective. This results in a single collection point from which a single latest-generation machine, controlled by a single technical figure, rationally redistributes samples throughout the hospital. Thus, the final result of that analysis reaches the unit's medical-biologist manager who must use the test. This logic guided the modernization of the analysis laboratory at the Madonna del Soccorso Hospital in San Benedetto del Tronto, Marche Region Italy.

A recurring phenomenon in healthcare facilities is the difficulty in sharing spaces among physicians. At the IRCCS Maugeri in Pavia, a structural reorganization of the outpatient clinics, led to significant efficiency improvements in pathways and, consequently, greater attractiveness for patients. Despite initial resistance from medical staff, teamwork was gradually stimulated, allowing patients to find multiple services in the same place.

If the obstacle to implementing innovative projects in the public sector mainly lies in a cultural issue and difficulty partnering with private entities that can guarantee success, in the private sector, it is necessary to prove that the project generates profit or savings. In the public sector, it is more challenging to recruit a project manager because formal competition is needed. Conversely, the private sector lacks the public sector's organization. A private structure optimizing procedures and costs for supply purchases is the Aurelia Hospital in Rome, where procurement is being outsourced: here, partners can negotiate on behalf of the structure as external entities, sharing objectives and results to obtain lower prices that would otherwise be impossible. Such an approach would currently be impossible in public healthcare companies, even though "the Italian model of public administration management is in a moment of great transformation, and the healthcare sector is certainly a precursor of innovative trends that can be experimented and implemented.

Many different experiences, compared during the Vision advanced training course organized by the Healthcare Management Academy of the University of Genoa, lead to one conclusion: each context needs to find its 'ideal' project manager, who today more than ever plays a crucial role in the healthcare field. In any situation, the project manager must be a guide capable of improving efficiency and care delivery through their skills, teamwork, and new technology assistance. Furthermore, they must always be characterized by the flexibility that allows them to change the project strategy in response to changes in the healthcare context: the project manager has great skill in managing time, resources, and budget, combined with the ability to communicate clearly with all project stakeholders.

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All authors equally contributed to the conception, design, execution, and manuscript preparation.

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EDITORIAL

From Regulations to Strategy for Sustainable Healthcare by 2030

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Keywords

Sustainability • Digitalization • Green Healthcare • Healthcare strategies

Dear Editor,

At the 28th United Nations Climate Change Conference, during Health Day on December 3, 2023, it emerged that "the climate change crisis is a health crisis [1]". With global warming, more infectious diseases are emerging, facilitated by heat waves, and abnormal weather events are jeopardizing access to clean water and quality food [2, 3]. However, the healthcare sector also has a high environmental impact: it is estimated that globally it contributes 4-5% of total greenhouse gas emissions into the atmosphere [3]. This is why attention to sustainability has also grown in the healthcare field, especially in recent years, in view of the 2030 Agenda goals.

According to a study conducted in 2023 by ALTIS, BCG, and CERISMAS, nearly 80% of the companies surveyed reported having defined a sustainability strategy or were in the process of developing one [4]. Institutions are also increasingly recognizing the need to adopt more responsible and environmentally friendly practices. There are several areas where intervention is possible: foremost among them is waste disposal, where it is crucial to promote reuse and recycling, limiting the use of single-use devices, provided that patient safety is not compromised. Since the onset of the Russia-Ukraine conflict and the resulting increase in energy costs, energy efficiency has become a priority for healthcare facilities. Energy bills have come to represent 2.3% of a healthcare company's expenses. Nationally, the amount has reached 1.6 billion euros, necessitating government intervention to cover this amount. Energy resource optimization interventions could lead to saving up to 30%, as outlined in the National Recovery and Resilience Plan (PNRR).

To reduce energy impact, healthcare companies must promote sustainable mobility for staff and patients. At the same time, they should prioritize suppliers who adopt ethical and environmentally friendly practices in the purchasing of medicines and other medical devices. Reducing waste also involves avoiding unnecessary exams, screenings, or inappropriate antibiotic prescriptions. Sustainable healthcare means efficient healthcare, and this also involves digitization, which enables the use of telemedicine, thereby reducing the need for travel. However, digital technology also optimizes resources, data storage, and online training, significantly reducing the use of paper.

Legislation to reduce energy consumption is already in place, starting with Legislative Decree 152 of April 3, 2006, which regulates environmental assessments, interventions, tools, and possible sanctions, however still needs to be implemented across many healthcare companies. The first to adopt sustainable practices must be healthcare personnel: it is estimated that employees' behaviors can reduce consumption by a few percentage points. To accelerate energy efficiency interventions, it is desirable to establish partnerships with the private sector where possible, due to significantly higher investment capacity and faster project execution. The provincial healthcare company of Caltanissetta, Sicily Italy [5], exemplified this by implementing a trigeneration plant, photovoltaic panels, and boiler replacement. The company's energy manager created synergies with private entities to complete all efficiency works by the end of 2024. It started with an energy assessment, considering both thermal and electrical energy profiles, annual and daily consumption, and potential consumption peaks. To estimate the effectiveness of the interventions, one must compare to the national average consumption cost per square meter. Based on all collected data and studies, the savings were calculated: in one year, Caltanissetta will save 450 tons of oil equivalent (toe), equivalent to removing 500 cars from the road daily. Additionally, a decalogue of good practices has been provided employees, enabling them to immediately adopt measures. A new hospital is also being designed, constructed with zero-impact materials and incorporating water recovery systems.

The green revolution has also involved the Western Friuli, Italy [6] healthcare company: the project began in 2022 and aims to achieve complete digitization of forms and administrative practices by 2025. The contract for integrated digital medical records in the two hospitals has already been awarded, electronic signatures have been adopted in departments for nurses and technicians, and desk printers have been abolished. Only one printer remains per floor within the facilities.

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The project includes the creation of a telemedicine room where doctors can be supported by technical and IT staff. This is also because digital training is lacking among today's doctors: there is a significant generational gap, but at the same time, future doctors and nurses will also need continuous updates on technological opportunities. The hospital of the future must consider experiences like the Mercy Virtual Hospital in Chesterfield, USA, which assists patients remotely through various telemedicine services. This model could be adopted to reduce numerous hospitalizations of elderly patients who could be managed through teleassistance and telemonitoring in other facilities or at home. To optimize resources, it would also be wise to consider reducing investments in favor of developing new solutions. However, this requires revisiting the standards that mandate the presence of at least one community hospital with 20 beds per 100,000 inhabitants.

Meanwhile, in Friuli, specialist outpatient clinics have been distributed throughout the territory: patients no longer need to travel for medical visits, but professionals move between various health districts, thus reducing travel distance and related emissions. Six years ago, the region initiated a tender that will result in the delivery of electric cars to the healthcare company. In line with the goal of reducing unnecessary travel, an agreement has been made with pharmacies for the delivery of vaccines to family doctors. Patients can book through the CUP (Single Booking Center) and find single-use items and dietary supplements. An agreement with the postal service is also being studied to handle administrative procedures there, so people do not have to physically visit healthcare company offices. Regarding public-private partnerships, this approach is being adopted for waste disposal.

The transition to sustainable healthcare requires a collective and timely commitment. As in all fields, it starts with the daily behaviors of everyone working within a healthcare company and extends to involving private partners, as well as adopting new strategies shared with local institutions and the government. It is an ambitious challenge to design healthcare that is more digital, equitable, and environmentally conscious, as well as an imminent challenge in light of the 2030 Agenda goals.

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Authors' contribution

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HEALTH PROMOTION

Vaccine Acceptance among travelers directed to areas with risk of dengue: a pilot study

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Keywords

Dengue • Vaccine hesitancy • Travelers • Prevention • Vaccine acceptance

Summary

Introduction. *Dengue is a vector-borne viral disease that causes a million of cases every year (including deaths). A tetravalent live-attenuated virus vaccine is available for this infection. The aim of our work was to study vaccine acceptance, attitudes and behaviors among travelers heading to areas with risk of dengue.*
Methods. *We conducted a cross-sectional study in February-April 2024 at the Travel Medicine Clinic of Rozzano (Italy), focusing on travelers directed to areas with risk of dengue. We collected the following information anonymously: travel destination, reason for travel, date/month of departure, length of stay, and accepted/refused vaccinations.*
Results. *58 travelers were included in our study and they chose 23 countries for their travel with a mean length of stay of 16.98 days. Five (8.62%) refused dengue vaccination because they considered the vaccination not necessary (80%), or for its cost (20%). There was no statistically significant difference between men and women in vaccination acceptance. Age and length of stay did not influence the percentage of refusals.*
Conclusions. *Although the results are limited by the small number of travelers, they highlighted the problem of vaccine hesitancy among travelers, and further efforts are needed to address this phenomenon.*

Introduction

Dengue is a vector-borne viral disease caused by the flavivirus dengue virus (DENV). Approximately 400 million cases and 22,000 dengue-related deaths occur worldwide each year. It has been reported in more than 100 countries in tropical and subtropical regions. A positive-stranded enveloped RNA virus (DENV) is principally transmitted by *Aedes* mosquitoes. It has four antigenically distinct serotypes, DENV-1 to DENV-4, each with different genotypes, three structural proteins and seven non-structural proteins [1].
In February 2023, the Italian Drug Agency (AIFA) authorized the use and marketing of TAK-003 (Qdenga®), a live attenuated tetravalent vaccine for the prevention of Dengue disease caused by all the virus serotypes. The vaccine also received approval from the European Medicines Agency (EMA) in December 2022 [2].
TAK-003 is based on a DENV2 backbone with recombinant strains expressing surface proteins for DENV1, DENV3 and DENV4. By using a backbone of DENV2 instead of yellow fever virus it has the potential to stimulate a broader humoral and cell mediated immunological reaction [3].
TAK-003 is administered as a subcutaneous injection, two doses with 3 months of interval. It is contraindicated in immunocompromised individuals, as well as in pregnant and breastfeeding women. It seems to be well tolerated and no serious adverse events reported [4].
TAK-003 induces antibody responses against all four serotypes of varying levels, highest for DENV2. The neutralizing antibody levels are higher in individuals with previous dengue fever compared to dengue naïve.
In 2024, the Italian Ministry of Health published a document named "Dengue - Global Update" [5] and, in the same year, the Italian Society of Travel Medicine (SIMVIM) formulated a list of indications to facilitate the healthcare workers in using dengue vaccine during their activity [6].
Several studies demonstrated that certain travel-related infections can be prevented through vaccination, however many travelers fail to seek or receive pre-travel vaccines. Several factors seem to contribute to the poor uptake of pre-travel vaccines such as low disease risk perceptions and vaccination costs [7-10], nonetheless, other determinants influencing individual travelers' decisions regarding pre-travel vaccination are largely unknown [11, 12].
Since January 30, 2024 the TAK-003 vaccine has been available in the Travel Medicine Clinic of Rozzano (ASST Melegnano Martesana).
The aim of our work was, therefore, to study vaccine acceptance, attitudes and behaviors among travelers directed to areas with risk of dengue.

Materials and methods

From February to April 2024, we conducted a cross-sectional study at the Travel Medicine Clinic of ASST Melegnano Martesana (Rozzano, Lombardy, Italy).

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We included adult travelers (≥18 years old) heading to areas with risk of Dengue. Travelers could be resident or domiciled in the Lombardy region and booked an appointment for counseling at the Travel Medicine Clinic of Rozzano, using an online reservation system. This system is used in Lombardy and allows travelers book an appointment for a counseling in the city/clinic with the lowest waiting times and the highest number of free slots. So we include in our study all the travelers who had an appointment at the Travel Medicine Clinic of Rozzano in the study period.
During the counseling, a travel medicine specialist gathered information about travelers' past medical history (including any underlying conditions or symptoms), informed them about the travel-connected risks and recommended malaria chemoprophylaxis and vaccinations, if necessary. Vaccinations could be accepted or refused by completing a consent form.

Statistics

Socio-demographic information (country of origin, age, gender) and other information such as travel destination, reason of the travel, date/month of departure, length of stay and the accepted/refused vaccinations were collected in an anonymous database.
From the answers percentages, means and standard deviations were calculated. Shapiro-Wilk test was performed to assess the non-normality of the variables "age" and "length of stay." Mann-Whitney test (for dichotomous variables), the Kruskal-Wallis test (for variables with more than two categories) and odds ratios were calculated to assess the relationship between dengue vaccination refusals and the collected variables. Data were processed using Stata SE, Version 12.1 (StataCorp, College Station, TX). The level of significance was set at $p < 0.05$.
The study was conducted in complete anonymity and approved by the Health Direction of ASST Melegnano Martesana (Vizzolo Predabissi, Milan, Italy).

Exclusion criteria

We excluded from the study travelers directed to areas not at risk for Dengue. The map of the areas with risk was retrieved from the CDC [13].
In accordance with the guidelines, we also excluded travelers who could not receive the vaccination for medical reasons (including women who were pregnant or breastfeeding) [14].
Information about the second dose was not collected due to the limited time span.

Results

From February to April 2024, we enrolled 58 adult travelers (50% female, 50% male). Their mean age was 42.15 years (SD 1.95); 98.27% were Italian. The destinations (and months) chosen from their travels are resumed in Table I.
Participants chose 23 countries for their travels; the most popular destinations were Thailand, Tanzania (including Zanzibar), Indonesia, Vietnam. The mean length of stay was 16.98 days (standard deviation 1.59), and the main reasons for travel were tourism (94.83%), work (3.45%), volunteering (1.72%). Travelers chose to go abroad principally in March, April, July and August.

Tab. I. Travelers' destinations and months chosen to travel.

	Destination	N	%
1	Angola	2	3.45
2	Antilles	1	1.72
3	Benin	1	1.72
4	Bolivia	2	3.45
5	Brazil	4	6.90
6	Cambodia	1	1.72
7	China	1	1.72
8	Colombia	3	5.17
9	Philippines	1	1.72
10	Ghana	1	1.72
11	Indonesia	5	8.62
12	Kenya	3	5.17
13	Madagascar	2	3.45
14	Mexico	2	3.45
15	Peru	2	3.45
16	Seychelles	2	3.45
17	Singapore	1	1.72
18	Sri Lanka	1	1.72
19	South Africa	2	3.45
20	Tanzania	7	12.07
21	Thailand	8	13.79
22	Uganda	1	1.72
23	Vietnam	5	8.62
	Month	**N**	**%**
	February	1	1.72
	March	11	18.97
	April	17	29.31
	May	2	3.45
	June	3	5.17
	July	10	17.24
	August	10	17.24
	September	4	6.90

Approximately 89.66% of our sample also received information about malaria chemoprophylaxis. Five travelers (8.62% of our sample) refused dengue vaccination especially because they considered the vaccination not necessary (80% of them) or for its cost (20% of them; the cost includes the price of the vaccine and the injection according to the regional price list). No one refused due to fear of side effects.
No one declared a past exposure to DenV virus or a past vaccination.
There was no statistically significant difference between men and women in vaccination refusals (p 0.64). Age and length of stay did not influence the percentage of refusal (all $p > 0.05$)
Table II shows the other vaccinations that travelers decided to accept and to refuse.

Tab. II. Vaccinations that travelers decided to accept and to refuse.

Vaccination	Considered sample	Accepted	%	Refused	%
Yellow fever	13	13	100	-	-
Typhoid fever	40	38	95	2	5
Hepatitis A	35	35	100	-	-
Polio	31	31	100	-	-
Diphtheria - pertussis - tetanus	24	24	100	-	
Men ACWY	9	7	77.78	2	22.22

Discussion

Traveling is inseparable from the modern way of life [15]. However, traveling to various places can expose people to infectious hazards. Moreover, other authors affirmed that travelers are potentially at higher risk of a broad range of infectious diseases and play a key role in their global spread [16].

Vaccine-preventable disease (VPD) in travelers are not limited to exotic diseases in developing countries. For example, a previous study demonstrated that non-immune adult US travelers are at significant risk of measles in wealthy, industrialized countries, including Western European countries and Mexico [17].

Vaccines protect the recipients at an individual level but also create a barrier against the transmission of infectious agents within the community. Both vaccines for tropical diseases and vaccines with routine indications can protect their recipients from infectious diseases associated with international travels [18].

Since the beginning of 2024 over two million dengue cases and over 500 dengue-related deaths have been reported globally. Most cases were reported in the WHO PAHO region with a cumulative number of 1 874 021 suspected cases reported until week 8 of 2024 (ending 25 February 2024). According to the PAHO report of 7 March 2024, this is an increase of 249% compared to the same period in 2023 [19].

Dengue is a mosquito-borne viral infection that has spread throughout the tropical world over the past 60 years and now affects over half of the world's population. The geographical range of dengue is expected to expand further due to ongoing global phenomena including climate change and urbanization [20].

In our study five travelers (8.62%) refused dengue vaccination.

Other studies demonstrated that the primary reason for refusing vaccines is a lack of knowledge about the severity of vaccine-preventable diseases [21].

However, vaccine hesitancy among travelers is influenced by the interplay of contextual conditions, individual characteristics, and specific factors related to vaccinations. Vaccine hesitancy is more prevalent in developed countries free of tropical diseases. Poor access to information or dissemination of inaccurate or incomplete data may construct an erroneous knowledge of immunobiological products. In this context, exaggerated accusations of the side effects and disparagement of the effectiveness of vaccines find fertile ground, especially among individuals with a lower educational level [22]. In our study, instead, no one refused for fear of side effects.

Lopes et al. observed that extreme cultural or religious motives may fuel reactions towards immunizations. Personality traits, political ideologies, idiosyncrasies, and the duration of travel are individual features that can affect the acceptance of the recommended vaccinations [22]. In our study, instead, age and length of stay did not influence the percentage of refusals.

Furthermore, the same authors affirmed that difficulties in the accessibility of the necessary services and products, including incompatibility of working hours, long distance, excessive waiting time, and high cost, may foster indifference towards vaccines, while past failures of immunization programs might shake travelers' confidence in vaccinations [22]. In our study, 80% of travelers who refused dengue vaccination considered the vaccination not necessary, 20% refused for its cost.

Similar evidence has been reported by Adongo et al. who observed that travelers' rejections of vaccinations are multidimensional constructs. Common reasons for the refusal of the recommended vaccines include doubts about their necessity, concerns about their safety, and cost issues. Ignorance of the risks of tropical infectious disease, as well as a lower level of education, fuels the omission of travel vaccinations. Other secondary dissuading factors may include mistrust against pharmaceutical companies and health authorities, anticipated pain from the injection, uncertainty about previously received vaccinations, lack of available time, and negligence for seeking appropriate pre-travel advice. Sometimes, the refusal of vaccines may be due to the belief that the recommended guidance limits personal autonomy and violates the sense of freedom that is often inextricably related to the procedure of traveling and the identity of travelers [23].

In our study there was no statistically significant difference between men and women in vaccination refusals. This is an unexpected result as women tend to refuse vaccination more than men [24, 25].

Among the other vaccinations that, in our study, have been proposed to travelers, meningococcal vaccine (ACWY) was the most refused (22.22%). This result is similar to what observed in other studies (but focused on pediatric population): in these studies parents considered this vaccination unnecessary. The explanation given by the opposing parents was the fear of side effects, poor information received and doubts about the actual efficacy of the vaccine [26, 27].

Limits

Our study has several limits. First, the limited time span: in fact it was impossible to collect information about the second dose acceptance. According to the vaccine schedule, the second injection is given 3 months after the first injection and our study was performed in February, march, and April so no one was eligible to receive the second dose.
The second limit was the number of enrolled patients: 58 travelers is a limited sample and it could not be representative of the entire population. Therefore, we encourage other authors to integrate our evidences with their findings.

Conclusions

Although the results are limited by the small number of participants, they highlight the problem of vaccine hesitancy among travelers. Despite the existing evidence of the value of vaccines in protecting public health, vaccine hesitancy represents a growing phenomenon. Achieving a wider vaccine acceptance could limit the spread of infectious diseases, and further efforts are needed to limit the phenomenon of vaccine hesitancy.

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Conflicts of interest statement

We declare no conflict of interest.

Authors' contributions

GT: had the idea of the article, analyzed data and wrote the article; IW: collected data and helped to conceptualize the ideas; AN: supervised the work and helped to conceptualize the ideas.

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COVID-19

Evolution of SARS-CoV-2 epidemics in pediatric population in Liguria (North-west Italy) from March 2020 to December 2022: what could we have learned?

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Keywords

SARS-CoV-2 • Pediatric population • Liguria

Summary

Introduction. *This retrospective analysis aims to follow the course of SARS-CoV-2 infections in pediatric population residing in Liguria, North-west Italy, from March 2020 to December 2022 and to relate it to the regional and national containment measures adopted, to assess the representativeness of the infection rate observed at the national level and to analyze the vaccination rates in different pediatric groups.*
Methods. *First episodes of SARS-CoV-2 infections registered in the national surveillance system were extracted and further anonymously analyzed for subjects aging ≤ 19 years. The absolute number of cases diagnosed daily during each year was compared to the number of residents in the region and graphical representations were used to visualize the trends in infection rates both annually and weekly in each year. Through narrative analysis, the relationship between changes in IR and key social events was analyzed. Applying the direct standardization method, the epidemiology of SARS-CoV-2 infection in pediatric population was compared with that observed in the same age group in Italy.*
All analyses were performed using Stata and Microsoft Excel.
Results. *In the study period, 106,537 (17.4%) cases of SARS-CoV-2 infection were registered in subjects ≤ 19 years, out of a total of 610,404 cases reported in Liguria during that period. In the summer of 2020 the IR was close to zero, while later we observed increases and decreases in the IR in relation to activities and social restrictions adopted. Direct standardization showed an almost perfect coincidence between the expected cases in Italy, based on the Liguria incidence, and the observed cases.*
Conclusions. *Our results show that, in absence of effective therapies and vaccines, strict non-medical interventions (e.g. use of masks, improving indoor ventilation, physical social distancing, general lockdown) can be the only actions to counter the spread of a respiratory infection.*

Introduction

SARS-CoV-2 is the etiological agent of the COVID-19 pandemic that began in China at the end of 2019 and subsequently spread around the world, affecting both children and adults. In Italy, as in all other parts of the world, the incidence of severe illness in the pediatric population was significantly lower compared to adults, with most pediatric patients exhibiting mild symptoms or even being asymptomatic [1]. Nonetheless, certain severe conditions, such as Multisystem Inflammatory Syndrome in Children (MIS-C), although rare, were observed with an epidemiology that followed that of the infection [2, 3].
The primary objective of this retrospective analysis was to follow the course of SARS-CoV-2 infections in individuals aged ≤ 19 years (pediatric population) residing in Liguria, Northwest Italy, from March 2020 to December 2022 and in relation to the regional and national containment measures adopted. Secondary, it aimed to assess the representativeness of infection rate observed in pediatric patients residing in Liguria at the national level and to analyze the vaccination rates in different pediatric groups. Regarding vaccinations, it should be noted that the vaccines were made available at the end of 2020 for people older than 18 years and in the first phase were administered to healthcare workers and fragile patients, while they were approved in June 2021 for the 11-17 age group and only in December for children aged 5-11. The vaccines have not been administered to children under the age of 5.

Materials and methods

First diagnosed episodes of SARS-CoV-2 infection registered in the national surveillance system [4] in Liguria, north-west Italy, from March 2020 to December 2022 were extracted and then further anonymously analyzed for subjects aging ≤ 19 years (pediatric population). This age cut-off was chosen to ensure that the entire school population was included up to the end of high school. In the first period, molecular tests based on RT-PCR (real-time polymerase chain reaction) were

Tab. I. Data and infection rate per 100,000 pediatric residents in Liguria by year.

Year	2020 (10 months)	2021	2022
Pediatric population, n	231,068	230,580	227,509
SARS-CoV-2 infections in pediatrics, n	6,867	18,957	80,713
Percentages of pediatric people with a first documented SARS-CoV-2 Infection, (95%CI)	2.97 (2.90-3.04)	8.22 (8.11-8.33)	35.48 (35.28-35.67)
Infection rate per 100,000 pediatric residents	2,971.85	8,221.44	35,476.84

mainly used to diagnose infection then, when antigenic tests became available and were equated with molecular tests, both were considered for diagnosis.

The absolute number of cases diagnosed daily during each year (March-December 2020, 2021, 2022) was compared to the number of residents in the region on January 1st of each year [5]. Graphical representations were used to visualize the trends in infection rates (infections per 100,000 residents, IR) both annually and weekly in each year. Through narrative analysis, we examined how changes in IR were related with key social events, such as containment measures and their modifications ordered by regional or national authorities, public activities such as crowds for recreational events and the opening or closing of schools.

The epidemiology of SARS-CoV-2 infection in pediatric population in Liguria was compared with that observed in the same age group in Italy [6], applying the direct standardization method.

Data on vaccinations were extracted [7] and the percentages of people who received a complete primary vaccination course according to vaccine type and age [8, 9] were calculated considering the age distribution of population in Liguria on January 1st, 2021 and 2022.

All analyses were performed using Stata [10] and Microsoft Excel.

Results

Between March 2020 and December 2022, 106,537 (17.4%) cases of SARS-CoV-2 infection were registered in population aged ≤ 19 years, out of a total of 610,404 cases reported in Liguria during that period. Table I reports the overall annual IR while Figure 1 describes the distribution of weekly IRs from March 2020 to December 2022, for the pediatric age in Liguria.

Distribution of residents and infections are further detailed in Tables SI and SII.

The percentage of population with a first documented SARS-CoV-2 Infection over the 3 years increased markedly starting from about 3% in 2020 and exceeding 35% in 2022 with an average of 15.6%, 95% CI (11.5-20.8). It should be noted that these data are underestimated because unreported/ undiagnosed cases were not included.

In the following analysis the IR is depicted yearly. The Figures 2, 3 and 4 are not directly comparable because different scales were utilized for each graph, for a clearer description of IR trends.

The year 2020. The IR trend is graphically depicted in Figure 2.

From March to May. On March 8th, the Italian government declared a nationwide lockdown, which included the closure of schools and an almost complete stop of public

Fig. 1. Weekly rates of SARS-CoV-2 infection in pediatric population residing in Liguria by age group, in the period 2020-2022.

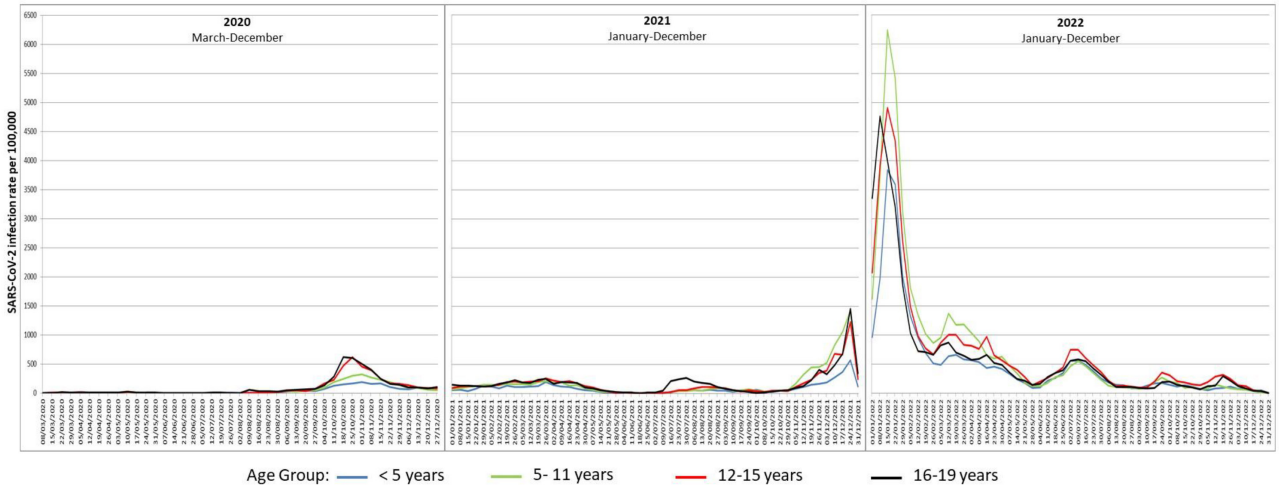


Fig. 2. Weekly rates of SARS-CoV-2 infection in pediatric population residing in Liguria by age group in 2020 (from March to December).

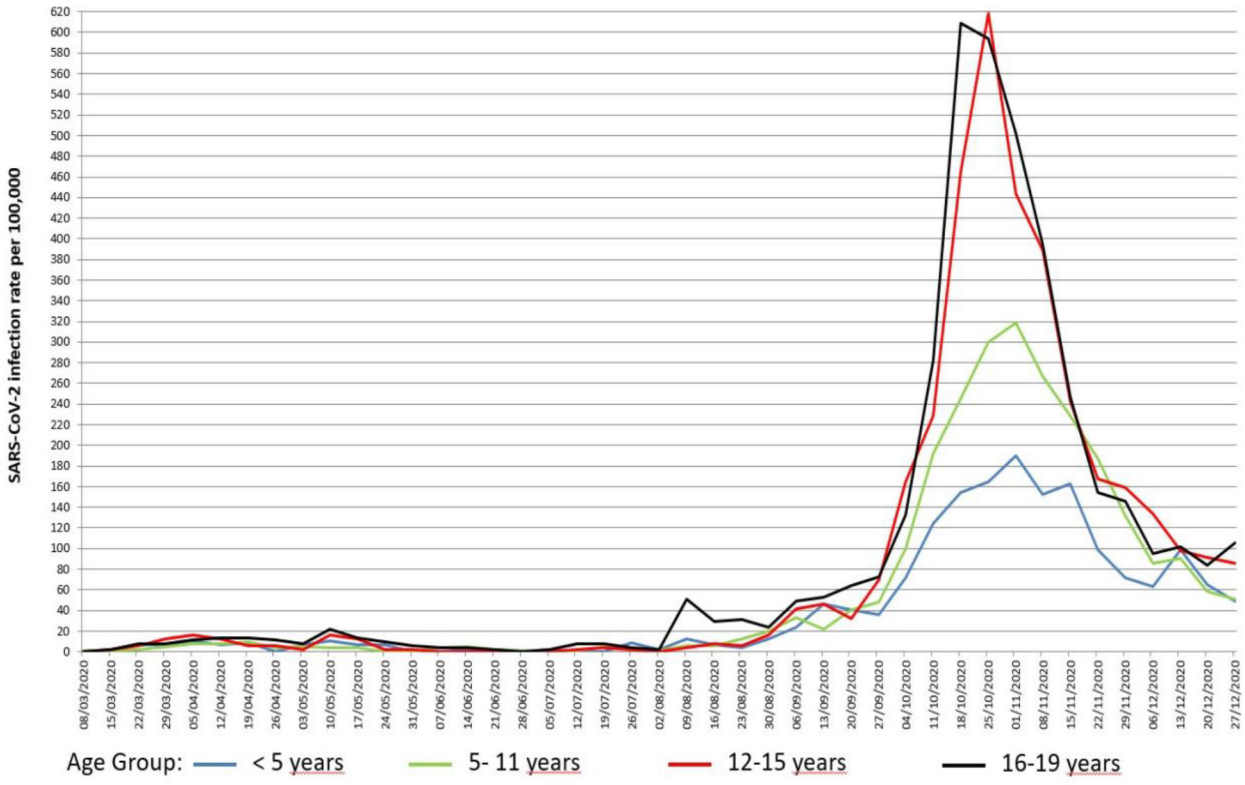


Fig. 3. Weekly rates of SARS-CoV-2 infection in pediatric population residing in Liguria by age group in 2021.

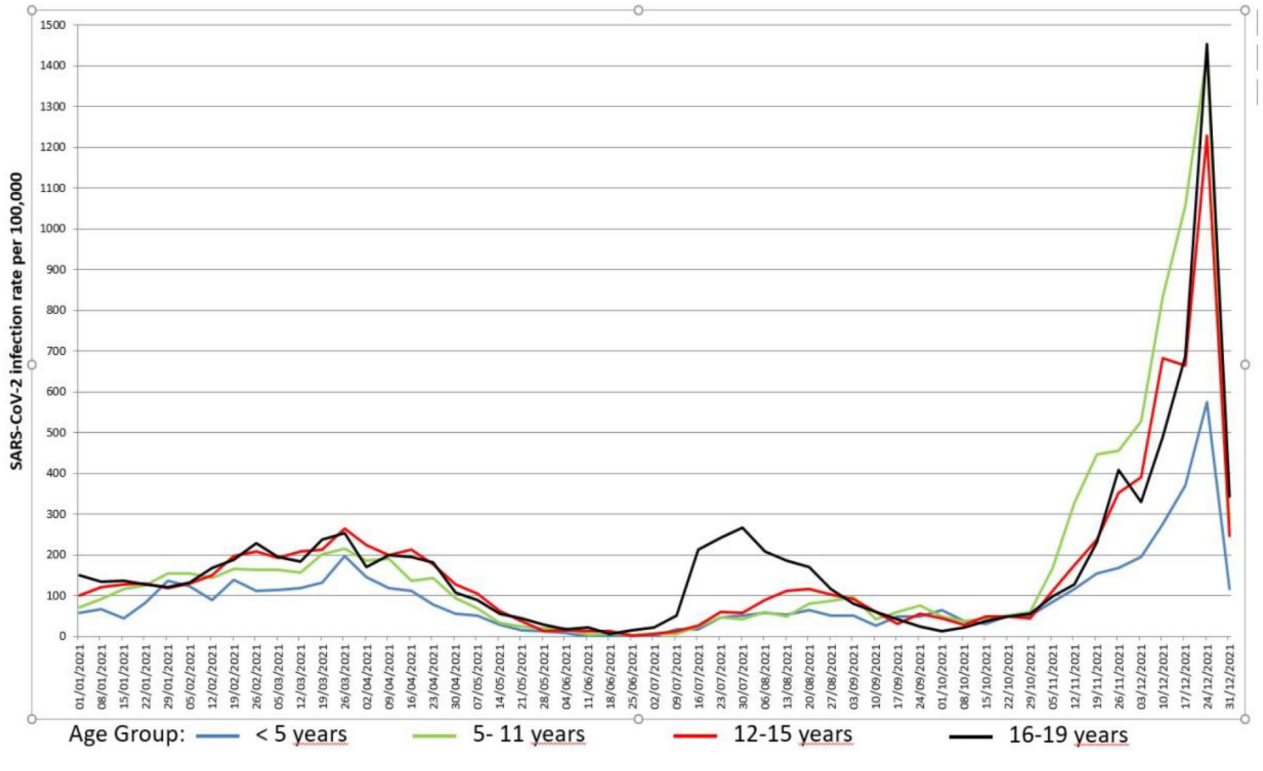


Fig. 4. Weekly rates of SARS-CoV-2 infection in pediatric population residing in Liguria by age group in 2022.

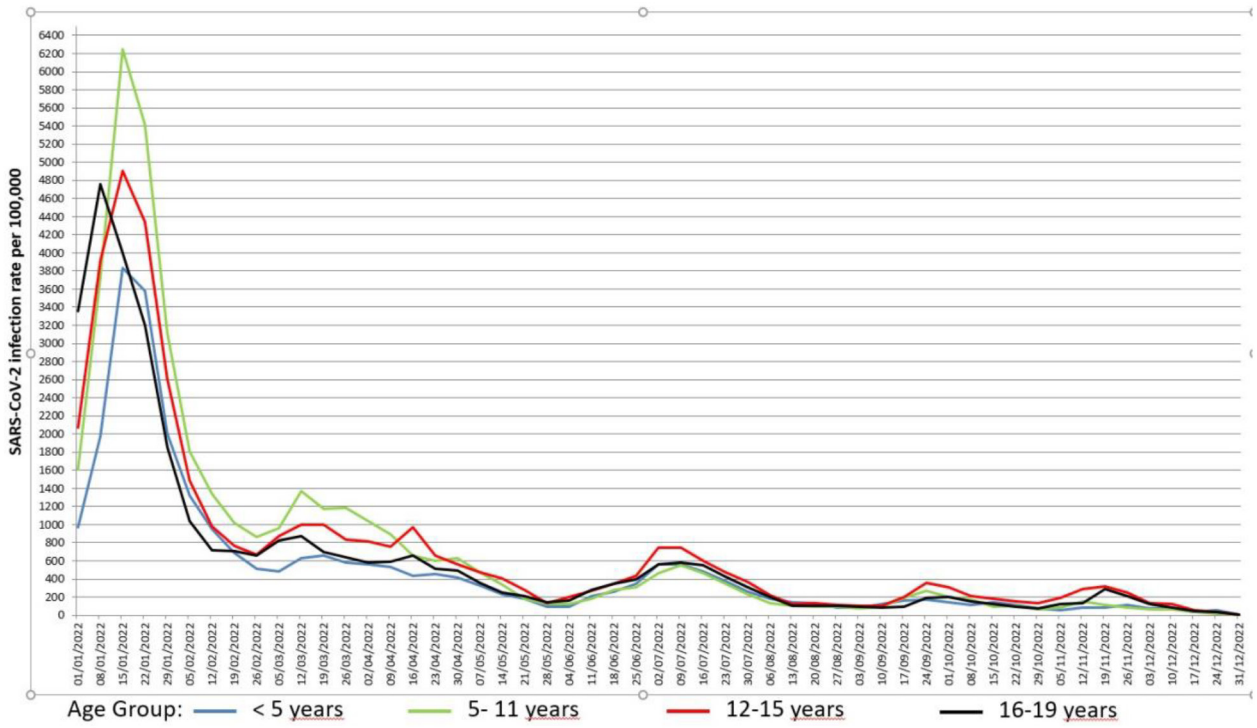
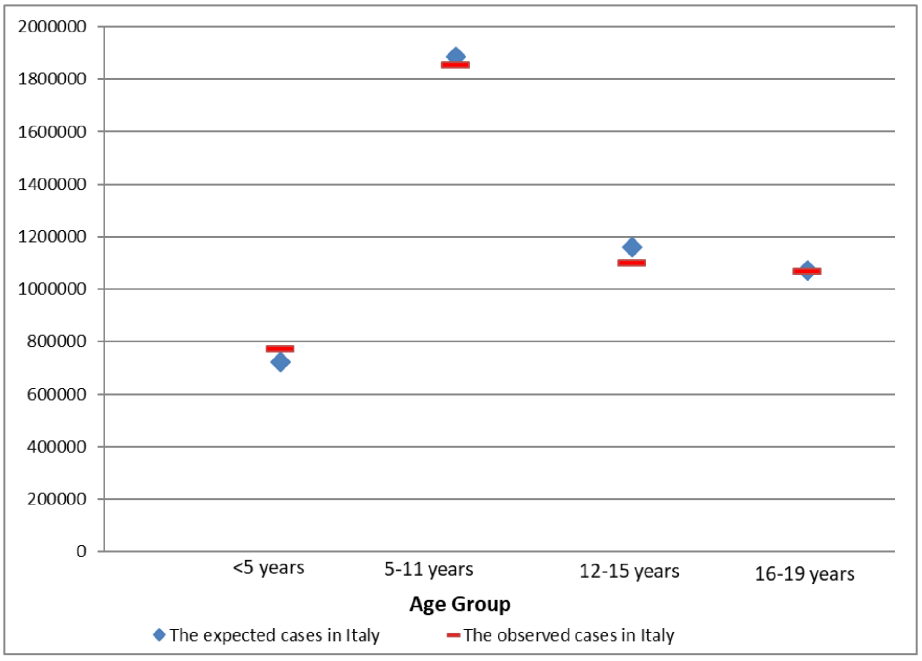


Fig. 5. Comparison of expected and observed SARS-CoV-2 infection cases in the Italian pediatric population according to the observed incidence in Liguria.



transportation, with no movement possible except for exceptional reasons. This first phase of the pandemic was characterized by an extremely limited availability of diagnostic tests, initially reserved for adults with severe clinical illness. Even when diagnostic tests became available in sufficient quantities, the number of children tested was small, mainly because of the very low clinical impact of the virus on the pediatric population. It is therefore plausible that the IR was largely underestimated during the first weeks of the pandemic. This consideration was true at least until May, when the availability of diagnostic tests improved significantly.

However, during these periods, the diagnosis of SARS-CoV-2 infection was still based only on molecular testing which likely underestimated the spread of the virus due to the difficulty in accessing testing.

From June to July. During this period the IR in the total and pediatric population showed values close to zero, with the consequent feeling in the public opinion that the epidemic at that time was now "behind us": the restrictions had been eased, with a gradual return to "normal" life. The ban on public gatherings, social distancing and the requirement to wear a mask indoors remained in force, while public transport could operate at 50% of its capacity. Noteworthy, even if the IR remained low throughout the summer of 2020, some epidemic clusters occurred in various parts of the nation, especially where prevention measures were not respected. For example, around mid-August holydays in Sardinia there was an epidemic cluster linked to gatherings of people without protective devices during events/parties in well-known nightclubs-discos.

From August to December. An increase of IR (60.3) was observed in 16-19 years old residents in Liguria from August 2nd, while the rate in other pediatric ages remained constantly low. From end of August 2020 the IR increased also in other age groups. This phenomenon could be related initially with an increase of the public transport capacity from 50% to 80% followed by the start of the new school year. From September 14th in-person teaching was activated for all classes in Liguria and the IR constantly increased in all ages group with a modest slowdown after 20th-21st September when regional elections were held, with polling stations opened in schools with consequent interruption of in-person teaching. The reopening of schools meant that thousands of students began attending school again, socialize in the school environment, but mainly outside school and on public transport. This was especially true for those in high school (12-19 years) even if an increase of IR could be observed for all pediatric ages. Consequently, new restrictions were adopted such as mandatory use of protective masks in closed places other than private homes and in all outdoor places; closure of all activities where people could gather (restaurants, theatres, cinema halls, gyms, swimming pools) from 6.00 pm. Furthermore, in Liguria, 75% of high school lessons switched to distance learning while elementary and secondary schools teaching remained in person. Public transport capacity decreased to 60%. After these measures there was a slight reduction in the IR in adolescents (Fig. 2, black line) not considered sufficient and not observed in the general population (data not shown). As a consequence of general epidemiology, a ban on outdoor circulation from 10.00 pm to 5.00 am was established, with travel permitted in this time slot only for work needs or proven health and necessity reasons; distance learning involved also secondary school, and the capacity of public transport was further reduced to 50%. Then, the curve, from the first days of November, reversed its dynamics and dropped rapidly over seven weeks, with a small flex for the 16-19 age group in concomitance with the Christmas holidays.

The year 2021. The IR trend is graphically depicted in Figure 3.

From January to October. From January 2021, a positive case of infection could also be defined by means of an antigen detection test (with sensitivity of at least 80% and a specificity 97% compared with that of RT-PCR), which, due to their simplicity and speed of execution, allowed better definition and control of the spread of the virus. Important limitations on travel and social life activities were introduced sporadically [mainly on New Year's Eve, January 1st and Easter (April 4th)]. Moreover, at the end of 2020 a nationwide vaccination program was implemented, starting with healthcare workers, followed by the general population in 2021. Noteworthy, in the second half of June (11th) the final phase of the European Football Championship began and the good performance of the Italian team led people (including many adolescents) to gather to watch the matches on large screens in the squares, in public places and in private homes, for quite long periods of time (2-3 hours for at least the last 3 matches) and to shout and hug in correlation with victories. This period was followed by an increase of the IR especially in the 12-19 years group. Then, the incidence continued to increase during the Olympic Games (weeks #29-31), although at a slower rate, since probably a smaller audience (and for shorter periods of time) crowded, despite the victories of Italian athletes in important competitions. In the following weeks the IR slowed down until the end of October.

From November to December. Starting in November, the IR began to rise again, with a dynamic completely different from that observed in the previous periods, reaching its highest peak of 2021 in all age groups, but especially in school-aged subjects, leading to further restrictions (requirement to wear masks in closed places). In this period the SARS-CoV-2 Delta variant was predominant, while the Omicron variant began to spread.

The year 2022. The IR trend is graphically depicted in Figure 4.

From January to December. From the beginning of 2022 the Omicron variant became predominant in Italy, but after the peak in January (IR > 6200) the IR decreased and restrictions were gradually removed.

How representative can these results be of Italian epidemiology in pediatrics? As shown in Figure 5, direct standardization shows an almost perfect coincidence between the expected cases in Italy, based on the Liguria incidence, and the observed cases.

The rates of vaccination. Starting from the last weeks of 2020, an anti SARS-Cov-2 vaccination campaign began in Italy, but pediatric patients were involved later and in different times (Tab. II).

Noteworthy, 68.1% of people aging 12-19 years received a complete cycle of vaccinations in 2021 versus 10.5% in 2022. This trend was more evident among adults, where the percentage was 82.8% in 2021 and only 4.1% in 2022.

Tab. II. Distribution of people who received a complete 1st vaccination course in Liguria by age group.

	Number of vaccinations/population (%)	
Age group	2021	2022
< 5 y	0/46,991	0/45,678
5-11 y	0/80,932	20,843/78,863 (26.4)
12-19 y	69,943/102,657 (68.1)	10,858/102,968 (10.5)
20-90+ y	1,066,108/1,287,915 (82.8)	52,125/1,281,718 (4.1)

Years: y.

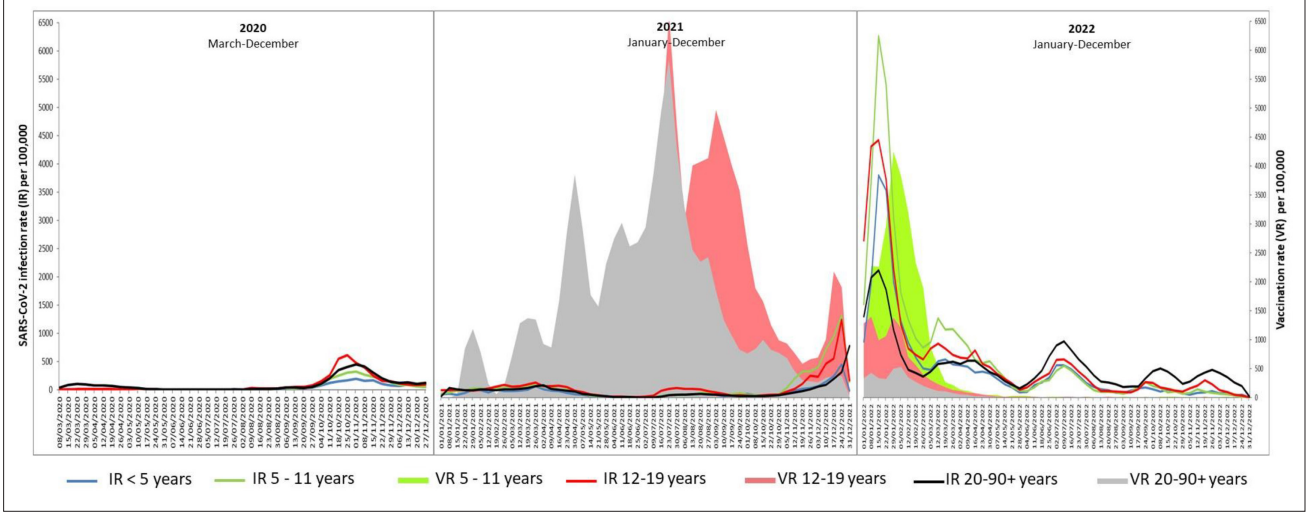
Figure 6 shows the SARS-CoV-2 infections and vaccinations rates per 100,000 residents in relation to the progress of the vaccination campaign for the different age groups. The highest rates of vaccinations were observed in 2 peaks at the beginning of the campaign for 12-19 years of age in 2021 and during the summer season, followed by a lower, third peak at the end of this year. At the beginning of the vaccination campaign for the youngest (5-11 years old), in the first four months of 2022, there was higher peak for this age group compared to both the adolescent/young (12-19 years old) and adult population.

Discussion

This retrospective study provides an overview of the first three years of the SARS-CoV-2 pandemic among pediatric residents in Liguria, northwestern Italy, and shows that approximately half of the pediatric population residing in this region had at least one documented SARS-CoV-2 infection by December 2022. Considering asymptomatic subjects or others not notified, it is likely that the prevalence of the infection is higher than reported in Italy and Western Europe in the same observation period [11]. Despite the relatively small population size in Liguria (resident population in January 2022 n = 1,509,277, population aged 0-19 years n = 227,509 (15.1%)), our results suggest that the trends observed in Liguria are representative of those across Italy in this population. Therefore, our results can be extrapolated to the broader Italian pediatric population and provide insight into management strategies for potential future pandemic respiratory infections in young people [12]. However, it is important to recognize a bias in the assessment of IR in the pediatric population during the early months of the pandemic due to the limited availability of diagnostic tests, which were primarily reserved for severe or symptomatic cases. As children and adolescents were often asymptomatic or had mild symptoms, this limitation may have contributed to an even greater underestimation of cases among them. Conversely, the reliability of IR data has increased with the improvement in testing capacity, particularly since mid-2020.

Our analysis shows a clear association between the incidence of SARS-CoV-2 in pediatric patients, especially adolescents, and specific gatherings and activities, such as sports events attended by large crowds and victory celebrations. This association underscores the role of certain events in facilitating the spread of the virus, as already highlighted [13]. Increased crowding on public transportation and the reopening of schools were also associated with rising IRs, suggesting that these settings played a significant role in the dynamics of transmission among adolescents [14, 15]. While transmission in pediatrics is likely to have occurred primarily within the family environment [16], schools have emerged as key sites for virus spread, as suggested by the observation of a higher incidence among school staff than in the general population, and particularly during periods of face-to-face teaching [14, 17]. The role of "social activities" is further confirmed by the increase of IR when the extra-scholastic containment measures were "relaxed" (December 2021-January 2022) [18, 20]. This period coincided in Italy with the replacement of the Delta

Fig. 6. Progress of the vaccination campaign (vaccination rate, VR) and infection rate (IR) of SARS-CoV-2 in the Ligurian population by age group.



variant by Omicron [21], which had a similar incubation period but a shorter generation interval [22, 23], further increasing the spread of the virus also in pediatrics. All these observations underline that, in absence of effective therapies and vaccines, only strict non-medical interventions such as promoting the use of masks, improving indoor ventilation, and advocating physical social distancing, up to general lockdown as an extreme measure, can be the only actions to counter the spread of a severe respiratory infection [18, 20]. However, these measures have come at a significant cost to human well-being, particularly in the pediatric population and especially in adolescents [24]. These aspects, with their pros and cons for the health of society, should be kept in mind in the future to identify the most appropriate control measures in the event of a new respiratory virus pandemic [12].

Final considerations must be made for vaccination programs, which represent a pivotal strategy for controlling infections. In Italy, vaccination against SARS-CoV-2 for young people started at the end of 2021 for those aging ≥18 years, but became available in June for those aged 12 to 18 years and only in December 2021 for children aged 5 to 11 years. There were differences in vaccination rates between the two groups of vaccine-eligible pediatrics, as observed in other series [26, 27], with subjects aged 12-19 years having higher rates, likely due to factors such as accessibility, peer influence, personal autonomy, and high educational background and family vaccination rates [27, 28]. In contrast, vaccination rates among children aged 5-11 years remained lower, as previously reported [29, 30], likely influenced by parental decisions shaped by concerns about safety, efficacy, and misinformation. Vaccination programs represent a central strategy for controlling infectious diseases, but the complexity of decision making, influenced by individual motivations, peer influence, and parental concerns, underscores the need for targeted public health initiatives to improve vaccine uptake in all age groups.

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The study does not require approval by an ethics committee (public data).

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MM, FB, RS, EC, CS, GI: conceptualization and methodology; MM, FB: data collection, analysis and interpretation; writing-original draft preparation: MM, FB, RS, EC, CS; writing-review and editing: MM, FB, RS, EC, CS, GI, IG; supervision MM, FB, RS, EC. MM and FB contributed equally to data collection, analysis and interpretation. All authors have agreed to the published version of the manuscript.

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Infectious Diseases

Epidemiological Analysis of Cases of Animal Bite Injuries at Rabies Prevention Centers Affiliated with Iranshahr University of Medical Sciences

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Keywords

Epidemiology • Animal bite • Dogs • Humans • Iranshahr

Summary

Objective. *Rabies remains a significant public health threat, particularly in developing countries. This study aimed to analyze the epidemiological characteristics of animal bite injuries in Iranshahr, Iran, from 2019 to 2021.*

Methods. *A descriptive analysis was conducted on 6,085 animal bite incidents reported to Iranshahr University of Medical Sciences' rabies prevention centers between April 2019 and March 2021. Data collected included demographic information (age, gender, occupation, nationality), type of animal involved (dog, cat, etc.), timing of the incident, injury severity, and treatment received. Statistical analysis was performed using SPSS version 19, ArcGIS version 10.8.2, and Excel 2019.*

Results. *The average age of victims was 25.22 years, with males constituting 66.9% of cases. A significant majority (67.1%) of bites occurred in rural areas, and 38% of victims were under 19 years old. Dogs were responsible for 89.8% of bites, followed by cats at 5.2%. The highest incidence was noted in spring (30.8%). The cumulative incidence rate was 151 per 100,000 population, peaking at 253 per 100,000 in Rask City and dropping to 131 per 100,000 during the first year of the COVID-19 pandemic. Among the sampled animals suspected of rabies, eight were confirmed positive.*

Conclusions. *The findings indicate that school-aged children and adolescents are particularly vulnerable to dog bites, highlighting the need for targeted educational programs. The presence of confirmed rabies cases in animals underscores the necessity for comprehensive control measures, including stray dog management and vaccination initiatives for domestic pets.*

Introduction

The incidence of animal bites presents a considerable public health challenge, not only due to immediate health consequences, but also due to potential economic burdens on nations. These bites, often resulting from interactions with pets, domestic, or wild animals, carry the risk of transmitting the rabies virus, particularly in regions where rabies is endemic [1, 2]. Dogs are the predominant contributors to human-animal bite injuries, constituting over 90%, followed by cats, humans, and rodents [3, 4]. In low-income countries, dogs are major culprits, leading to increased rabies prevalence and higher fatality rates, exacerbated by limited access to anti-rabies post-exposure treatment [1, 5]. The global human mortality attributed to canine rabies is staggering, reaching an estimated 60,000 annually, with Asia and Africa bearing a significant burden, particularly in rural areas [6].

Despite the evident severity, rabies control measures face underinvestment in affected countries, largely attributed to the lack of reliable data and limited awareness regarding the disease's burden and associated risk factors [7]. The escalating number of animal bites necessitates increased governmental procurement of vaccines and medicines, imposing a financial burden on health budgets, as exemplified in Iran, where a significant portion is allocated for rabies prevention [4, 8]. The annual cost of rabies vaccination in Iran highlights the financial strain, totaling 12 million dollars for rabies prevention treatment [9]. Notably, the majority of reported animal bites, exceeding 10 million cases annually, are concentrated in Asia and Africa, with dogs being the primary source [10].

The indigenous presence of jackals in Iran's wildlife has been a longstanding source of infection for domestic animals [5, 11]. Additionally, the country employs an early prevention and treatment system, irrespective of the rabies virus carrier status in animals, to prevent the disease. Despite efforts to strengthen healthcare and control rabies, it remains a significant endemic disease and a major public health challenge nationwide, with rising incidence reported in all provinces [12]. The COVID-19 pandemic has globally heightened rabies cases and mortality with disruptions during quarantine potentially leading to underreporting of zoonotic cases

and delays in addressing suspected rabid dogs [13, 14] Reduced vehicular traffic during quarantine has extended the survival time of stray dogs, evading potential collisions with vehicles. Overall, numerous disruptions in rabies control during the COVID-19 pandemic have notably affected low-income countries [13, 14].

The lack of epidemiological information hinders disease prevention and control efforts. Understanding factors contributing to health challenges, transmission modes, prevention strategies, and the prevalence of gasping syndrome, along with associated mortality due to climatic and population differences, is crucial [7]. Particularly vulnerable are specific regions, notably border provinces like Sistan and Baluchestan, characterized by potential local virus exchange between animals in neighboring countries and Iran [4]. This highlights the need for increased attention to this infectious disease, especially in southeast Iran. Political will and inter-sectoral coordination are vital for enhancing surveillance systems to control the disease effectively. Implementing interventions to prevent animal selectivity and reduce the burden on the healthcare system can significantly aid relevant authorities [1, 7].

Animal bites, especially those leading to rabies, pose a significant public health threat in many regions, including Iranshahr. Understanding the epidemiological patterns of animal bites is crucial for developing effective prevention and control strategies to mitigate the risk of rabies transmission. By providing insights into the demographic characteristics of individuals bitten by animals, the types of animals responsible for bites, and the temporal and spatial patterns of incidents, this study contributes to the broader body of knowledge on animal bite epidemiology. Such information can be used to guide future research and inform public health practice in similar settings. Therefore, this study was conducted to determine the epidemiological patterns of animal bite in Iranshahr, southeast of Iran during the years of 2019 to 2021.

Methods and materials

Study design

In this descriptive study, a total of 6085 instances of animal bites were systematically documented National Rabies Surveillance System over a three-year timeframe (2019-2021). The comprehensive data collection occurred within the rabies prevention centers affiliated with Iranshahr University of Medical Sciences, spanning across 12 registered counties. Compilation of the dataset was carried out by extracting data from the records maintained by animal bite treatment Center. The study participants comprised all individuals who sought medical attention for animal bites during the stipulated period, undergoing a spectrum of preventive, therapeutic, and follow-up interventions within the specialized rabies prevention and treatment units. Moreover, an individual case of animal bite was operationally defined as an individual seeking care at the rabies unit due to both an actual animal bite and the presence of fear concerning rabies infection.

Data Collection

Data collected from selected animal bite cases are organized into three sections: temporal and spatial trends of incidents, and the occurrence details, differentiated by the covered counties and the location of incidents (urban or rural areas). The type of events leading to animal bites, such as provoking animals, sudden attacks, contact with a suspected rabid animal, defense against an attacking animal, and engaging in play or feeding animals, along with the number of injuries and the owner's information, constitute the second section. This part includes demographic data and healthcare measures undertaken for animal bite cases, such as age, gender, occupation, nationality, and patterns of health services received for the bitten individuals (washing with soap and water, wound disinfection, dressing, suturing, serum therapy, and vaccination). The examination of the serum injection time (for timeliness and delay status), assessment of previous rabies vaccination history, the number of wounds (single, double, triple, or more than three wounds or injuries), and the pattern of injuries (day, month, and year) are also included. The third section pertains to information on actions taken for the attacking animals, encompassing the type of animal (dog, cat, wildlife, or domesticated animals), the type of dog and cat (owner or stray), the status of the bitten animal after the incident (killed, alive under care), and the sampling status from the attacking animal (conducted or not conducted). The outcome of the test for the attacking animal is also documented.

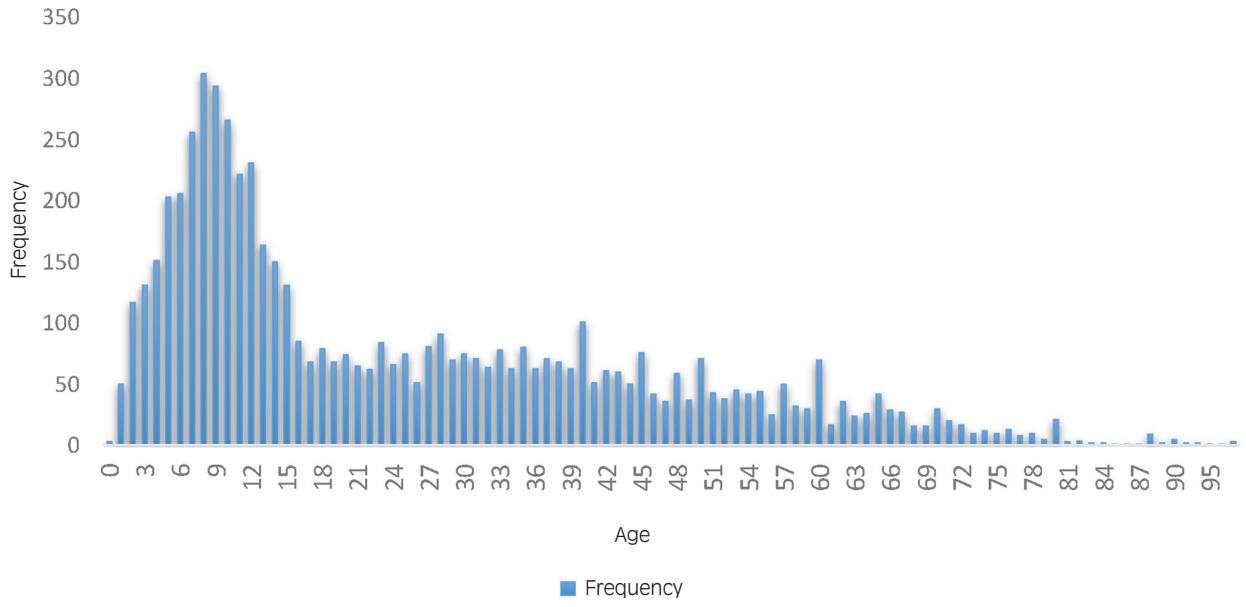
Statistical analysis

Using SPSS 19 software, data analysis was performed, employing descriptive statistics such as mean and standard deviation. Subsequently, frequency tables and percentages were generated to illustrate relative frequencies. The association between age and gender was examined using an independent t-test. Moreover, the Cochran-Armitage trend test was utilized to evaluate the incidence over three years based on the year. Furthermore, ArcGIS 10.3 and Microsoft Office 2019 will be utilized for mapping the distribution and generating visual representations. The significance level was set at $p < 0.05$.

Results

Of the 6085 injured patients in the study, the mean age of the victims was 25.22 ± 20.14. The age range of the injured individuals varied from 1 to 100 years and 2562 cases (42.10%) under 15 years (Fig. 1). There was no significant difference between the mean age of men (22.8 years) and women (30.11 years) ($p = 0.76$). In this study, the annual incidence of animal bites per 100,000 population was examined for the years 2019, 2020, and

Fig. 1. The frequency of animal bite cases according to the age.



2021. The respective incidences were 199, 131, and 143 for each year, respectively. The Cochran-Armitage trend test was employed to assess the trend in animal bites incidence before and after the COVID-19 pandemic. The results indicated a statistically significant trend ($p < 0.001$) in both periods.

Iranshahr city had the highest frequency with 1144 (18.8%) cases. However, in the three-year cumulative incidence, the cities of Rask (253/100000) and Bampur (240/100000) showed the highest cumulative incidence (Fig. 2). 4478 (73.7%) cases of bites were reported as a sudden attack by an attacking animal, with only one case reported as a result of contact with an animal suspected of rabies. The highest frequency of injuries related to one injury was reported at 3001 (49.3%). Additionally, the frequency of bites in rural areas was reported to be 4083 (67.1%), higher than in urban areas at 2002 (32.9%). Finally, 641 (10.5%) of the bites were from the owner of an attacking animal, with the remaining cases being 5444 (89.5%) individual cases other than the owner of the animal (Tab. I).

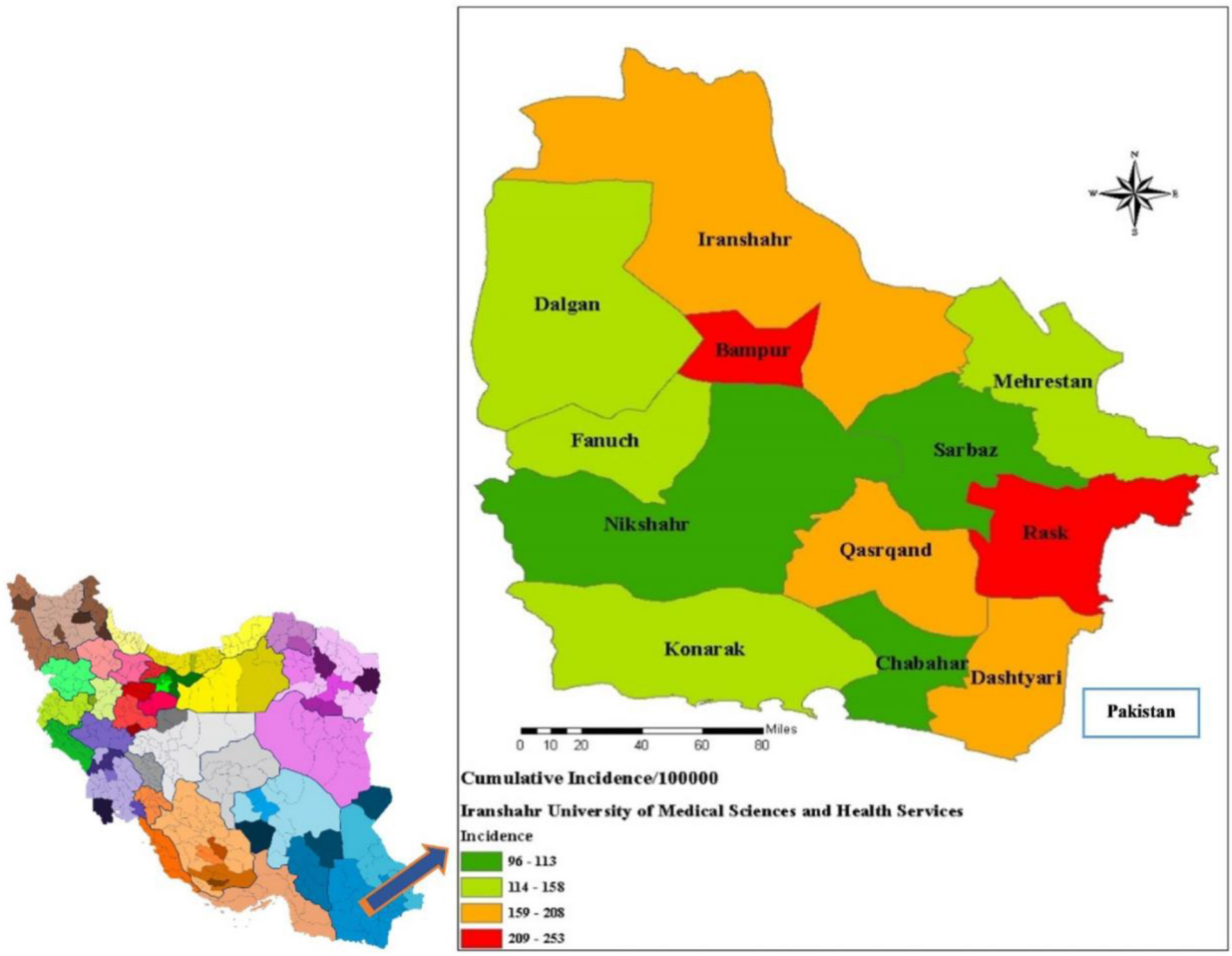
Most of the observed wounds, 6029 (99.1%) were washed with soap and water, while in 56 cases (less than 1%) this process was neglected. In the disinfection of the bite site, 752 (12.4%) cases were not disinfected. It is worth mentioning that 83 (1.4%) cases required stitches, and this procedure was performed in 13 cases. Regarding the delay of vaccination, 5790 (95.2%) cases were referred with a delay of less than 48 hours (timely referral). Out of the total cases of animal bites, only 15 cases did not require vaccination. In addition, 2080 (34.2%) of the reported bites received treatment with serum. Out of these, 10 individuals were administered serum 4 to 7 days post-bite, while 1858 (89.2% of serum-treated cases) received serum within 12 hours of the bite. Furthermore, 4071 (66.9%) cases were male, and 2014 (33.1%) were female. Among the affected occupations, students accounted for the highest frequency of 2315 (38%) cases. There were 118 (1.9%) non-Iranian cases and the remaining 5967 (98.1%) were Iranian cases. Only 70 (1.2%) cases had a history of prior rabies vaccination (Tab. II).

Dogs were responsible for the majority of bites, accounting for 5,462 (89.8%), while wildlife animals caused 189 (3.1%) bites during the three-year period. It is important to highlight that 4,397 (72.3%) of the bite incidents involved the owner's dogs, and 110 (1.8%) of the attacking animals were either bitten by people or killed by onlookers. A total of 14 animals were examined, with 8 confirmed as having animal rabies by the Pasteur Institute of Iran. Furthermore, based on the data collected, 7 (1%) of the infected animals exhibited symptoms and passed away. Additionally, 3,657 (60.1%) cases of invasive animals were either not tracked or had an unknown outcome (Tab. III).

Discussion

The results of this study have shown, animal bite incidents constituted 30.7% of cases before the COVID-19 pandemic, indicating a significant public health issue. During the pandemic, there was a slight increase in the number of animal bites, which warrants further investigation of the factors contributing to this trend. According to a similar study conducted in India, there was an increase in cases of animal bites during the COVID-19 pandemic in the second to tenth week [13]. The increase observed during the pandemic is consistent with findings in other regions, suggesting that animal behavior may have changed during the pandemic [15, 16]. Geographically, Iranshahr city emerged as a hotspot,

Fig. 2. The cumulative incidence of animal bite per 100,000 population in Iranshahr.



Tab. I. The status of the temporal and spatial trend of animal bite cases.

Variable	Category	Frequency	%	Variable	Category	Frequency	%
The year of the bite	2019	2526	41.5	The cause of the bite	Harassing the animal	676	11.1
	2020	1688	27.7		Sudden attack	4478	73.6
	2021	1871	30.7		Contact with an animal suspected of rabies	1	0.0
City	Iranshahr	1144	18.8		Defense against with the animal	267	4.4
	Bampur	484	8.0		Care of the game and feeding the animal	663	10.9
	Chabahar	808	13.3	Number of injuries	1 injury	3001	49.3
	Dashtyari	370	6.1		2 injuries	1845	30.3
	Dalgan	355	5.8		3 injuries and more	1239	20.4
	Rask	504	8.3	Bite of the owner of the animal	Yes	641	10.5
	Mehrestan	326	5.4		No	5444	89.5
	Sarbaz	679	11.2	Bite area	City	2002	32.9
	Fanoj	256	4.2		Village	4083	67.1
	Qasrqand	374	6.1				
	Konarak	344	5.7				
	Nikshahr	441	7.2				

contributing 18.8% of cases, emphasizing the need for targeted urban interventions. In a study conducted by Sarani in Iranshahr, 54.4% and 54.6% of cases were reported in the cities and villages, respectively [17]. Rask and Bampur cities were identified as areas with the highest cumulative incidence, which require tailored

Tab. II. Demographic information and measures taken for animal bite cases.

Variable		Frequency	Percent	Variable		Frequency	Percent
Washed with soap and water	Yes	6029	99.1	Gender	Man	4071	66.9
	No	56	0.90		Female	2014	33.1
Disinfection of the bite site	Yes	5333	87.6	Job	Health and medical worker	21	0.30
	No	752	12.4		Veterinary personnel	4	0.10
Dressing the bite site	Yes	83	1.4		Employee of other departments	114	1.9
	No	6002	98.6		Rancher/Farmer	249	4.1
Stitch the bite	Yes	13	0.20		Housewife	1177	19.3
	No	6072	99.8		Student	2315	38.0
Zero round vaccination delay	40 days and more	3	0.0005		University student	25	0.40
	11 to 20 days	11	0.20		Child	655	10.8
	4 to 10 days	82	1.3		Other jobs	1525	25.1
	48 to 72 hours	184	3.0	Nationality	Iranian	5967	98.1
	Less than 48 hours	5790	95.2		Non-Iranian	118	1.9
	No need for vaccination	15	0.20	History of rabies vaccination	Yes	70	1.2
Serum injection time	4 to 7 days after the bite	10	0.20		No	6015	98.8
	12 to 72 hours after the bite	212	3.5	Perform serum therapy	Yes	3265	53.7
	Less than 12 hours after the bite	1858	30.5		No	2820	46.3
	No need for serum therapy	4005	65.8				

Tab. III. Determining the occurrence of bites and the condition of the attacking animal.

Variable		Frequency	Percent	Variable		Frequency	Percent
Type of attacking animal	Dog	5462	89.8	Sampling the invasive animal	Yes	14	0.20
	Cat	315	5.2		No	6071	99.8
	Wildlife animals	189	3.1	Test result	Positive	8	0.10
	Domestic pets	119	2.0		Negative	6077	99.9
Type of dog and cat	The owner	4397	72.3	Follow-up status of the attacking animal	Symptoms and death	7	0.10
	The tramp	1688	27.7		With no sign	2421	39.8
The state of the attacking animal	Killed	110	1.8		Untracked/uncertain	3657	60.1
	Alive/abandoned	5975	98.2				

prevention measures. Particularly, rural areas were burdened with 67.1% of cases, emphasizing the unique dynamic of animal-human interactions, which aligns with other studies across the country that emphasize the universal value of context-specific interventions and consistent challenges [4, 5].

According to this study, most wounds were cleaned with soap and water, which highlights the importance and effectiveness of this cleaning procedure in reducing rabies transmission risk. The finding that less than 1% of cases did not undergo cleaning is concerning. A study conducted by Savu et al. [3] suggested that wound management protocols and guidelines might not be followed, potentially compromising wound care efficacy and safety. Moreover, in 12.4% of cases, the bite site was not disinfected. Numerous studies have shown that proper disinfection of the bite site is crucial for reducing the risk of rabies infection and transmission [18, 19]. As a result, improved disinfection protocols are necessary, particularly in Iranshahr, a rabies-prone area. Additionally, suturing was reported in 1.4% of the cases, which may be necessary for certain types of wounds or in cases where there is significant tissue damage. Nevertheless, suturing alone cannot prevent rabies transmission, and disinfection and immunization procedures must also be followed to ensure that the virus is not transmitted [20]. Out of the total sample, 40 days or more, 11 to 20 days, and 4 to 10 days of vaccination delays were observed for 3 people, 11 people, and 82 people, respectively. Delays in treatment can have a significant impact on the prognosis and outcome of rabies infection [19, 21]. Therefore, when bitten by a potential rabies carrier, individuals should receive timely and appropriate vaccinations.

In 53.7% of bite cases, serum treatment was administered, indicating that a high number of victims sought medical attention and received the necessary treatment. The gender distribution among the bitten

individuals revealed that 66.9% were male, highlighting men's higher susceptibility to dog bites. The gender distribution of animal bites was found to be consistent across various investigations. For instance, studies conducted in Iran [2, 4, 8], and southern India [22] all reported a higher proportion of men affected, likely due to occupational exposure and increased contact with biting animals. Moreover, the pattern of students being the most affected occupational group (38%) suggests that this demographic group may be at higher risk of dog bite injuries. The results of this study align with previous research, demonstrating that students engage in more interactive behavior with animals, leading to a higher likelihood of animal bites [2, 4]. Approximately 1% of animal bites were attributed to non-Iranians, since non-Iranians may be less familiar with local wildlife and the precautions necessary to avoid animal bites.

In the study, dogs accounted for 89.8% of bite incidents; in contrast, wildlife animals were responsible for just 3.1% of reported cases. Furthermore, the majority of bites were caused by owned dogs, accounting for 72.3%. A study conducted by Fragoso et al. (2022) found that 87.2% of dog bites occurred in comparison to other forms of animal aggression [23]. Another similar study found that owned dogs played an important role in the epidemiology of dog bites, further supporting their dominance [24]. Out of 14 animals sampled, eight were confirmed by the Pasteur Institute of Iran to be positive for animal rabies; additionally, seven cases of the attacked animals showed symptoms and ultimately died. The deaths of seven animals further highlight the importance of this issue and the need for further investigation and control. In 73.6% of the cases, sudden animal attacks were responsible for the bites, while 43% were recorded as injuries, and 10.5% involved an attacking animal attacking its owners. By examining other studies that have also focused on animal attacks, similarities and differences can be observed. Previous studies demonstrated a high incidence of bites on owners of attacking animals, which suggests there may be underlying factors influencing the nature of these interactions, which suggests further investigation is warranted [16, 25].

The strength and limitation of study

The purpose of this study was to analyze the epidemiological patterns of animal bites in Iranshahr, an area in which there has been limited research in the past. The dataset of over 6,000 cases across three years provides a solid basis for studying factors affecting bite incidents. Additionally, the use of ArcGIS for spatial mapping adds value by identifying geographical hotspots for animal bites, representing a novel approach in this field. This study relies on data collected by rabies prevention centers, which may not capture all cases of bites, particularly those that do not seek medical attention. The findings may also be context-specific to Iranshahr and might not be applicable to other regions with different conditions. Lastly, there is a potential bias towards more severe cases, as milder instances may be underrepresented.

Conclusions

In conclusion, educational programs must prioritize school-aged children and adolescents to reduce the incidence of animal, particularly dogs, bites. Additionally, organizations involved in rabies control should focus on implementing comprehensive control programs, including the relocation of stray dogs and widespread vaccination of owned dogs, to effectively address the issue of confirmed rabies cases in animals. The frequency and severity of animal bites may vary across different geographic areas and populations. Factors such as population demographics, pet ownership, and behavior, can significantly impact bite incidents.

Public health policymakers should consider these contextual factors when attempting to prevent dog bite incidents and ensure public safety. In order to do so, responsible pet ownership and adequate education regarding responsible dog ownership should be taken into account. Therefore, the results of this study can inform public health policies and interventions aimed at reducing the incidence of animal bites and improving the management of individuals bitten by animals. This includes targeted educational programs, vaccination campaigns, and measures to control stray animal populations. Veterinary and public health services should work together to develop regular vaccination and sterilization programs for stray animals in order to decrease the number of animal bite cases. Furthermore, community engagement and awareness campaigns should emphasize responsible pet care, the dangers of stray animals, as well as bite prevention strategies, particularly in high-risk areas.

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Ethics approval and consent to participate

In accordance with ethical guidelines, all data extraction procedures adhered strictly to ethical standards. Data were collected without the inclusion of any personally identifiable information. Furthermore, during the analysis phase, the data were aggregated to ensure anonymity and confidentiality of the participants. This study protocol has been approved by the ethical committee of Iranshahr University of Medical Sciences under code number: IR.IRSHUMS.REC.1402.009.

Data availability

The results drawn from this study are sufficiently supported by the data in the article and its appendices, as acknowledged by the authors.

Conflicts of Interest statement

None.

Funding/Support

None.

Authors' contributions

HK: conceptualization; data curation; methodology; investigation; writing-review & editing. VR: conceptualization; methodology; formal analysis, project administration; supervision; writing-original draft; writing-review & editing. MJ: data curation; methodology; formal analysis, investigation; writing-review & editing. AB: data curation; methodology; formal analysis, investigation; writing-original draft. AP: data curation; investigation; writing-original draft.

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Non Comunicable Diseases

Global Disparities in Colorectal Cancer: Unveiling the Present Landscape of Incidence and Mortality Rates, Analyzing Geographical Variances, and Assessing the Human Development Index

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Keywords

Incidence • Mortality • Colorectal cancer • Geographical disparities • Human Development Index

Summary

Background. *Colorectal cancer poses a major global health threat, with increasing incidence and mortality rates worldwide. This study examined the incidence and mortality rates of colorectal cancer globally in 2020 and explored the relationship with the Human Development Index (HDI).*

Material and methods. *This research utilizes data from the International Agency for Research on Cancer's (IARC) GLOBOCAN 2020 project, an esteemed source of up-to-date international cancer statistics. Age-standardized incidence rates (ASIR) and age-standardized mortality rates (ASMR) per 100,000 individuals were calculated. The association between ASIR, ASMR, and the HDI was analyzed using Pearson correlation, considering a statistical significance threshold of $p < 0.05$.*

Results. *In 2020, a total of 1,931,590 new colorectal cancer cases were recorded globally, with a male predominance of 55.18%. The global colorectal cancer ASIR was 19.5 per 100,000 (23.4 in males, 16.2 in females). Furthermore, there were 935,173 colorectal cancer-related mortality, with males accounting for 55.13%. The overall colorectal cancer ASMR was 9 (11 in males, 7.2 in females). A strong positive correlation emerged between ASIR and ASMR (0.895, $p \leq 0.001$), HDI (0.794, $p \leq 0.001$), life expectancy (0.724, $p \leq 0.001$), education (0.743, $p \leq 0.001$), and income (0.706, $p \leq 0.001$). Similarly, positive correlations were also found between ASMR and HDI (0.638, $p \leq 0.001$), life expectancy (0.569, $p \leq 0.001$), education (0.631, $p \leq 0.001$), and income (0.512, $p \leq 0.001$).*

Conclusions. *This global analysis highlights rising colorectal cancer incidence and mortality as a major public health threat worldwide. The findings reveal a positive association between a country's development level, as measured by HDI, and colorectal cancer incidence and mortality.*

Introduction

Colorectal cancer poses a major global health concern, with rising incidence and mortality rates worldwide [1, 2]. In 2018, there were 1,849,518 new cases of colorectal cancer, accounting for 10% of all newly diagnosed cancers globally [3]. Additionally, there were 880,792 deaths attributed to colorectal cancer, representing 9.2% of all cancer-related deaths [3]. It ranks third among the most common cancers and stands as the second leading cause of cancer-related deaths [1, 2]. The geographical distribution of colorectal cancer exhibits substantial disparities, with higher rates reported in developed countries compared to developing nations [4]. These variations can be attributed to differences in risk factors, healthcare infrastructure, and socioeconomic factors [5, 6].

Colorectal cancer arises from the malignant transformation of the colon or rectal epithelium and is influenced by a complex interplay of genetic and environmental factors [7]. Lifestyle choices, such as diet, physical activity, and tobacco use, have been identified as modifiable risk factors for colorectal cancer [8, 9]. Additionally, age, family history of the disease, and certain hereditary syndromes contribute to an individual's susceptibility to colorectal cancer [10]. This highlights the need for public health strategies promoting increased physical activity, healthy diets, smoking cessation, and other beneficial lifestyle changes as part of comprehensive colorectal cancer control.

Research on the global burden of colorectal cancer has identified the Human Development Index (HDI) as a significant factor influencing its incidence and mortality rates. The HDI is a composite metric of social and economic development that includes factors such as life expectancy, education, and income [11]. Research has shown a positive correlation between higher HDI levels and increased colorectal cancer incidence, attributed to increased availability and utilization of screening and diagnostic procedures in more developed nations [4, 12, 13]. In 2018, the incidence of colorectal cancer was highest in areas with very high HDI, with a rate of 61.4 cases per 100,000 population. High

HDI areas had an incidence rate of 24.1, followed by medium HDI areas at 6.35, and low HDI areas at 3.6. The mortality rate due to colorectal cancer also varied based on the level of development, with very high HDI areas having a mortality rate of 27.1, followed by high HDI areas at 13, medium HDI areas at 3.9, and low HDI areas at 2.75 [3].

Though colorectal cancer incidence has declined in some high-income countries, it is rising in several low- and middle-income regions, underscoring the pressing need for comprehensive prevention and control strategies [14]. Early detection through screening programs, coupled with effective treatment modalities, can significantly improve patient outcomes and reduce mortality rates [1]. This paper aims to explore global colorectal cancer incidence, mortality, and geographical disparities, correlating them with the HDI. By analyzing available data, we aim to pinpoint key drivers of the colorectal cancer burden and propose evidence-based strategies for prevention, early detection, and treatment. Understanding the worldwide landscape of colorectal cancer is vital for guiding public health policies and interventions to mitigate its impact on individuals and communities.

Materials and Methods

This research utilizes data from the International Agency for Research on Cancer's (IARC) GLOBOCAN 2020 project, an esteemed source of up-to-date international cancer statistics. The database includes information on the incidence and mortality rates of different types of cancer across 184 countries. It covers a wide range of cancer types, age groups, genders, and global regions. Developed by the World Health Organization (WHO), GLOBOCAN enables researchers to thoroughly investigate and compare cancer rates based on multiple criteria. As a highly reliable data source, GLOBOCAN provides the foundation for analyzing colorectal cancer incidence and mortality in this study [14-16].

This study primarily analyzes the Age-Standardized Incidence Rate (ASIR) and Age-Standardized Mortality Rate (ASMR) of colorectal cancer. The analysis categorizes and presents the rates based on multiple criteria: Continents: Latin America and Caribbean, Africa, Northern America, Oceania, Europe, Asia. WHO regions: Africa (AFRO), East Mediterranean (EMRO), Americas (PAHO), South-East Asia (SEARO), Europe (EURO), Western Pacific (WPRO). Global regions: Southeastern Asia, Western Asia, South-Central Asia, Eastern Asia, North America, South America, Central America, Middle Africa, Western Africa, Southern Africa, Northern Africa, Eastern Africa, Central/Eastern Europe, Southern Europe, Northern Europe, Western Europe, Caribbean, Australia/New Zealand, Melanesia, Micronesia, Polynesia. Income level: Low-income, lower-middle income, upper-middle income, High-income. The standardized rates allow comparative analysis of colorectal cancer incidence and mortality across these different geographic regions and economic groups.

Human Development Index (HDI)

The HDI is a comprehensive measure that assesses a country's achievements in key dimensions of human development. These dimensions include education, life expectancy, and per capita income. By taking the geometric mean of normalized indices for each dimension, the HDI produces values that range from 0 to 1. In essence, the HDI provides a multi-faceted evaluation of human development by combining health, education, and economic prosperity metrics [17].

Statistical analysis

This study presents 2020 incidence and mortality rates for colorectal cancer, including both raw and Age-Standardized rates per 100,000 individuals. Geographical distribution maps were created based on the Age-Standardized rates. The methodology has been extensively detailed in previous reports [12, 13, 18-20]. Specifically, the Pearson correlation method was used to analyze the relationship between ASIR and ASMR of colorectal cancer and the Human Development Index (HDI) and its components. A p-value < 0.05 was considered statistically significant, with all reported P-values being two-sided. SPSS software (Version 26.0, SPSS Inc.) performed the statistical analyses.

Results

Geographical distribution in the world

In 2020, there were 1,931,590 new global colorectal cancer cases – 1,065,960 (55.18%) in men and 865,630 (44.82%) in women. The ASIR was 19.5 overall, 23.4 for men and 16.2 for women. The sex ratio of new cases was 1.23 (Fig. 1).

Additionally, 935,173 deaths were attributed to colorectal cancer that year. Of these, 515,637 (55.13%) occurred in men and 419,536 (44.87%) in women. The ASMR was 9 overall, 11 for men and 7.2 for women. The sex ratio for mortality was also 1.23 (Fig. 2).

Geographical distribution based on the continents

For ASIR, Europe had the highest rate at 30.4 (37.9 for men, 24.6 for women), followed by Oceania at 29.8 (33.8 for men, 26.1 for women), then Northern America at 26.2 (29.4 for men, 23.4 for women). Rates were lower in Asia at 17.6 (21.1 for men, 14.3 for women), Latin America/Caribbean at 16.6 (18.7 for men, 15.1 for women), and Africa at 8.4 (9.4 for men, 7.6 for women). Asia had the highest proportion of cases (52.25%), followed by Europe (26.91%), North America (9.34%), Latin America/Caribbean (6.98%), Africa (3.42%), and Oceania (1.06%) (Tab. I, Fig. 1).

For ASMR, Europe again had the highest rate at 12.3 (16.1 for men, 9.5 for women), followed by Oceania at 9.3 (11.2 for men, 7.5 for women). Rates were lower in Asia at 8.6 (10.6 for men, 6.8 for women), Latin America/

Fig. 1. Distribution of new Colorectal Cancer cases worldwide in 2020.

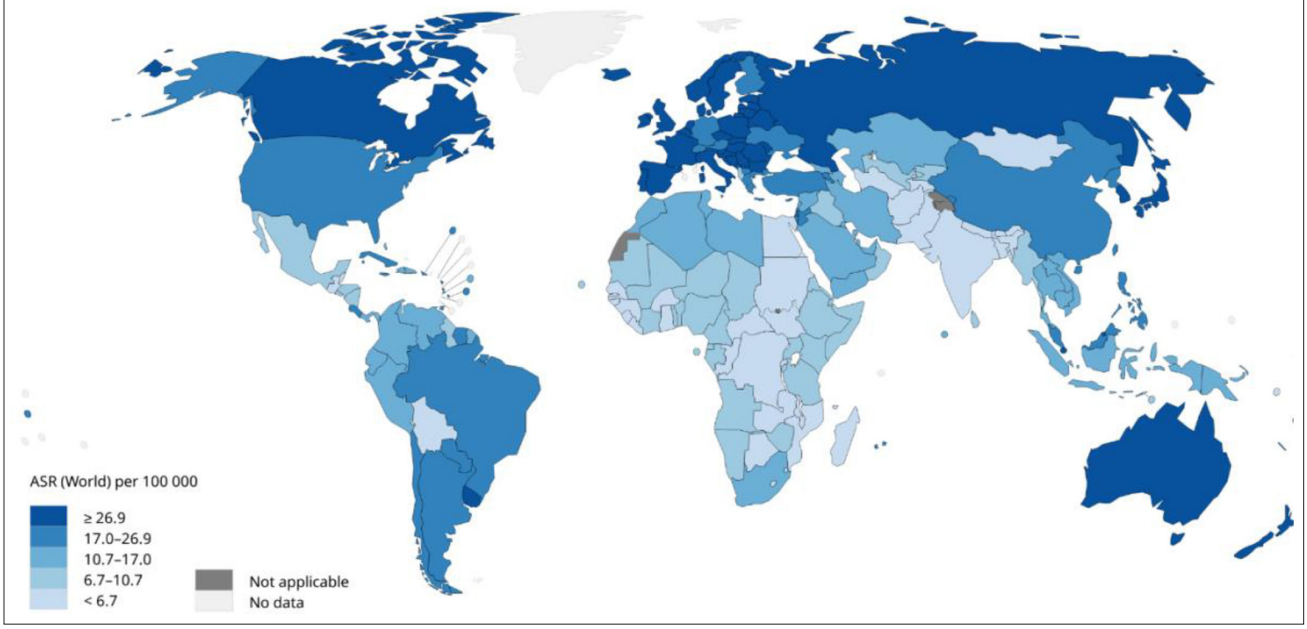
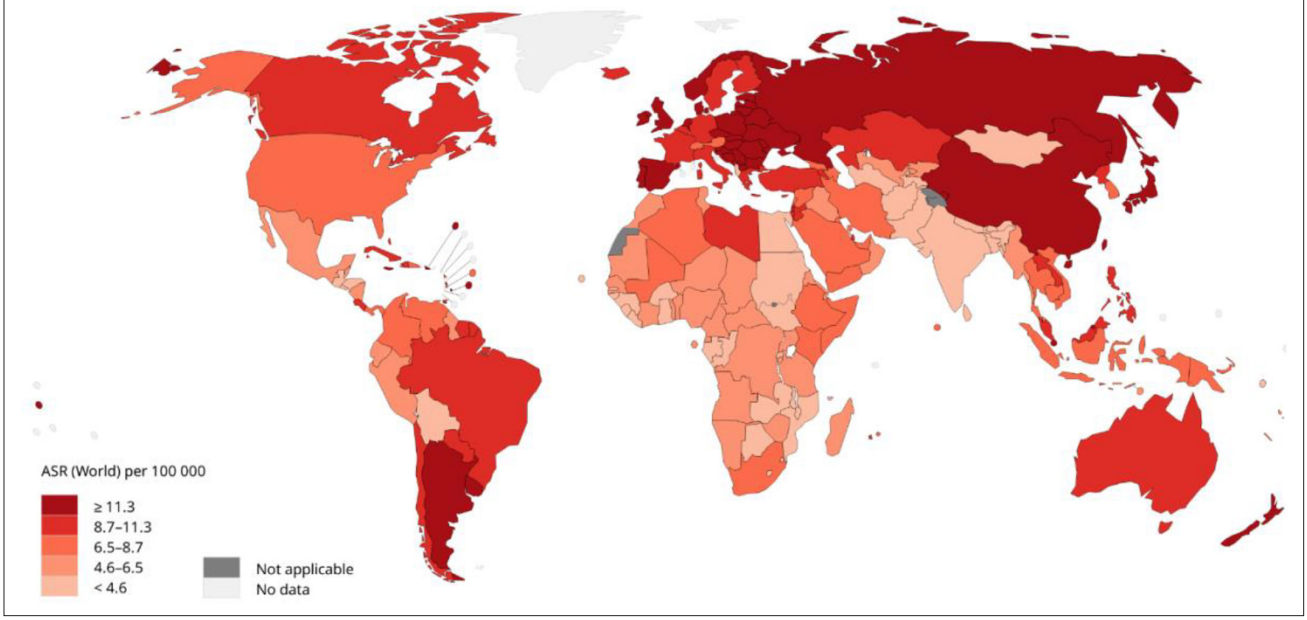


Fig. 2. Distribution of Colorectal Cancer mortality worldwide in 2020.



Caribbean at 8.2 (9.7 for men, 6.8 for women), Northern America at 8.2 (9.4 for men, 7.3 for women), and Africa at 5.6 (6.3 for men, 5.0 for women). Mirroring incidence, Asia had the most deaths (54.15%) followed by Europe (26.17%), Latin America/Caribbean (7.42%), Northern America (6.84%), Africa (4.58%), and Oceania (0.81%) (Tab. II, Fig. 2).

Geographical distribution according to the WHO classification

The ASIR for colorectal cancer varied by WHO region. The highest rate was in EURO at 28.8 (36 for men, 23.3 for women), followed by WPRO at 25.3 (30.6 for men, 20.5 for women), PAHO at 20.7 (23.3 for men, 18.5 for women), EMRO at 9 (10.2 for men, 7.9 for women), AFRO at 8.4 (9.5 for men, 7.5 for women), and SEARO at 7 (8.5 for men, 5.5 for women). WPRO had the highest proportion of cases (42.36%), followed by EURO (28.72%), PAHO (16.34%), SEARO (7.35%), AFRO (2.63%), and EMRO (2.61%) (Tab. I).

For ASMR, EURO again had the highest rate at 12 (15.6 for men, 9.3 for women), followed by WPRO at 11.5 (14.3 for men, 9 for women), PAHO at 8.1 (9.4 for men, 7 for women), AFRO at 5.8 (6.7 for men, 5.2 for

Tab. I. The age-standardized incidence rate of Colorectal Cancer in different regions of the world in 2020.

Population Numbers		All			Men			Women		
		Numbers	Crude Rate	ASR (W)	Numbers	Crude Rate	ASR (W)	Numbers	Crude Rate	ASR (W)
World		1 931 590	24.8	19.5	1 065 960	27.1	23.4	865 630	22.4	16.2
WHO regions	WHO Africa (AFRO)	50 696	4.5	8.4	26 243	4.7	9.5	24 453	4.4	7.5
	WHO Americas (PAHO)	315 518	30.8	20.7	162 356	32.2	23.3	153 162	29.5	18.5
	WHO East Mediterranean (EMRO)	50 403	6.9	9.0	28 269	7.5	10.2	22 134	6.3	7.9
	WHO Europe (EURO)	554 569	59.4	28.8	300 443	66.4	36.0	254 126	52.9	23.3
	WHO South-East Asia (SEARO)	141 928	7.0	7.0	83 942	8.1	8.5	57 986	5.9	5.5
	WHO Western Pacific (WPRO)	818 060	41.6	25.3	464 483	46.5	30.6	353 577	36.6	20.5
Continents	Africa	66 198	4.9	8.4	34 060	5.1	9.4	32 138	4.8	7.6
	Asia	1 009 400	21.8	17.6	576 754	24.3	21.1	432 646	19.1	14.3
	Europe	519 820	69.4	30.4	281 714	77.9	37.9	238 106	61.5	24.6
	Latin America and the Caribbean	134 943	20.6	16.6	67 218	20.9	18.5	67 725	20.4	15.1
	Northern America	180 575	49.0	26.2	95 138	52.1	29.4	85 437	45.9	23.4
	Oceania	20 654	48.4	29.8	11 076	51.8	33.8	9 578	44.9	26.1
Income levels	High income	819 143	66.6	30.2	450 564	73.5	36.2	368 579	59.7	25.0
	Upper middle income	887 025	30.4	21.4	490 846	33.4	25.5	396 179	27.3	17.8
	Low middle income	194 954	6.4	7.4	109 105	7.1	8.6	85 849	5.8	6.3
	Low income	29 542	4.9	8.8	14 959	5.0	9.7	14 583	4.8	8.0
Global regions	Australia and New Zealand	19 644	64.8	33.2	10 491	69.6	37.4	9 153	60.0	29.2
	Caribbean	11 454	26.3	18.2	5 327	24.8	18.5	6 127	27.8	17.8
	Central America	19 535	10.9	10.4	10 181	11.6	12.0	9 354	10.2	9.1
	Central and Eastern Europe	172 950	59.0	29.3	89 189	64.7	38.4	83 761	54.0	23.4
	Eastern Africa	18 306	4.1	7.9	8 888	4.0	8.6	9 418	4.2	7.5
	Eastern Asia	757 849	45.2	25.9	431 501	50.4	31.2	326 348	39.7	21.0
	Melanesia	804	7.2	11.4	466	8.2	14.2	338	6.2	9.0
	Micronesia	93	16.9	16.6	51	18.4	19.5	42	15.5	14.2
	Middle Africa	5 767	3.2	6.8	3 045	3.4	7.7	2 722	3.0	6.1
	Northern Africa	20 858	8.5	9.7	10 662	8.6	10.4	10 196	8.3	9.1
	Northern America	180 575	49.0	26.2	95 138	52.1	29.4	85 437	45.9	23.4
	Northern Europe	81 638	76.8	33.6	44 464	84.7	39.2	37 174	69.1	28.8
	Polynesia	113	16.5	15.5	68	19.6	19.2	45	13.4	11.9
	South America	103 954	24.1	18.5	51 710	24.4	20.6	52 244	23.9	16.8
	South-Central Asia	102 987	5.1	5.5	61 252	5.9	6.6	41 735	4.3	4.4
	South-Eastern Asia	106 995	16.0	14.8	60 505	18.1	18.4	46 490	13.9	11.9
	Southern Africa	7 684	11.4	13.7	3 919	11.8	16.7	3 765	11.0	11.7
	Southern Europe	123 588	80.6	31.9	71 009	94.7	40.6	52 579	67.0	24.5
	Western Africa	13 583	3.4	6.7	7 546	3.7	7.9	6 037	3.0	5.7
	Western Asia	41 569	14.9	16.8	23 496	16.1	19.9	18 073	13.6	14.0
	Western Europe	141 644	72.2	28.7	77 052	80.0	34.3	64 592	64.7	23.9

women), EMRO at 5.1 (5.8 for men, 4.5 for women), and SEARO at 4 (4.9 for men, 3.1 for women). WPRO had the highest proportion of cases (42.36%), followed by EURO (28.16%), PAHO (14.27%), SEARO (8.57%), AFRO (3.65%), and EMRO (2.99%) (Tab. II).

Geographical distribution in the countries

The study revealed that China, the United States of America, and Japan had the highest number of new colorectal cancer cases, with 555,477, 155,008, and 148,505 cases, respectively. On the other hand, Sao Tome and Principe, Vanuatu, and Comoros had the lowest number of cases, with 8, 10, and 20 cases, respectively. Furthermore, Hungary (45.3 per 100,000), Slovakia (43.9), and Norway (41.9) had the highest ASIR of colorectal cancer, while Guinea (3.3), The Republic of the Gambia (3.7), and Bhutan (3.8) had the lowest (Tab. S1). When it comes to mortality, China recorded the highest number of colorectal cancer cases (286,162 cases), followed by Japan (59,912 cases), and the United States of America (54,443 cases). Conversely, Sao Tome and Principe (5 cases), Vanuatu (9 cases), and Comoros (13 cases) had the lowest number of cases. Slovakia (21),

Tab. II. The age-standardized mortality rate of Colorectal Cancer in different regions of the world in 2020.

Population Numbers		All			Men			Women		
		Numbers	Crude Rate	ASR (W)	Numbers	Crude Rate	ASR (W)	Numbers	Crude Rate	ASR (W)
World		935 173	12.0	9.0	515 637	13.1	11.0	419 536	10.9	7.2
WHO regions	WHO Africa (AFRO)	34 132	3.0	5.8	17 634	3.2	6.7	16 498	2.9	5.2
	WHO Americas (PAHO)	133 422	13.0	8.1	69 081	13.7	9.4	64 341	12.4	7.0
	WHO East Mediterranean (EMRO)	27 975	3.8	5.1	15 702	4.2	5.8	12 273	3.5	4.5
	WHO Europe (EURO)	263 314	28.2	12.0	141 801	31.3	15.6	121 513	25.3	9.3
	WHO South-East Asia (SEARO)	80 084	4.0	4.0	47 876	4.6	4.9	32 208	3.3	3.1
	WHO Western Pacific (WPRO)	396 048	20.2	11.5	223 433	22.4	14.3	172 615	17.9	9.0
Continents	Africa	42 875	3.2	5.6	22 046	3.3	6.3	20 829	3.1	5.0
	Asia	506 449	10.9	8.6	288 525	12.2	10.6	217 924	9.6	6.8
	Europe	244 824	32.7	12.3	131 885	36.5	16.1	112 939	29.2	9.5
	Latin America and the Caribbean	69 435	10.6	8.2	34 976	10.9	9.4	34 459	10.4	7.3
	Northern America	63 987	17.3	8.2	34 105	18.7	9.7	29 882	16.0	6.8
	Oceania	7 603	17.8	9.3	4 100	19.2	11.2	3 503	16.4	7.5
Income levels	High income	340 272	27.6	10.5	185 111	30.2	13.2	155 161	25.1	8.2
	Upper middle income	461 511	15.8	10.8	256 244	17.5	13.3	205 267	14.1	8.6
	Low middle income	112 556	3.7	4.3	63 703	4.1	5.1	48 853	3.3	3.6
	Low income	20 392	3.4	6.2	10 343	3.4	6.9	10 049	3.3	5.5
Global regions	Australia and New Zealand	7 038	23.2	9.5	3 755	24.9	11.4	3 283	21.5	7.7
	Caribbean	6 983	16.0	10.4	3 307	15.4	11.0	3 676	16.7	9.8
	Central America	10 439	5.8	5.5	5 494	6.2	6.4	4 945	5.4	4.7
	Central and Eastern Europe	93 384	31.9	14.5	48 378	35.1	20.2	45 006	29.0	11.0
	Eastern Africa	13 236	3.0	5.9	6 365	2.9	6.4	6 871	3.1	5.5
	Eastern Asia	368 072	21.9	11.8	208 090	24.3	14.7	159 982	19.4	9.2
	Melanesia	452	4.1	6.7	279	4.9	8.8	173	3.2	4.8
	Micronesia	53	9.7	9.5	29	10.5	11.7	24	8.8	7.8
	Middle Africa	4 228	2.4	5.2	2 222	2.5	5.9	2 006	2.2	4.6
	Northern Africa	11 530	4.7	5.4	5 900	4.8	5.9	5 630	4.6	5.0
	Northern America	63 987	17.3	8.2	34 105	18.7	9.7	29 882	16.0	6.8
	Northern Europe	33 768	31.8	11.4	17 811	33.9	13.5	15 957	29.7	9.6
	Polynesia	60	8.8	8.4	37	10.7	10.9	23	6.8	6.3
	South America	52 013	12.1	8.9	26 175	12.3	10.2	25 838	11.8	7.8
	South-Central Asia	59 206	2.9	3.2	35 848	3.5	3.9	23 358	2.4	2.5
	South-Eastern Asia	57 064	8.5	7.9	32 205	9.6	10.1	24 859	7.4	6.1
	Southern Africa	3 943	5.8	7.2	2 052	6.2	9.1	1 891	5.5	5.9
	Southern Europe	55 406	36.1	11.5	31 583	42.1	15.1	23 823	30.4	8.5
	Western Africa	9 938	2.5	5.1	5 507	2.7	6.1	4 431	2.2	4.3
	Western Asia	22 107	7.9	8.9	12 382	8.5	10.7	9 725	7.3	7.3
	Western Europe	62 266	31.7	10.2	34 113	35.4	13.1	28 153	28.2	7.8

Hungary (20.2), and Croatia (19.6) had the highest ASMR of colorectal cancer, while Bangladesh (2.3), Bhutan (2.5), and Nepal (2.5) had the lowest (Tab. S2).

ASIR and ASMR

Globally, there was a statistically significant positive correlation of 0.895 ($p \leq 0.001$) between the ASIR and ASMR of colorectal cancer.

ASIR and HDI

Analysis revealed a significant positive correlation of 0.794 ($p \leq 0.001$) between the ASIR of colorectal cancer and the HDI. Furthermore, positive correlations emerged between the ASIR and specific HDI dimensions. Namely, the ASIR correlated positively with life expectancy at birth (0.724, $p \leq 0.001$), education levels (0.743, $p \leq 0.001$), and income per capita (0.706, $p \leq 0.001$) (Tabs. III, S1, S2).

ASMR and HDI

The ASMR for colorectal cancer showed a significant positive correlation of 0.638 with the HDI ($p = 0.001$). Positive correlations were also found between the ASMR

Tab. III. The relationship between the incidence and mortality of Colorectal Cancer with the HDI and its components.

Incidence and mortality rates			HDI	Life expectancy at birth	Mean years of schooling	Gross national Income (GNI) per capita
ASIR	Boys	r p-value	0.757 0.001	0.677 0.001	0.715 0.001	0.652 0.001
	Girls	r p-value	0.811 0.001	0.749 0.001	0.757 0.001	0.749 0.001
	Total	r p-value	0.794 0.001	0.724 0.001	0.743 0.001	0.706 0.001
ASMR	Boys	r p-value	0.604 0.001	0.519 0.001	0.606 0.001	0.459 0.001
	Girls	r p-value	0.626 0.001	0.575 0.001	0.620 0.001	0.535 0.001
	Total	r p-value	0.638 0.001	0.569 0.001	0.631 0.001	0.512 0.001

and life expectancy at birth (0.569, $p \leq 0.001$), education levels (0.631, $p \leq 0.001$), and income per capita (0.512, $p \leq 0.001$) (Tabs. III, S1, S2).

Discussion

This comprehensive analysis reveals stark global disparities in colorectal cancer incidence and mortality, underscoring the impact of geographic differences and human development levels. With over 1.9 million new cases and 0.9 million deaths in 2020, the data highlights the considerable worldwide burden of this disease.

Geographically, incidence and mortality rates varied greatly by continent. Europe had the highest age-standardized rates while Africa had the lowest, likely reflecting disparities in risk factors, genetics, and screening access [21]. Rates also differed by WHO region, with EURO and WPRO having the highest burdens and EMRO, AFRO, and SEARO the lowest. These regional variances further emphasize how geographic factors influence colorectal cancer outcomes.

When observing the data at a country level, the highest number of new colorectal cases were recorded in China, United States, and Japan, while the lowest were in Sao Tome and Principe, Vanuatu, and Comoros. Interestingly, Hungary, Slovakia, and Norway had the highest ASIR, while Guinea, The Republic of Gambia, and Bhutan had the lowest. This discrepancy between the number of cases and ASIR can be attributed to the differences in population sizes, healthcare infrastructure, and cancer surveillance among these countries [2].

A significant positive correlation was found between global colorectal cancer ASIR and ASMR, suggesting that rising incidence rates are often paired with increasing mortality burdens [22, 23].This pattern indicates that many regions lack adequate early detection and treatment access needed to reduce colorectal cancer mortality despite rising incidence levels. Improving screening programs and treatment availability, particularly in less developed areas, is critical to curb worldwide colorectal cancer mortality rates and mitigate the impact of increasing incidence.

The study also found positive correlations between colorectal cancer's standardized incidence and mortality rates and various HDI dimensions, including life expectancy at birth, education levels, and income. This indicates that higher human development is linked to greater colorectal cancer incidence and mortality, possibly due to several factors. These include increased life expectancy resulting in more cases among older populations, dietary and lifestyle changes accompanying development, and improved detection enabled by advanced healthcare systems [24]. This complex relationship between development and colorectal cancer epidemiology highlights the need for multifaceted control strategies encompassing prevention, screening, treatment, and research.

As noted in previous research, men consistently exhibited higher colorectal cancer incidence and mortality rates than women across all global regions analyzed [4, 12, 13, 18-20]. This sex disparity highlights the need for targeted strategies that take into account differences in risk factors, screening behaviors, treatment access, and outcomes between males and females. Gender-specific prevention and control initiatives should be considered to equitably address the worldwide colorectal cancer burden for both sexes.

These disparities could be attributed to a variety of factors, including differences in dietary habits, healthcare infrastructure, access to screening programs, and prevalence of risk factors such as smoking and obesity. For example, higher rates in developed regions might reflect better detection and reporting mechanisms, as well as lifestyle factors such as diet and physical inactivity. Conversely, lower rates in less developed regions could indicate underreporting and limited access to healthcare services [25-28].

Moreover, the observed positive correlation between the Human Development Index (HDI) and colorectal cancer incidence and mortality underscores the impact of socioeconomic factors on health outcomes. Countries with higher HDI tend to have better healthcare systems and more widespread use of screening programs, which can lead to higher detection rates. However, these same countries also exhibit lifestyle factors that increase colorectal cancer risk, such as higher consumption of red and processed meats.

It is also crucial to address potential data quality issues in the GLOBOCAN database. Variations in data collection methods, reporting accuracy, and completeness can affect the reliability of the reported incidence and mortality rates [14]. For instance, underreporting in low-income countries may lead to an underestimation of the true burden of colorectal cancer in these regions. The GLOBOCAN database relies on a combination of cancer registry data, vital statistics, and modeling techniques to estimate cancer incidence and mortality. While this approach allows for comprehensive global estimates, it also introduces potential sources of error [2, 12-14, 29].
This global analysis provides valuable insights into the varying colorectal cancer incidence and mortality rates across countries and regions. The findings can help guide targeted prevention and treatment initiatives tailored to local contexts. Further research should delve deeper into the specific factors driving regional disparities worldwide to inform more effective, context-specific strategies for combating colorectal cancer.
Overall, the results underscore the urgent need for an integrated global approach that accounts for regional differences in colorectal cancer epidemiology, socioeconomic conditions, and local healthcare capacity. Only through coordinated global action can we hope to confront the rising worldwide burden of colorectal cancer. Moving forward, global collaboration and resource mobilization focused on prevention, early detection, treatment access, research, and health system strengthening will be essential to equitably and sustainably reduce the threat posed by this disease worldwide.

Limitations of the study

The quality of cancer data in GLOBOCAN varies, especially for medium or low HDI countries. Thus, estimates for some countries may rely on limited regional cancer recordings or be extrapolated from neighboring countries [29]. See Table S1, Tables I and II for further details on data quality issues across countries.

Conclusions

In conclusion, this study provides valuable insights into the global disparities in colorectal cancer incidence and mortality rates. It underscores the need for comprehensive strategies to reduce colorectal cancer burden, particularly in regions and countries with high incidence and mortality rates. Such strategies should include improving access to early detection and treatment, promoting lifestyle changes, and strengthening cancer surveillance systems.

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Data availability

The data used in this study can be retrieved in the tables provided in the text of the article. In addition, the data used in the present study is freely available in the globocan website (https://gco.iarc.fr/).

Conflicts of interest statement

There is no conflict of interest in this study.

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Author's contributions

DD: Data curation, writing-original draft, preparation, reviewing, editing, methodology, and software. AMH: Data curation, writing-original draft, preparation, visualization, investigation, project administration, validation, reviewing, editing, methodology, and software. SK: Conceptualization, writing-original draft, and investigation.

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Supplementary Materials

Tab. S1. Standardized rate of incidence and mortality of Colorectal Cancer in the countries of the world.

Population	ASIR	ASIR in males	ASIR in females	ASMR	ASMR in males	ASMR in females
Afghanistan	5.7	6.3	5.1	3.8	4.2	3.5
Albania	7.7	8.8	6.8	3.8	4.4	3.4
Algeria	15.3	16.5	14.2	8.3	9.0	7.7
Angola	7.2	9.6	5.2	5.2	7.0	3.8
Argentina	25.1	31.0	20.6	12.6	16.3	9.9
Armenia	20.1	22.2	18.5	11.3	12.2	10.6
Australia	33.1	37.3	29.2	8.9	10.8	7.2
Austria	21.0	26.5	16.4	8.7	11.6	6.3
Azerbaijan	14.2	17.8	11.5	8.6	11.3	6.6
Bahamas	16.0	20.5	12.4	10.7	13.5	8.6
Bahrain	13.9	13.7	14.6	7.1	6.8	7.5
Bangladesh	3.8	4.2	3.3	2.3	2.6	2.0
Barbados	25.1	30.5	20.4	16.1	20.9	11.9
Belarus	30.2	39.4	24.8	14.1	19.7	10.9
Belgium	35.3	43.6	28.0	10.0	12.6	7.8
Belize	6.2	5.9	6.6	6.0	5.3	6.6
Benin	7.7	11.3	5.0	5.7	8.5	3.7
Bhutan	3.8	5.4	1.9	2.5	3.7	1.1
Bolivia, Plurinational State of	5.7	6.3	5.1	3.4	3.9	2.9
Bosnia and Herzegovina	27.0	34.6	20.8	14.5	19.6	10.5
Botswana	4.5	4.3	4.5	2.6	2.5	2.6
Brazil	19.4	21.7	17.6	9.0	10.3	7.9
Brunei Darussalam	34.9	42.2	27.7	14.6	18.1	11.2
Bulgaria	27.4	36.6	20.3	14.7	20.7	10.3
Burkina Faso	3.8	3.6	3.8	3.1	3.0	3.1
Burundi	6.9	7.4	6.6	5.6	6.1	5.2
Cabo Verde	8.8	12.6	7.7	3.5	5.0	3.0
Cambodia	12.3	13.7	11.2	7.4	8.4	6.7
Cameroon	7.1	8.0	6.4	5.2	5.9	4.6
Canada	31.2	34.7	27.9	9.9	12.0	8.0
Central African Republic	6.5	7.2	6.0	5.4	6.1	4.9
Chad	6.9	7.9	6.0	5.7	6.5	5.0
Chile	19.9	22.6	17.7	9.4	11.0	8.1
China	23.9	28.6	19.5	12.0	14.8	9.4
Colombia	16.9	17.3	16.7	8.2	8.5	7.9
Comoros	4.5	3.7	5.2	3.0	2.3	3.7
Congo, Democratic Republic of	6.7	7.1	6.3	5.1	5.5	4.8
Congo, Republic of	6.3	6.9	5.8	4.4	5.0	4.0
Costa Rica	17.2	17.6	16.8	9.5	10.2	8.8
Côte d'Ivoire						
Croatia	36.3	50.8	24.9	19.6	28.2	13.5
Cuba	20.1	17.9	22.0	11.3	10.7	11.8
Cyprus	24.3	35.6	14.3	10.7	14.0	7.9
Czechia	33.7	44.4	25.2	12.3	17.0	8.6
Denmark	40.9	47.1	35.6	11.8	13.7	10.2
Djibouti	6.9	7.8	5.9	5.3	6.1	4.6
Dominican Republic	12.9	13.2	12.5	7.5	8.0	7.0
Ecuador	12.9	12.5	13.2	6.4	6.4	6.3
Egypt	6.1	5.8	6.2	3.4	3.3	3.4

▶

Tab. S1 *(follows)*. Standardized rate of incidence and mortality of Colorectal Cancer in the countries of the world.

Population	ASIR	ASIR in males	ASIR in females	ASMR	ASMR in males	ASMR in females
El Salvador	8.5	9.5	7.7	4.5	5.1	4.1
Equatorial Guinea	6.9	8.3	5.5	4.8	5.7	3.9
Eritrea	7.5	8.0	7.1	5.8	6.3	5.5
Estonia	28.3	35.6	23.9	13.8	18.6	11.1
Eswatini	4.1	4.9	3.2	3.0	3.8	2.2
Ethiopia	8.9	9.9	8.1	6.8	7.5	6.2
Fiji	10.9	11.7	10.3	6.8	8.1	5.9
Finland	25.7	29.4	22.8	8.8	10.9	7.2
France	30.1	36.3	24.9	10.4	13.3	8.1
Gabon	7.3	8.8	5.9	4.2	5.0	3.3
Gaza Strip and West Bank						
Georgia	15.6	18.8	13.5	8.3	10.6	6.8
Germany	25.8	30.4	21.8	9.9	12.9	7.3
Ghana	3.9	4.4	3.6	2.8	3.2	2.5
Greece	26.9	34.4	20.5	10.7	14.1	7.8
Guatemala	5.7	6.0	5.4	3.6	3.8	3.4
Guinea	3.3	3.9	2.9	2.6	3.1	2.3
Guinea-Bissau	4.7	5.9	3.8	3.8	4.9	3.1
Guyana	8.5	9.4	7.5	5.0	5.8	4.3
Haiti	12.5	11.6	13.2	8.7	8.2	9.2
Honduras	8.0	8.5	7.6	4.2	4.6	3.9
Hungary	45.3	62.0	33.1	20.2	29.0	14.0
Iceland	28.5	32.8	24.3	9.5	10.9	8.1
India	4.8	6.0	3.7	2.8	3.6	2.1
Indonesia	12.4	16.5	8.6	6.7	9.2	4.6
Iran, Islamic Republic of	13.9	15.9	11.9	7.3	8.3	6.3
Iraq	8.7	10.8	6.9	5.4	6.8	4.4
Ireland	34.9	42.6	27.9	12.4	15.7	9.4
Israel	21.9	24.5	19.8	9.0	10.3	7.9
Italy	29.3	34.2	25.2	10.1	12.7	8.1
Jamaica	21.1	26.4	16.3	13.4	17.2	9.8
Japan	38.5	47.3	30.5	11.6	14.7	8.9
Jordan	17.7	17.2	18.4	9.6	9.7	9.6
Kazakhstan	15.6	18.0	14.3	9.2	11.7	7.6
Kenya	10.5	11.9	9.7	7.5	8.7	6.9
Korea, Democratic Republic of	18.8	22.8	15.9	10.9	13.5	8.7
Korea, Republic of	27.2	34.9	20.6	7.8	10.8	5.5
Kuwait	12.5	13.1	11.9	6.6	7.0	6.1
Kyrgyzstan	7.8	8.8	7.0	5.4	5.9	4.9
Lao People's Democratic Republic	15.0	16.1	14.2	8.9	10.1	7.9
Latvia	36.8	48.8	30.1	12.3	15.9	10.4
Lebanon	12.2	15.2	9.5	6.7	8.8	5.0
Lesotho	5.3	7.8	4.0	3.8	6.0	2.8
Liberia	4.9	5.5	4.4	3.9	4.4	3.5
Libya	15.7	16.7	15.1	10.2	11.0	9.8
Lithuania	27.6	36.4	22.3	11.7	16.1	9.4
Luxembourg	26.3	29.7	23.7	8.7	11.2	6.4
Madagascar	6.2	5.6	6.8	4.7	4.3	5.1
Malawi	4.9	6.3	4.1	3.9	5.0	3.3
Malaysia	19.6	21.2	18.0	10.2	11.0	9.4
Maldives	13.0	16.4	9.3	7.4	10.5	4.1

▶

Tab. S1 *(follows).* Standardized rate of incidence and mortality of Colorectal Cancer in the countries of the world.

Population	ASIR	ASIR in males	ASIR in females	ASMR	ASMR in males	ASMR in females
Mali	9.2	8.8	9.6	7.5	7.2	7.7
Malta	25.7	31.1	21.2	10.1	11.9	8.6
Mauritania	7.2	8.6	6.1	5.4	6.5	4.6
Mauritius	17.8	21.9	14.7	7.9	9.5	6.6
Mexico	10.6	12.4	9.1	5.4	6.4	4.6
Mongolia	6.3	6.6	6.1	4.0	4.0	4.0
Montenegro	27.4	35.2	21.1	13.7	21.5	7.8
Morocco	11.3	12.9	9.9	6.2	7.2	5.4
Mozambique	4.1	3.6	4.4	3.2	2.8	3.5
Myanmar	9.7	11.8	8.2	5.8	7.3	4.8
Namibia	8.2	10.8	6.4	5.8	7.6	4.4
Nepal	4.3	5.5	3.4	2.5	3.2	1.9
New Zealand	33.8	38.3	29.7	12.3	14.5	10.3
Nicaragua	10.5	10.4	10.5	6.0	5.8	6.0
Niger	7.0	8.0	5.9	5.8	6.6	4.9
Nigeria	7.3	8.6	6.0	5.5	6.5	4.5
North Macedonia	26.1	26.6	26.1	13.0	13.9	12.3
Norway	41.9	45.4	38.7	13.5	15.1	12.1
Oman	9.9	11.2	7.7	5.7	6.2	4.5
Pakistan	5.3	6.2	4.4	3.0	3.5	2.5
Panama	13.9	16.3	11.7	7.3	9.0	5.8
Papua New Guinea	11.3	14.5	8.4	6.9	9.2	4.8
Paraguay	18.6	20.5	16.7	9.3	10.5	8.1
Peru	11.4	11.6	11.1	5.6	5.9	5.3
Philippines	18.8	23.7	15.1	10.1	13.4	7.8
Poland	30.5	41.7	21.9	16.1	22.8	11.3
Portugal	39.4	55.2	26.6	13.0	18.6	8.8
Puerto Rico	26.3	32.1	22.0	12.4	15.7	9.9
Qatar	15.7	13.6	20.6	9.0	8.0	10.9
Republic of Moldova	30.0	44.3	19.7	17.6	26.7	11.3
Romania	30.9	41.9	22.4	14.8	21.1	10.2
Russian Federation	27.8	34.4	23.9	13.9	18.6	11.3
Rwanda	5.3	6.6	4.2	4.0	4.9	3.1
Saudi Arabia	13.9	16.1	10.9	7.3	8.7	5.6
Senegal	6.7	7.4	6.2	5.1	5.7	4.7
Serbia	33.6	46.4	22.8	16.7	23.7	11.1
Sierra Leone	5.0	6.0	4.1	4.1	5.0	3.3
Singapore	33.0	38.6	27.4	16.2	19.8	12.8
Slovakia	43.9	60.7	31.1	21.0	29.6	14.8
Slovenia	39.6	55.8	25.4	11.7	16.1	8.4
Solomon Islands	6.7	6.5	7.0	4.2	4.9	3.5
Somalia	9.3	10.1	8.6	7.7	8.4	7.1
South Africa	14.6	17.6	12.5	7.5	9.5	6.2
South Sudan	5.7	6.3	5.1	4.5	5.1	4.0
Spain	35.8	47.7	25.4	11.5	15.5	8.2
Sri Lanka	7.8	7.7	7.9	3.7	3.8	3.7
Sudan	6.3	6.6	6.0	3.9	4.2	3.6
Suriname	18.1	21.3	15.9	11.3	14.3	8.8
Sweden	27.8	30.5	25.2	10.8	12.1	9.7
Switzerland	22.3	25.7	19.4	7.5	9.1	6.2
Syrian Arab Republic	12.9	14.4	11.7	8.2	9.4	7.2
Tajikistan	4.7	6.7	2.9	3.2	4.5	2.0

▶

Tab. S1 *(follows)*. Standardized rate of incidence and mortality of Colorectal Cancer in the countries of the world.

Population	ASIR	ASIR in males	ASIR in females	ASMR	ASMR in males	ASMR in females
Tanzania, United Republic of	8.5	7.7	9.3	6.3	5.8	6.8
Thailand	16.9	19.0	15.2	8.4	9.7	7.5
The Netherlands	41.0	48.4	34.3	13.5	16.2	11.1
The Republic of the Gambia						
Timor-Leste	8.9	10.1	7.9	5.0	6.2	4.0
Togo	8.2	12.1	5.0	6.3	9.3	3.8
Trinidad and Tobago	18.5	23.0	14.7	11.0	13.7	8.8
Tunisia	12.7	14.0	11.7	6.4	7.3	5.6
Turkey	20.6	26.2	16.2	10.1	13.0	7.8
Turkmenistan	6.2	7.0	5.7	3.8	4.3	3.3
Uganda	6.7	7.8	6.0	5.0	5.9	4.4
Ukraine	25.5	33.6	20.5	12.9	18.1	9.9
United Arab Emirates	13.1	11.5	17.3	6.9	6.2	8.7
United Kingdom	34.1	40.0	29.0	11.4	13.5	9.6
United States of America	25.6	28.7	22.9	8.0	9.4	6.7
Uruguay	32.0	40.6	25.6	14.3	19.3	10.9
Uzbekistan	8.9	9.5	8.5	5.2	5.7	4.8
Vanuatu	5.2	4.2	6.3	4.8	4.2	5.4
Venezuela, Bolivarian Republic of	14.2	15.0	13.4	7.8	8.6	7.1
Viet Nam	14.1	17.6	11.6	7.0	9.1	5.5
Yemen	10.7	12.0	9.5	7.7	8.6	6.9
Zambia	5.6	6.3	5.3	4.0	4.8	3.7
Zimbabwe	8.9	10.4	8.0	6.4	7.8	5.6

Tab. S2. Human development index and its components for different countries of the world.

HDI rank	Population	HDI	Life expectancy at birth	Mean years of schooling	Gross national Income (GNI) per capita
1	Norway	0.96	82.40	12.90	66494
2	Switzerland	0.96	83.80	13.40	69394
3	Ireland	0.96	82.30	12.70	68371
4	Germany	0.95	81.30	14.20	55314
4	Iceland	0.95	83.00	12.80	54682
7	Australia	0.94	83.40	12.70	48085
7	Sweden	0.95	82.80	12.50	54508
9	The Netherlands	0.94	82.30	12.40	57707
10	Denmark	0.94	80.90	12.60	58662
11	Finland	0.94	81.90	12.80	48511
12	Singapore	0.94	83.60	11.60	88155
13	Belgium	0.93	81.60	12.10	52085
14	Canada	0.93	82.40	13.40	48527
14	New Zealand	0.93	82.30	12.80	40799
14	United Kingdom	0.93	81.30	13.20	46071
17	United States of America	0.93	78.90	13.40	63826
18	Austria	0.92	81.50	12.50	56197
20	Japan	0.92	84.60	12.90	42932
21	Israel	0.92	83.00	13.00	40187
22	Korea, Republic of	0.92	83.00	12.20	43044
23	Luxembourg	0.92	82.30	12.30	72712
24	Slovenia	0.92	81.30	12.70	38080
25	Spain	0.90	83.60	10.30	40975
26	Czechia	0.90	79.40	12.70	38109
26	France	0.90	82.70	11.50	47173
28	Malta	0.90	82.50	11.30	39555
29	Italy	0.89	83.50	10.40	42776
30	Estonia	0.89	78.80	13.10	36019
30	United Arab Emirates	0.89	78.00	12.10	67462
32	Cyprus	0.89	81.00	12.20	38207
33	Greece	0.89	82.20	10.60	30155
34	Poland	0.88	78.70	12.50	31623
35	Lithuania	0.88	75.90	13.10	35799
37	Latvia	0.87	75.30	13.00	30282
38	Portugal	0.86	82.10	9.30	33967
39	Slovakia	0.86	77.50	12.70	32113
40	Saudi Arabia	0.85	75.10	10.20	47495
41	Bahrain	0.85	77.30	9.50	42522
42	Hungary	0.85	76.90	12.00	31329
43	Chile	0.85	80.20	10.60	23261
44	Croatia	0.85	78.50	11.40	28070
45	Qatar	0.85	80.20	9.70	92418
46	Argentina	0.85	76.70	10.90	21190
47	Brunei Darussalam	0.84	75.90	9.10	63965
48	Montenegro	0.83	76.90	11.60	21399
49	Belarus	0.82	74.80	12.30	18546
49	Romania	0.83	76.10	11.10	29497
49	Russian Federation	0.82	72.60	12.20	26157
53	Kazakhstan	0.83	73.60	11.90	22857
54	Turkey	0.82	77.70	8.10	27701
55	Bulgaria	0.82	75.10	11.40	23325
56	Oman	0.81	77.90	9.70	25944
56	Uruguay	0.82	77.90	8.90	20064
58	Bahamas	0.81	73.90	11.40	33747

▶

Tab. S2 *(follows).* Human development index and its components for different countries of the world.

HDI rank	Population	HDI	Life expectancy at birth	Mean years of schooling	Gross national Income (GNI) per capita
58	Panama	0.82	78.50	10.20	29558
60	Barbados	0.81	79.20	10.60	14936
61	Costa Rica	0.81	80.30	8.70	18486
62	Kuwait	0.81	75.50	7.30	58590
63	Georgia	0.81	73.80	13.10	14429
63	Malaysia	0.81	76.20	10.40	27534
65	Serbia	0.81	76.00	11.20	17192
66	Mauritius	0.80	75.00	9.50	25266
67	Trinidad and Tobago	0.80	73.50	11.00	26231
68	Albania	0.80	78.60	10.10	13998
70	Iran, Islamic Republic of	0.78	76.70	10.30	12447
71	Cuba	0.78	78.80	11.80	8621
72	Armenia	0.78	75.10	11.30	13894
73	Sri Lanka	0.78	77.00	10.60	12707
76	Bosnia and Herzegovina	0.78	77.40	9.80	14872
76	Mexico	0.78	75.10	8.80	19160
78	Peru	0.78	76.70	9.70	12252
78	Ukraine	0.78	72.10	11.40	13216
80	Thailand	0.78	77.20	7.90	17781
82	North Macedonia	0.77	75.80	9.80	15865
83	Colombia	0.77	77.30	8.50	14257
84	Brazil	0.77	75.90	8.00	14263
84	Ecuador	0.76	77.00	8.90	11044
87	China	0.76	76.90	8.10	16057
88	Azerbaijan	0.76	73.00	10.60	13784
89	Dominican Republic	0.76	74.10	8.10	17591
90	Lebanon	0.74	78.90	8.70	14655
91	Algeria	0.75	76.90	8.00	11174
91	Republic of Moldova	0.75	71.90	11.70	13664
93	Fiji	0.74	67.40	10.90	13009
94	Tunisia	0.74	76.70	7.20	10414
97	Mongolia	0.74	69.90	10.30	10839
98	Jamaica	0.73	74.50	9.70	9319
98	Maldives	0.74	78.90	7.00	17417
98	Suriname	0.74	71.70	9.30	14324
101	Venezuela, Bolivarian Republic of	0.71	72.10	10.30	7045
102	Botswana	0.74	69.60	9.60	16437
103	Jordan	0.73	74.50	10.50	9858
104	Paraguay	0.73	74.30	8.50	12224
106	Libya	0.72	72.90	7.60	15688
107	Uzbekistan	0.72	71.70	11.80	7142
108	Belize	0.72	74.60	9.90	6382
108	Bolivia, Plurinational State of	0.72	71.50	9.00	8554
110	Indonesia	0.72	71.70	8.20	11459
111	Philippines	0.72	71.20	9.40	9778
112	Turkmenistan	0.72	68.20	10.30	14909
114	Gaza Strip and West Bank	0.71	74.10	9.20	6417
115	South Africa	0.71	64.10	10.20	12129
117	Egypt	0.71	72.00	7.40	11466
118	Viet Nam	0.70	75.40	8.30	7433
119	Gabon	0.70	66.50	8.70	13930
120	Kyrgyzstan	0.70	71.50	11.10	4864
121	Guyana	0.68	69.90	8.50	9455
121	Morocco	0.69	76.70	5.60	7368

▶

Tab. S2 *(follows)*. Human development index and its components for different countries of the world.

HDI rank	Population	HDI	Life expectancy at birth	Mean years of schooling	Gross national Income (GNI) per capita
123	Iraq	0.67	70.60	7.30	10801
124	El Salvador	0.67	73.30	6.90	8359
125	Cabo Verde	0.67	73.00	6.30	7019
126	Tajikistan	0.67	71.10	10.70	3954
127	Nicaragua	0.66	74.50	6.90	5284
128	Guatemala	0.66	74.30	6.60	8494
129	Namibia	0.65	63.70	7.00	9357
130	India	0.65	69.70	6.50	6681
131	Bhutan	0.65	71.80	4.10	10746
132	Honduras	0.63	75.30	6.60	5308
134	Bangladesh	0.63	72.60	6.20	4976
137	Lao People's Democratic Republic	0.61	67.90	5.30	7413
138	Ghana	0.61	64.10	7.30	5269
139	Eswatini	0.61	60.20	6.90	7919
140	Vanuatu	0.61	70.50	7.10	3105
141	Kenya	0.60	66.70	6.60	4244
141	Timor-Leste	0.61	69.50	4.80	4440
143	Nepal	0.60	70.80	5.00	3457
144	Cambodia	0.59	69.80	5.00	4246
145	Angola	0.58	61.20	5.20	6104
145	Equatorial Guinea	0.59	58.70	5.90	13944
145	Zambia	0.58	63.90	7.20	3326
148	Myanmar	0.58	67.10	5.00	4961
149	Congo, Republic of	0.57	64.60	6.50	2879
150	Zimbabwe	0.57	61.50	8.50	2666
151	Solomon Islands	0.57	73.00	5.70	2253
152	Syrian Arab Republic	0.57	72.70	5.10	3613
153	Cameroon	0.56	59.30	6.30	3581
154	Comoros	0.55	64.30	5.10	3099
154	Pakistan	0.56	67.30	5.20	5005
156	Papua New Guinea	0.56	64.50	4.70	4301
157	Mauritania	0.55	64.90	4.70	5135
158	Benin	0.55	61.80	3.80	3254
159	Rwanda	0.54	69.00	4.40	2155
160	Uganda	0.54	63.40	6.20	2123
161	Côte d'Ivoire	0.54	57.80	5.30	5069
161	Nigeria	0.54	54.70	6.70	4910
163	Madagascar	0.53	67.00	6.10	1596
164	Tanzania, United Republic of	0.53	65.50	6.10	2600
165	Lesotho	0.53	54.30	6.50	3151
166	Djibouti	0.52	67.10	4.10	5689
167	Senegal	0.51	67.90	3.20	3309
168	Togo	0.52	61.00	4.90	1602
169	Afghanistan	0.51	64.80	3.90	2229
170	Haiti	0.51	64.00	5.60	1709
171	Sudan	0.51	65.30	3.80	3829
172	The Republic of the Gambia	0.50	62.10	3.90	2168
173	Liberia	0.48	64.10	4.80	1258
174	Congo, Democratic Republic of	0.48	60.70	6.80	1063
174	Ethiopia	0.49	66.60	2.90	2207
174	Malawi	0.48	64.30	4.70	1035
177	Guinea	0.48	61.60	2.80	2405
178	Guinea-Bissau	0.48	58.30	3.60	1996
179	Yemen	0.47	66.10	3.20	1594
180	Eritrea	0.46	66.30	3.90	2793

▶

Tab. S2 *(follows).* Human development index and its components for different countries of the world.

HDI rank	Population	HDI	Life expectancy at birth	Mean years of schooling	Gross national Income (GNI) per capita
181	Mozambique	0.46	60.90	3.50	1250
182	Sierra Leone	0.45	54.70	3.70	1668
183	Burkina Faso	0.45	61.60	1.60	2133
184	Burundi	0.43	61.60	3.30	754
184	Mali	0.43	59.30	2.40	2269
186	South Sudan	0.43	57.90	4.80	2003
187	Chad	0.40	54.20	2.50	1555
188	Central African Republic	0.40	53.30	4.30	993
189	Niger	0.39	62.40	2.10	1201

Non Comunicable Diseases

Comparing the trend of colorectal cancer before and after the implementation of the Population-Based National Cancer Registry in Iran

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Keywords

Cancer registration • Colorectal cancer • Trend Analysis • Iran • ITS

Summary

Introduction. *Colorectal cancer is the third most common malignancy and the second leading cause of cancer deaths worldwide. This disease is the fourth most common malignancy in Iran. Since knowing the trend of this cancer is necessary for planning; this study aimed to compare the trend of colorectal cancer before and after implementing the Population-Based National Cancer Registry.*
Methods. *In this time series analysis using secondary data, the autoregressive integrated moving average (ARIMA) was used to predict the future trend. An Interrupted Time Series (ITS) regression model was also used to compare the incidence and mortality of colorectal cancer before and after the setting up of the Iranian National Population-Based Cancer Registry (INPCR).*
Results: *Among Iranian men, an increasing trend in the incidence (from 16.8 in 2019 to 19.5 per 100,000 in 2027) and deaths of colorectal cancer for the coming years was predicted (from 10.2 in 2019 to 11.2 per 100,000 in 2027). A similar pattern was also observed for the incidence of this cancer among females (from 11 in 2019 to 12.3 per 100,000 in 2027), but a reverse pattern was predicted for the trend of deaths among women (from 2.06 in 2019 to 1.93 per 100,000 in 2027). During the years after the implementation of the INPCR, the trend of cases (β: 0.33, $p < 0.001$) as well as deaths due to colorectal cancer was significantly increasing (β: 0.08, $p < 0.001$) among the Iranian population.*
Conclusions. *Probably, part of the increase in the incidence and mortality of colorectal cancer could be due to the improvement of the registration and reporting system of new cancer cases.*

Introduction

Colorectal cancer is a lethal disease and the second leading cause of cancer deaths worldwide [1]. Colorectal cancer morbidity and mortality rates differ around the world. Globally, colorectal cancer is the second most commonly diagnosed cancer in females and the third in males. Rates of both incidence and mortality are substantially higher in males compared to females [2].
Recognized risk factors for colorectal cancer include a positive family history, consumption of processed meats [3], smoking [4], excess body fat [5], a diet containing low fiber and insufficient consumption of dairy products as well as a low level of regular physical activity [6]. Colorectal cancer is the fourth most common malignancy in Iran [7]. The Iranian lifestyle has slowly changed to a Western lifestyle during the last three decades [8]. In recent years, the Iranian population has been facing demographic changes and economic and social developments, which can have significant effects on cancer patterns and trends [9].
The increasing trend of colorectal cancer could be partly due to demographic and lifestyle changes in the Iranian population, lower consumption of vegetables and fruits higher intake of red meat, and the community transition to a sedentary lifestyle [10]. The prominence of cancer registry systems in developing countries is not doubted. Accurate epidemiologic data on cancer is essential, both for research and for the planning and evaluation of programs in cancer prevention and control [11]. Efforts to register cancer in Iran began in the 1950s. In the late 2000s, regional population-based cancer registries were established in some provinces of Iran [12], and several reports were published [13-15]. Because this population-based cancer registration system had some limitations including disagreement in method and data collection as well as lack of appropriate structures and adequate financial support, in the early 2010s the Iranian Ministry of Health planned to launch the Iranian National Population-Based Cancer Registry (INPCR). The main aim of INPCR was to aggregate population-based cancer data at the national level [12]. Up to the year 2014, almost 98% of the Iranian population has been covered by INPCR [12]. Cancer registration is an important part of cancer control programs, and registration data can be used widely in etiologic research, evaluation of the effects of preventive measures, and program development in healthcare services [16]. The use of the cancer registration system in developed countries has led to a reduction in cancer deaths [17]. Cancer registration has shown the effects of early diagnosis and prevention campaigns at a population level [18]. Since knowing the trend of this cancer in the country is necessary for planning, the current study aimed to compare the trend

of colorectal cancer before and after implementing the Population-Based National Cancer Registry in Iran.

Materials and methods

Study design and data source

In this time series analysis using secondary data, we obtained the figures of new cases and deaths due to colorectal cancer from the Gapminder website, which is available at https://www.gapminder.org/data/. These data included all registered new cases and deaths due to colorectal cancer in Iran, per 100,000 populations for both Males and Females which have been diagnosed and registered from 1990 to 2019. Data from this website has been used in previous studies [19, 20].

Data analysis

To compare the average incidence and mortality before and after 2008 the paired t-test was used.

ARIMA model

To predict the future trend, the Autoregressive Integrated Moving Average (ARIMA (p, d, q)) was used. The ARIMA model as a time series analysis prediction method is a combination of an autoregressive and a moving average model [21] which is based on the fitting value of the past data sequence to extrapolate into the future (2020-2027). ARIMA model has been widely used in disease trend prediction [22]. This model is denoted ARIMA (p, d, q) where p is the number of time lags (the order of the model), q is the order of the moving average model, and d is the degree of differencing [22]. The process of the ARIMA model generating involves three steps. First, the Augmented Dickey-Fuller (ADF) test was used to assess the stationarity. Second, p and q were determined from autocorrelation function (ACF) and partial autocorrelation function (PACF) plots. The ACF plot indicates that the time series data follows the AR or autoregressive model. The AR time series model is obtained if the ACF plot decays towards zero or follows a sine wave pattern [23]. PACF gives the partial correlation of a stationary time series with its own lagged values, regressed the values of the time series at all shorter lags [24]. Third, to select the appropriate prediction model, p and q were replaced into the model from smallest to largest values. To select the best model, Akaike's information criterion (AIC) was used [25].

After selecting the best model according to minimum AIC and assessing the fitness of the selected models using different tests the ARIMA (p, d, q) model was used to predict the future trend based on current data. By considering annual time intervals, 30 years from 1990 to 2019 were accounted for in the time series model and the prediction was made up to 2027.

Interrupted time series regression

An Interrupted time series (ITS) was also used to compare the incidence and mortality of colorectal cancer before and after the setting up of the INPCR. In the ITS model, the dependent variable is measured before and after the intervention [26]. In the late 2000s, regional population-based cancer registries were established in some provinces of Iran [12], therefore, 2008 was chosen as the cut-off point for comparing the incidence and mortality of colorectal cancer. Data analyses were conducted using the ITSM (Interactive Time Series Modeling) for prediction, Stata 2017 software for Interrupted Time Series, and Excel 2010 for data management and graphs. The significance level was set at 0.05.

Results

Trend Analysis

According to our results, the average and standard deviation of registered new colorectal cancer cases from 1990 to 2019 among Iranian men and women were 11.9±2.4 and 8.7±1.1 cases per 100,000 populations, respectively. The highest incidence rate of colorectal cancer in men was 16.8 per 100,000 people in 2019, and the lowest rate was 9.29 in 1990. Among women, the highest recorded incidence was 11 in 2019, and the lowest incidence was 7.3, in 1990. Also, the average and standard deviation of registered new deaths due to colorectal cancer from 1990 to 2019 among men and women were 8.4 ± 1.01 and 2.4 ± 0.39 deaths per 100,000 populations, respectively (Tab. I).

Figure 1 shows the annual changes in incidence and mortality by gender. There were more fluctuations among men compared to women, both in incidence and mortality (Fig. 1). The average incidence before and after 2008 among men was 10.24± 0.87 and 14.35 ± 1.65, respectively (p = 0.0001). The average incidence before and after 2008 among women was 7.89 ± 0.49 and 9.91 ± 0.74, respectively (p = 0.0001) (Tab. II).

Prediction

An increasing trend in the incidence as well as deaths due to colorectal cancer for the coming years has been predicted (Fig. 2). Among Iranian men, an increasing trend in the incidence (from 16.8 in 2019 to 19.5 per 100,000 in 2027, ARIMA model with p = 1, q = 1, and AIC = 102 was used [ARIMA (1, 1, 1)] as well as deaths of colorectal cancer for the coming years was predicted (from 10.2 in 2019 to 11.2 per 100,000 in 2027, ARIMA model with p = 1, q = 1, and AIC = 180 was used [ARIMA (1, 2, 1)] (Fig. 2).

A similar pattern also was observed for the incidence of this cancer among females (from 11 in 2019 to 12.3 per 100,000 in 2027, ARIMA model with p = 2, q = 1, and AIC = 144 was used [ARIMA (2, 1, 1)] (Fig. 2), but a reverse pattern was predicted for the trend of deaths among the women (from 2.06 in 2019 to 1.93 per 100,000 in 2027, ARIMA model with p = 1, q = 1, and AIC = 158 was used (ARIMA (1, 2, 1)) (Fig. 2).

Interrupted Time series

The incidence and mortality trends were compared

Tab. I. The incidence and deaths of cancers among the Iranian population, 1990-2019 (proportion per 100,000 population).

Year	Registered cases in Men	Change	Registered Cases in Women	Change	Registered Deaths in Men	Change	Registered Deaths in Women	Change
1990	9.29	-	7.3	-	7.65	-	3.22	-
1991	9.36	0.07	7.33	0.03	7.62	-0.03	3.16	-0.06
1992	9.37	0.01	7.34	0.01	7.57	-0.05	3.12	-0.04
1993	9.6	0.23	7.47	0.13	7.59	0.02	3.05	-0.07
1994	9.54	-0.06	7.45	-0.02	7.5	-0.09	3	-0.05
1995	9.66	0.12	7.51	0.06	7.48	-0.02	2.93	-0.07
1996	9.95	0.29	7.71	0.2	7.51	0.03	2.84	-0.09
1997	9.89	-0.06	7.76	0.05	7.45	-0.06	2.76	-0.08
1998	9.83	-0.06	7.73	-0.03	7.38	-0.07	2.69	-0.07
1999	9.58	-0.25	7.58	-0.15	7.23	-0.15	2.62	-0.07
2000	10	0.42	7.83	0.25	7.33	0.1	2.55	-0.07
2001	10.6	0.6	8.15	0.32	7.5	0.17	2.5	-0.05
2002	10.7	0.1	8.18	0.03	7.57	0.07	2.43	-0.07
2003	10.8	0.1	8.19	0.01	7.68	0.11	2.36	-0.07
2004	11	0.2	8.3	0.11	7.79	0.11	2.31	-0.05
2005	11.5	0.5	8.59	0.29	8.02	0.23	2.26	-0.05
2006	11.9	0.4	8.78	0.19	8.22	0.2	2.22	-0.04
2007	11.9	0	8.82	0.04	8.33	0.11	2.17	-0.05
2008	12.1	0.2	8.91	0.09	8.48	0.15	2.14	-0.03
2009	12.4	0.3	9.02	0.11	8.69	0.21	2.12	-0.02
2010	12.7	0.3	9.16	0.14	8.87	0.18	2.1	-0.02
2011	13.1	0.4	9.36	0.2	8.99	0.12	2.09	-0.01
2012	13.4	0.3	9.5	0.14	9.11	0.12	2.08	-0.01
2013	13.8	0.4	9.7	0.2	9.33	0.22	2.09	0.01
2014	14.5	0.7	9.97	0.27	9.6	0.27	2.11	0.02
2015	15.3	0.8	10.3	0.33	9.93	0.33	2.13	0.02
2016	15.8	0.5	10.6	0.3	10.1	0.17	2.13	0
2017	16	0.2	10.7	0.1	10.1	0	2.11	-0.02
2018	16.4	0.4	10.8	0.1	10.1	0	2.08	-0.03
2019	16.8	0.4	11	0.2	10.2	0.1	2.06	-0.02
P trend	0.001	0.001	0.001	0.008	0.001	0.001	0.001	0.0001

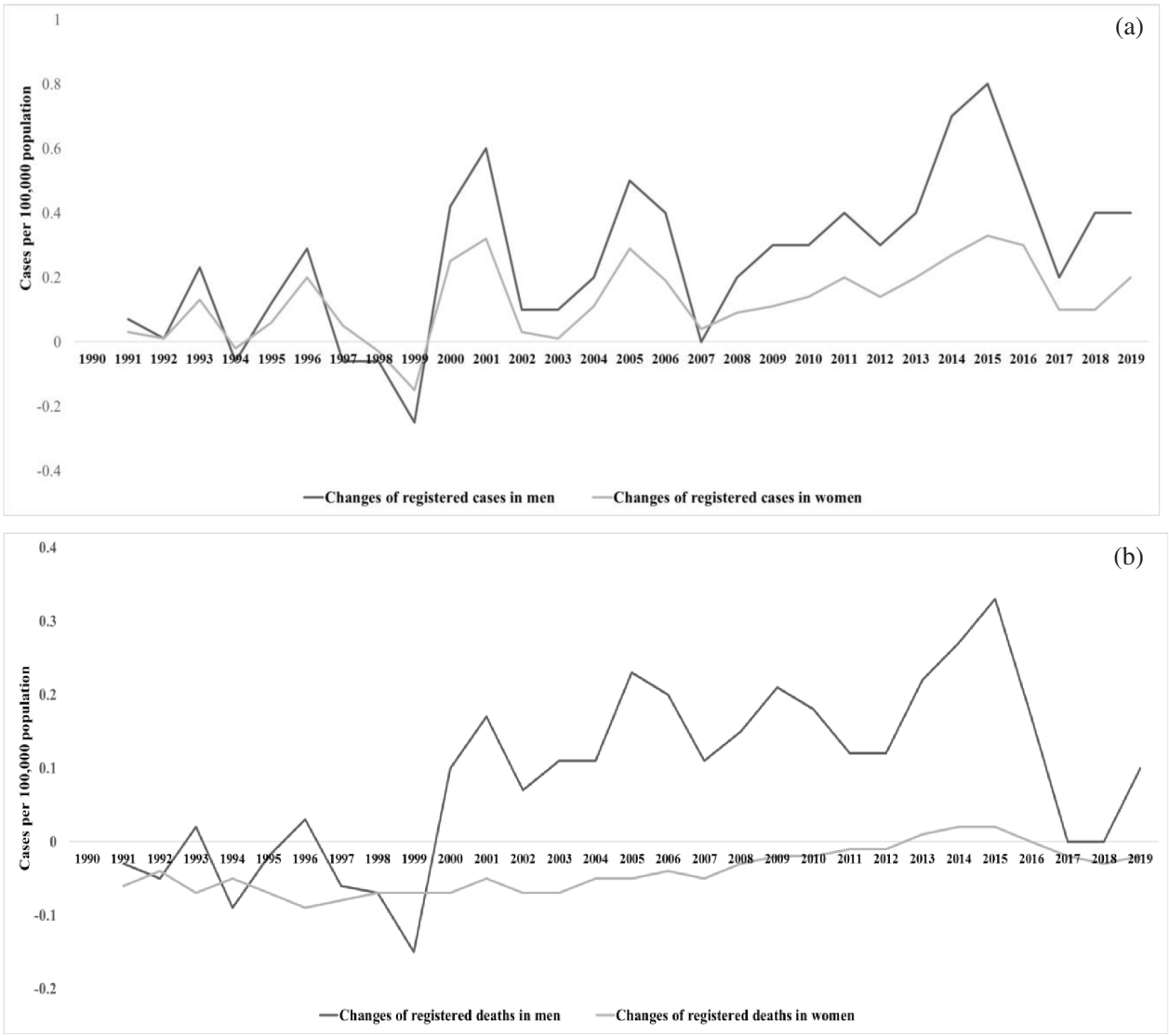
Change: The difference in each year's cases from the previous year.

before and after 2008 through an ITS analysis, the post-intervention (after the implementation of the INPCR) slope changes are significant for the incidence (β: 0.33, $p < 0.001$) and deaths due to colorectal cancer (β: 0.08, $p < 0.001$) (Data not shown). In other words, after the implementation of the INPCR, the number of registered cases as well as deaths had a statistically significant increasing trend among the Iranian population. Although, before and after 2008, the slope of the regression line related to the incidence of the disease is positive, but the incidence has increased more steeply after this year (Fig. 3a). Regarding deaths, the slope of the regression line was negative before 2008, while after the implementation of the INPCR, the registration of deaths due to colorectal cancer increased (Fig. 3b).

Discussion

This study investigated the incidence of colorectal cancer and its mortality in Iran for 29 years, to assess the impact of the national cancer registry on the trend of this cancer in Iran. The results showed that the incidence and mortality rate in Iran increased between 1990 and 2019. Consistent with the results of the present study, Yazdizadeh et al., concluded that the incidence of colorectal cancer in

Fig. 1. The trend of changes in incidence (a) and deaths (b) of colorectal cancer according to gender, 1990-2019 (proportion per 100,000 population).



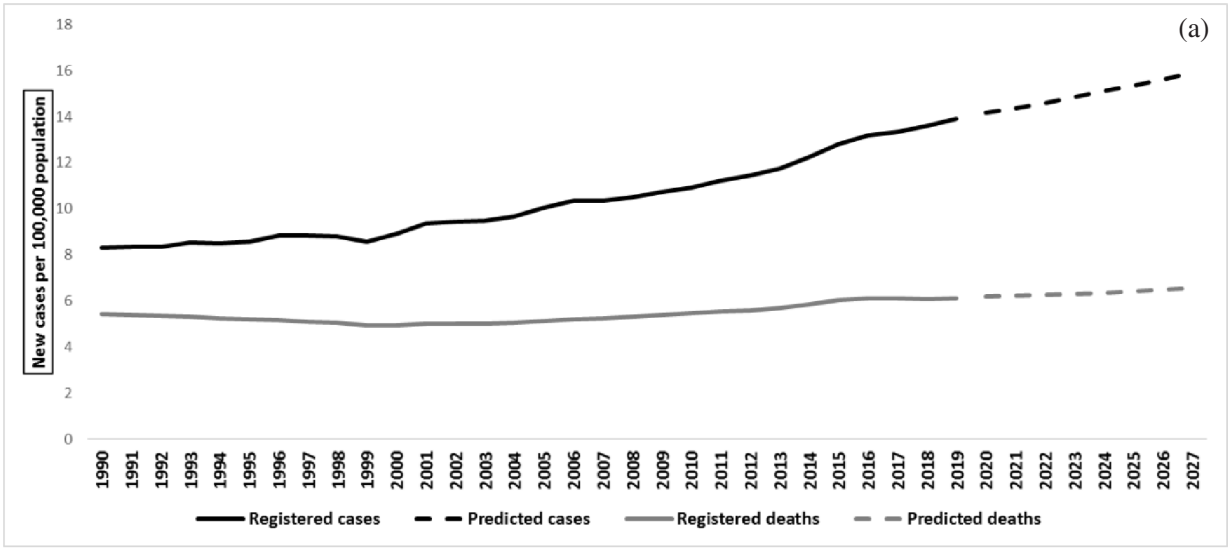
Tehran has increased by 82% over the past 30 years [27]. The results of Mousavi et al.'s study also confirm the increasing trend of colon cancer in Iran [28]. An increasing trend in the incidence of colorectal cancer has also been reported in some European [29, 30] and African [31] countries. An increasing mortality trend has also been reported in several countries in Latin America, the Caribbean, and Asia [32, 33] and this may reflect limited access to early diagnosis and treatment [34]. A study in Iran showed that the five-year survival rate of colorectal cancer is 41 percent and the median survival time is estimated to be 3.5 years [35].

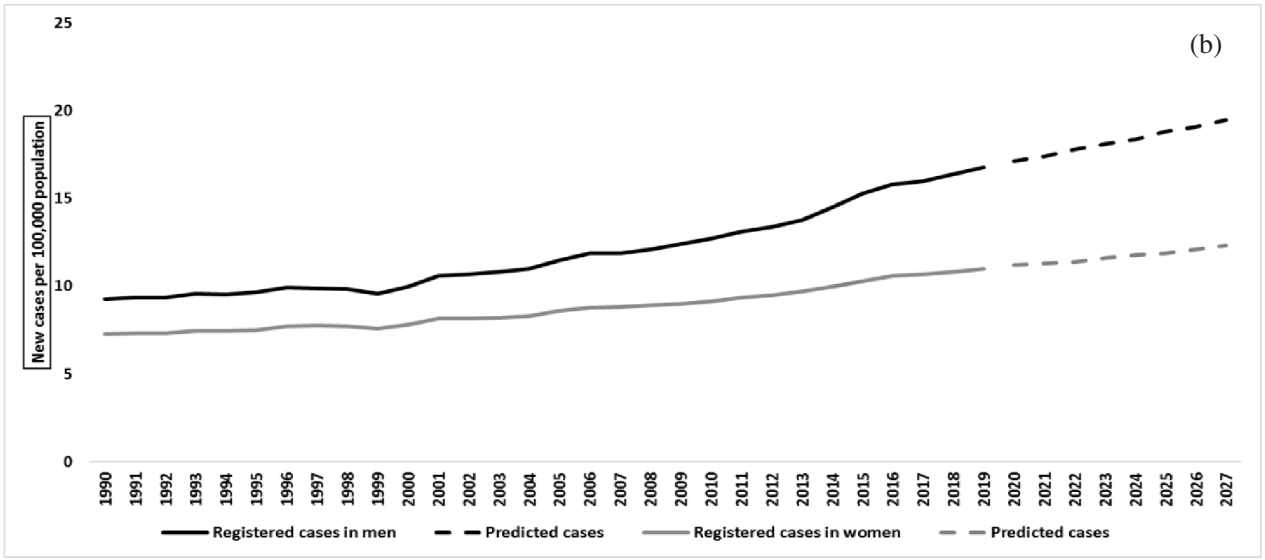
Tab. II. Comparing the average incidence and deaths of colorectal cancer (proportion per 100,000 population), before and after 2008.

Variable	Year	Average	SD	p*
Cases in Men	Before 2008	10.24	0.87	0.0001
	After 2008	14.35	1.65	
Cases in Women	Before 2008	7.89	0.49	0.0001
	After 2008	9.91	0.74	
Deaths in Men	Before 2008	7.63	0.29	0.0001
	After 2008	9.45	0.62	
Deaths in Women	Before 2008	2.67	0.34	0.0001
	After 2008	2.10	0.02	

* Based on paired t-test.

Fig. 2. The prediction of the total incidence and deaths (a), incidence by gender (b), and deaths of colorectal cancer by gender (c), 1990-2027 (proportion per 100,000 population).





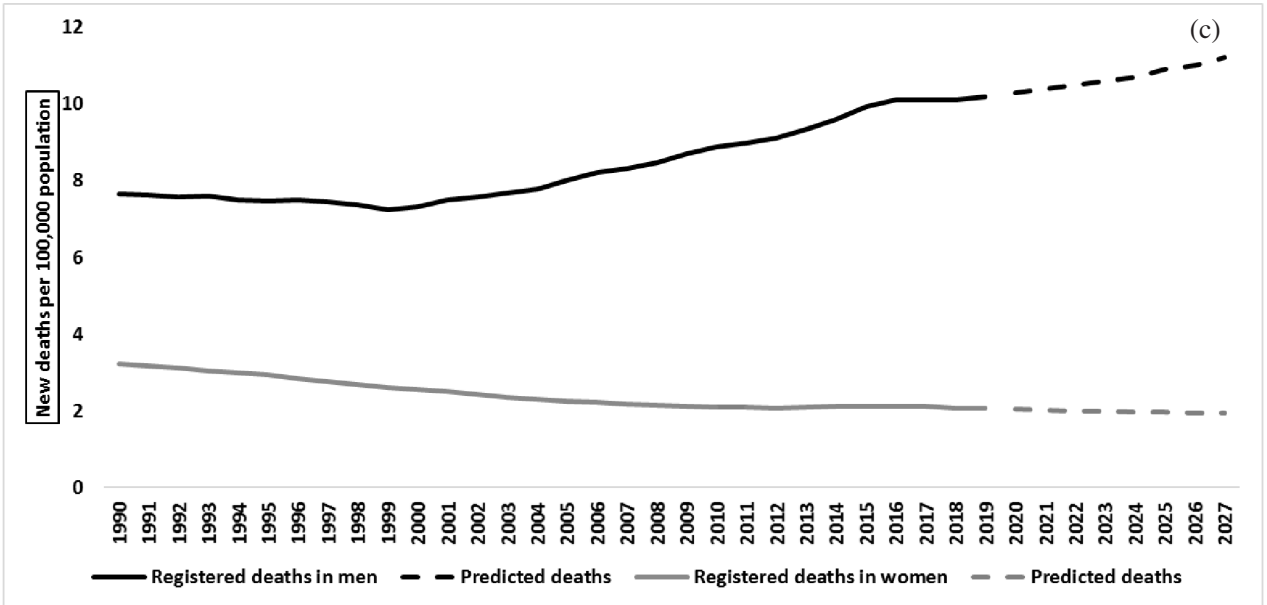
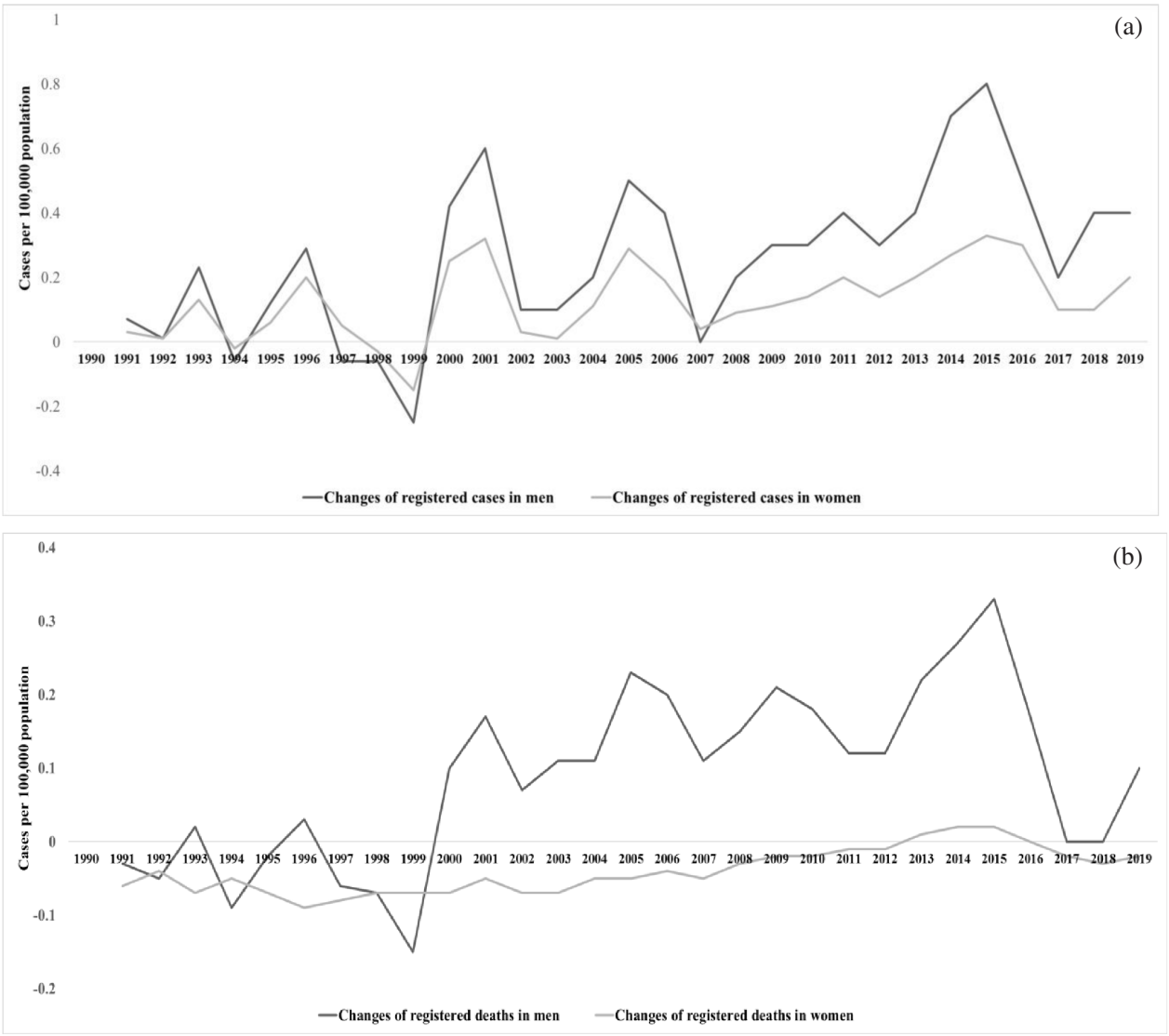


Fig. 3. Interrupted time series analysis of the total number of colorectal cancer cases (a) and deaths (b) from 1990 to 2019 (proportion per 100,000 population), before and after 2008.



A systematic review reported that the average 5-year overall survival rate in the Iranian population is estimated to be 52.5% [36]. A more favorable trend for females regarding mortality was also observed in the present study, which may be attributable, in part, to differential sex exposure to major environmental risk factors. Other studies worldwide confirmed that overall survival is better for women than for men [35]. When the trends of incidence and mortality before and after 2008 were compared, a statistically significant difference was observed before and after this date in terms of incidence and mortality. Since the late 2000s, a population-based registration program in the country as a complement to pathology-based registration has been established and the coverage of the cancer registration system in Iran has been improved [12]. A similar trend of incidence during this period has been observed in the skin [37] and stomach [38, 39] cancers. The current study showed that, during the years after the implementation of the INPCR, the number of registered cases as well as deaths had a significant increasing trend among the Iranian population. Although, before and after 2008, the slope of the regression line related to the incidence of the disease is positive, but the incidence has increased more steeply after this year. Regarding deaths, the slope of the regression line was negative before 2008, while during the years after the implementation of the INPCR, the trend of deaths due to colorectal cancer increased. This implies that probably some colorectal cancer deaths have been missed during the years before the implementation of the INPCR. A study in Canada using ITS analysis to determine the impact of the colorectal cancer screening guideline on the incidence rates of colon and rectal cancer among Canadians showed that the post-guideline slope changes are significant for both cancers [40]. Another study in Taiwan evaluated the influence of a nationwide screening program through the ITS analysis. They concluded that the implementation of this screening program effectively

reduced colorectal cancer mortality [41]. Based on the above explanations, it can be concluded that at least part of the observed increase in the incidence of colorectal cancer in Iran could be due to the improvement of the approach to collecting information related to the cancer registration system. Another explanation for the increase in the incidence of colorectal cancer in Iran could be the increase in the prevalence of risk factors [42]. Diet plays an important role in the development of colon cancer [43, 44]. Iran, as a developing country in the Persian Gulf region, has been faced with the increasing prevalence of cancer risk factors, an aging population, and population growth in recent decades [12]. One of the reasons for the increase in the trend of cancers especially colorectal cancer in Iran is the change in eating habits. In the past decades, fast foods have gradually replaced traditional Iranian foods, which are mainly high in fiber. Studies show that fat consumption in Iran has increased and this has led to an increase in obesity [8, 45]. Obesity and lack of regular physical activity are positively correlated with the risk of developing colorectal cancer [46, 47]. This is while estimates show that only one-third of the Iranian adult population engages in regular physical activity and the prevalence of smoking in Iran is approximately 14% [48].

Our results showed that the incidence and mortality of colorectal cancer are increasing in the whole Iranian population. Colorectal cancer survival is strongly related to the stage of disease diagnosis [49]. For colorectal cancer, accurate and standardized surgery can increase patient survival and significantly reduce the risk of recurrence [50]. In addition, estimates show that in developing countries, a small percentage of patients with colorectal cancers receive radiotherapy [51].

Despite the valuable results, the present study had limitations. First, lack of access to individual data such as family history, age, dietary pattern, and physical activity. Secondly, the observed difference in the incidence and mortality rate of colorectal cancer before and after the implementation of the cancer registration system could be partially due to confounding effects, which could not be adjusted in the present study.

Conclusions

Implementation of population-based cancer registration programs, improved the cancer registration system and the probably part of the increase in the incidence and mortality of colorectal cancer could be attributable to the improvement of the registration and reporting system of new cancer cases. This study provides evidence for the need for further analysis of the cancer registry system. Considering the preventability of colorectal cancer and the increase in the incidence and mortality of this disease, educational interventions are necessary, especially regarding screening programs and early diagnosis methods. Finally, the impact of the cancer registration system should be considered in the interpretation of the results of all cancer research in Iran.

Ethical consideration

This study was reviewed and approved by the ethics committee of Baqiyatallah University of Medical Science (IR.BMSU.REC.1402.033). Patient consent is not applicable.

Data availability statement

The data presented in this study are available on request from the corresponding author.

Informed consent statement

Not applicable.

Conflicts of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Fundings

This study does not have a funding source.

Authors' contributions

Conceptualization, Methodology, Project administration, Supervision, writing – original draft, Writing – review & editing: all authors. All authors read and approved the final manuscript.

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Non Comunicable Diseases

Burden attributable to Iodine deficiency in Iran from 1990 to 2019: findings from Global Burden of Disease study

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Keywords

Epidemiology • Iodine • Iodine deficiency • Micronutrient deficiency • Age-standardized disability-adjusted life years • Iran

Summary

Introduction. *Iodine is necessary for the synthesis of thyroid hormones which rely on sufficient levels of iodine. Iodine deficiency (ID) gives rise to various diseases. This is the first study presenting the epidemiology of ID in the Iranian population from 1992 to 2019.*

Methods. *This study was performed based on the analysis of global burden of disease (GBD) study data. Epidemiological indices including prevalence, incidence, and age-standardized disability-adjusted life years (DALYs) were compared in all provinces located in Iran between 1992 and 2019.*

Results. *The studies' collective conclusions showed that Iran's age-standardized DALYs rate (ASDR) for iodine deficiency dropped from 14.76 to 5.92. Additionally, the ASDR for Iodine Deficiency is clearly trending lower for all provinces. The ASDR for iodine deficiency peaked in 1990 in middle-aged people of both sexes. But later in the year, the pattern changed, with males and older age groups in particular reporting a larger ASDR of iodine deficiency.*

Conclusions.*The findings of this study show that the burden of iodine deficiency disorder has decreased in different provinces, all age and, males, but some provinces and groups still need more regulations to reduce the burden of iodine deficiency.*

Introduction

The manufacturing of thyroid hormones depends on iodine, a non-metallic trace element that is vital to human health [1]. The thyroid gland, a vital organ in the body, contains the largest iodine stores and relies on sufficient iodine levels to produce thyroid hormones, such as thyroxine (T4) and triiodothyronine (T3), which are essential for the proper functioning of the liver, kidneys, muscles, and central nervous system [2, 3]. Evidence shows that adults require a daily intake of 150 micrograms of iodine to maintain thyroid hormone synthesis and overall homeostasis. Iodine deficiency stands as one of the most common nutrient deficiencies, resulting in reduced intrathyroidal synthesis of T4 and subsequently elevating thyroid-stimulating hormone (TSH) concentrations in the blood [4, 5]. This deficiency gives rise to various diseases: in adults, severe deficiency manifests as hypothyroidism, goiter, mental disability, and decreased fertility, while in children, it can cause goiter, intellectual/physical developmental impairments, deafness, and cretinism [4]. Many people worldwide suffer from iodine insufficiency, particularly in areas where iodine-deficient soil and food are prevalent [6]. The primary dietary sources of iodine are foods high in the mineral, such as fish, meat, milk, and eggs [7]. Despite global efforts to address iodine deficiency, including in Iran, where universal salt iodization (USI) has been implemented, understanding the burden of iodine deficiency in specific populations remains critical. This study aims to assess the burden of iodine deficiency in Iran from 1990 to 2019, utilizing data from the Global Burden of Disease (GBD) study. Iran also set up committees to monitor on the project's efficacy [5].

An international initiative run by the University of Washington's Institute for Health Metrics and Evaluation (IHME) is the global burden of diseases, injuries, and risk factors research (GBD). This endeavor affords several nations the chance to assess and contrast their respective state of health on an international level [8]. While there have been limited studies on iodine deficiency in Asia based on the GBD database, these studies do not specifically focus on the Iranian population. Hence, we utilized the GBD database to ascertain the burden

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attributed to iodine deficiency in Iran from 1992 to 2019. This study seeks to fill the research gap by examining the burden of iodine deficiency in Iran over the past three decades using GBD data, with a focus on understanding trends and identifying at-risk populations [9].

Method and material

In this study, GBD data were used. The GBD study was managed by the Institute for Health Metrics and Evaluation (IHME) to estimate the burden and epidemiology of 369 diseases and injuries, 87 risk factors, and the burden of disease during a 30-year period, from 1990 to 2019. The study was conducted in 204 countries and territories [10]. The methodological and statistical reports for the GBD study are provided here [10, 11]. In summary, the GBD data was gathered from epidemiological characteristics of different illnesses and injuries through a range of data sources, such as disease-specific registries, health surveys, and vital registration systems [11]. The data is clear, standard, and consistent amongst several sources. The GBD global data on iodine deficiency in Iran were used in this investigation. In order to increase the accuracy of estimation from partial reports, GBD used a complex statistical model to estimate the burden of disease and injury for various populations. This model comprises DisMOD-MR 2.1, a valid and dependable Bayesian meta-regression tool [11-13].

Data

We obtained age-standardized disability-adjusted life years (DALYs) for iodine deficiency in Iran from the GBD database, stratified by sex and year (1990-2019). DALYs were calculated by multiplying the prevalence of iodine deficiency by specific disability weights, derived from a variety of data sources, including disease registries, health surveys, and vital registration systems [8].

Index

In the GBD study, DALYs are calculated by multiplying the prevalence of Iodine deficiency by specific disability weight. The disability-adjusted life years were extracted from a number of Iodine deficiencies in Iran. We have rated DALYs for males, female, and both sexes in age-standardized rates per 100,000 from 1990 to 2019. Also, choropleth maps were created to visualize the geographical distribution of age-standardized DALY rates for iodine deficiency across Iranian provinces in 1990 and 2019, highlighting regional variations and changes over time. We included 95% uncertainty intervals for all estimates, calculated using a Bayesian approach to account for variability and uncertainty in the data, providing a more robust understanding of the burden of iodine deficiency.

Statistical Analysis

We employed an ordinary least squares simple linear regression model to evaluate trends in DALYs over time, as this model is suitable for analyzing temporal trends in continuous data from 1990 to 2019. We used mathematical methods and models for these analyses. All other analyses were performed via Python (version 3.10; Python Software Foundation). We evaluated the association between the DALYs rate for iodine deficiency across years and Iran provinces. The libraries used for these analyses were Pandas, Matplotlib, Numpy, Seaborn, and Geopandas. Python was chosen due to its robust data analysis and visualization libraries, such as Pandas for data manipulation, Numpy for working with arrays, Matplotlib, and Seaborn for visualization, and Geopandas for geographical analysis. Significance was assessed using a threshold of 0.05.

Results

National Level

Between 1990 and 2019, the Age-standardized DALYs rate (ASDR) of Iodine Deficiency decreased globally, with the MENA area and Iran experiencing the same trend. Iran's ASDR of Iodine Deficiency decreased from 14.76 (9.53-21.73) in 1990 to 5.92 (3.44-9.61) in 2019, as was noted. Also, ASDR of Iodine Deficiency in 1990 for the Global Scale and MENA region were 46.84(28.64-76.01) and 38.34 (23.72-57.53), Decreased to 30.69 (17.32-53.12) and 21.61 (13.25-33.41) in 2019, respectively as shown in Table I and Figure 1.

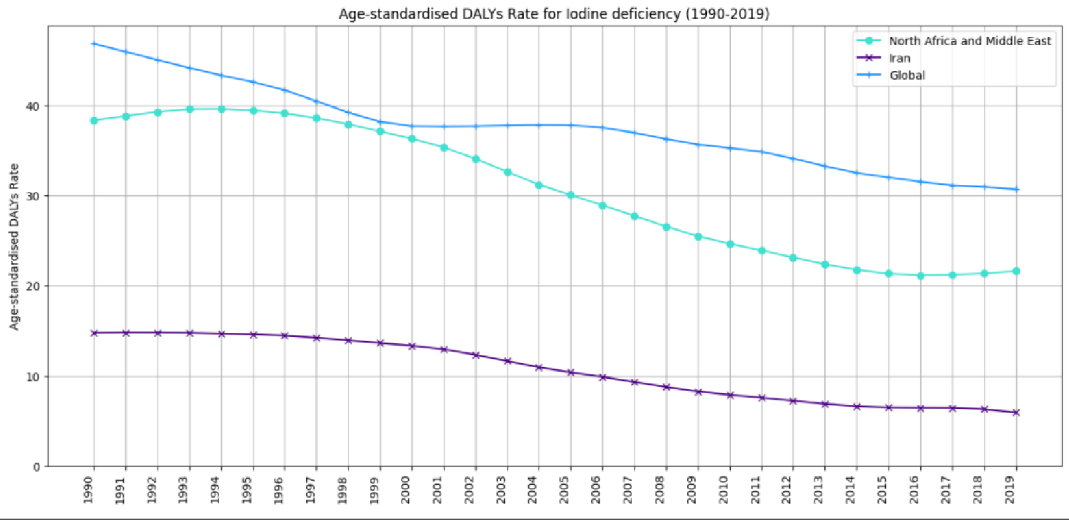
Sub-national Level

At the sub-national level, for all the provinces, there is a clear downward trend in the ASDR of Iodine Deficiency from 1990 to 2019. In 1990, the provinces of South Khorasan [19.7 (12.59-28.39)], Kurdistan [18.76 (12.05-27.43)], and Khorasan-e-Razavi [18.46 (11.95-26.93)], which are all border provinces, had highest ASDR related to iodine deficiency. After three decades in 2019,

Tab. I. Burden of Iodine deficiency in the world, Iran, and Middle East North Africa in 1990 and 2019.

	Iran			Mena			World		
	1990	2019	Percentage change	1990	2019	Percentage change	1990	2019	Percentage change
Prevalence	434.97	285.12	-34.43	1,602.52	942.86	-41.16	2,833.70	2,215.54	-21.81
DALY rate per 100000	13.15	6.12	-53.46	35.56	21.88	-38.47	46.73	31.52	-32.54
Age-standardized DALY rate per 100000	14.76	5.93	-59.82	38.35	21.62	-43.62	46.85	30.70	-34.47

Fig. 1. Trends in the age-standardized DALY rate of Iodine deficiency in Iran, Middle East and North Africa, and world from 1990 to 2019.



Sistan Baluchistan [7.87 (4.51-12.69)], Kerman [7.23 (4.24-11.71)] and South Khorasan [7.15 (4.08-11.62)] provinces had the highest ASDR respectively. In addition, Alborz [12.7 (7.83-19.57) in 1990 and 5.99 (3.44-9.73) in 2019], Mazandaran [12.7 (7.83-19.57) in 1990 and 6.1 (3.56-9.66) in 2019], and Tehran [8.04 (4.44-13.32) in 1990 and 2.58 (1.17-4.92) in 2019] provinces had the lowest ASDR related to iodine deficiency in both 1990 and 2019, as detailed in Table II and illustrated in Figures 2 and 3.

Age and Gender Disparities

In 1990, the ASDR of iodine deficiency reached its peak among middle-aged individuals of both genders. However, during the same year, there was a shift in the pattern, with older age groups, particularly males, experiencing a higher ASDR of iodine Deficiency. In 1990, the age group of 45-49 years exhibited the highest ASDR for iodine deficiency in males and females. In 2019, the age group of 45-49 years remained the highest ASDR among females, while among males, the age group of 75-79 years had the highest. In 1990, ASDR of iodine deficiency in females was 18.19 (11.7-26.93) and in males was 11.49 (7.40-16.83). In 2019, these values reached the 7.49 (4.34-12.33) and 4.41 (2.54-7.16) in females and males, respectively. Then, The Ratio of ASDR of iodine deficiency of females to males was 1.58 in 1990. This ratio has slightly increased and reached 1.7 in 2019, as shown in Table III and Figure 4.

Discussion

Based on the current results, iodine deficiency ASDR in Iran follows the global decremental trends in the past three decades. We observed this reduction in at-risk provinces revealing proper counter-actions against iodine deficiency. However, some parts of Iran still require more attention to mitigate iodine deficiency including; Sistan Baluchistan, Kerman, and South Khorasan. Age and gender-wise, the highest iodine deficiency ASDR remained unchanged in females from 1990 to 2019 with the highest value in age 45-49. In contrast, we observed a 30-year shift in age for the highest ASDR in males, reaching from 45-49 to 75-79. Concurrently, the ratio of iodine deficiency ASDR of females to males had an incremental trend from 1990 to 2019.

Proper policy-making has led to a significant reduction of iodine deficiency disorders (IDD) in past decades using a sustainable way of supplementing iodine by salt iodization programs leading to various health and economic outcomes especially in low- and middle-income countries [14, 15]. Salt iodizing was begun 19 1990 in Iran, however, there was no mandatory law for that until 1994; Since 1996, Iran has become a part of the global program of IDD prevention and followed all criteria to eliminate iodine deficiency [16]. Two decades after these health policies, nationwide investigations in 2001 and 2007 demonstrated the possible eradication of iodine deficiency [17].

In line with these proper implementations of iodine supplementation, the burden attributable to Iodine deficiency in Iran has also decreased as we found the same trends in ASDR. As previously reported, iodine deficiency-related death and DALYs consist of a wide spectrum of disorders in age and gender groups including fetus miscarriage, stillbirth, and increased risk of perinatal mortalities, neonatal goiter and neurocognitive impairment following hypothyroidism, child and adolescent goiter retarded physical and mental development and also adults goiter, hypothyroidism, mental dysfunctions, *etc.* [18]. based on our findings these iodine deficiency-related deaths and DALYs were significantly reduced after three decades. However, some providences showed relatively higher ASDR including Sistan Baluchistan, Kerman, and South Khorasan. The higher confidence intervals observed in these provinces are likely due to smaller population sizes or variability

Tab. II. Burden of Iodine deficiency across province of Iran in 1990 and 2019.

Provinces	1990		2019		Percentage change in age-standardized rates between 1990 and 2019
	ASDR	Interval	ASDR	Interval	
Alborz	12.70	7.83-19.57	5.99	3.44-9.73	-0.53
Ardebil	15.45	10.04-22.30	6.60	3.83-10.64	-0.57
Bushehr	14.99	9.43-22.04	6.27	3.55-10.07	-0.58
Chahar Mahaal and Bakhtiari	17.80	11.49-26.21	6.43	3.64-10.25	-0.64
East Azarbayejan	15.48	9.83-22.90	6.46	3.69-10.29	-0.58
Fars	15.80	10.12-23.02	6.28	3.58-10.37	-0.60
Gilan	16.14	10.49-23.81	6.49	3.75-10.23	-0.60
Golestan	16.48	10.51-24.15	6.85	3.88-11.11	-0.58
Hamadan	17.64	11.40-25.62	6.73	3.87-10.84	-0.62
Hormozgan	16.02	10.23-23.39	6.67	3.91-10.59	-0.58
Ilam	16.73	10.57-24.56	6.82	3.95-10.96	-0.59
Isfahan	14.25	8.92-21.51	6.43	3.62-10.28	-0.55
Kerman	15.62	9.97-23.00	7.23	4.24-11.71	-0.54
Kermanshah	17.45	11.34-25.67	6.72	3.86-10.85	-0.62
Khorasan-e-Razavi	18.46	11.95-26.93	7.14	4.19-11.44	-0.61
Khuzestan	13.93	8.67-20.52	6.17	3.62-9.93	-0.56
Kohgiluyeh and Boyer-Ahmad	17.44	11.05-25.28	6.66	3.82-10.76	-0.62
Kurdistan	18.76	12.05-27.43	6.89	4.02-11.36	-0.63
Lorestan	18.15	11.53-26.70	6.88	3.92-11.05	-0.62
Markazi	17.45	11.00-25.32	6.71	3.89-10.62	-0.62
Mazandaran	12.33	7.47-19.11	6.10	3.56-9.66	-0.51
North Khorasan	18.26	11.78-26.69	6.95	4.08-11.02	-0.62
Qazvin	16.35	10.47-24.15	6.31	3.58-10.13	-0.61
Qom	15.05	9.54-22.13	6.16	3.56-9.90	-0.59
Semnan	15.85	10.14-23.33	6.64	3.78-10.71	-0.58
Sistan and Baluchistan	18.31	11.76-26.76	7.87	4.51-12.69	-0.57
South Khorasan	19.70	12.59-28.39	7.15	4.08-11.62	-0.64
Tehran	8.04	4.44-13.32	2.58	1.17-4.92	-0.68
West Azarbayejan	15.81	9.96-23.32	6.76	3.81-10.95	-0.57
Yazd	14.58	9.21-21.92	6.28	3.64-10.04	-0.57
Zanjan	16.80	10.74-24.29	6.76	3.93-10.93	-0.60

in data collection practices. In line with our results, Mirahmad et al. found a significant proportion of adults in south Khorasan demonstrated evidence of thyroid dysfunctions [19]. Two studies were conducted between 2010 and 2015 in Khorasan and Lorestan provinces to evaluate iodine concentrations in commercially iodized salts and found lower than standard concentrations of iodine in a significant number of these packages [20, 21]. Despite that Iran is among the successful countries in eliminating iodine deficiency compared to MENA region countries [22], public health measures and regular assessment of global programs of IDD prevention especially in provinces with the highest ASDR are mandatory.

In terms of age and gender disparities of highest iodine deficiency ASDR from 1990 to 2019, while no change was shown among females, the male group with the highest ASDR shifted from ages 45-49 in 1990 to 75-79 in 2019. This shift in peak ASDR among males may be attributed to age-related dietary changes, including lower appetite, food costs, and food access, as well as increased insulin resistance. Studies have shown that insulin resistance is a risk factor for higher thyroid volume in iodine-deficient areas, which may explain the increased risk of iodine deficiency-related thyroid disorders in older males [23, 24]. It is crucial for public health policies to focus on monitoring iodine deficiency in the elderly, especially males.

On the other hand, we observed an increased ratio of females to males for iodine deficiency-related ASDR. This emerging trend is alarming as females, especially in pregnancy and lactating require more iodine as the disorders not only affect females only, but also have irreversible effects on fetus, and breast-fed child physical and mental development [4]. pregnant and Lactating mothers have very high requirements of iodine and so have more risk of iodine deficiency ASDR as they have higher renal iodine losses, higher needs of iodine

Fig. 2. Age-standardized DALY rate of Iodine deficiency across Iran provinces in 1990 and 2019.

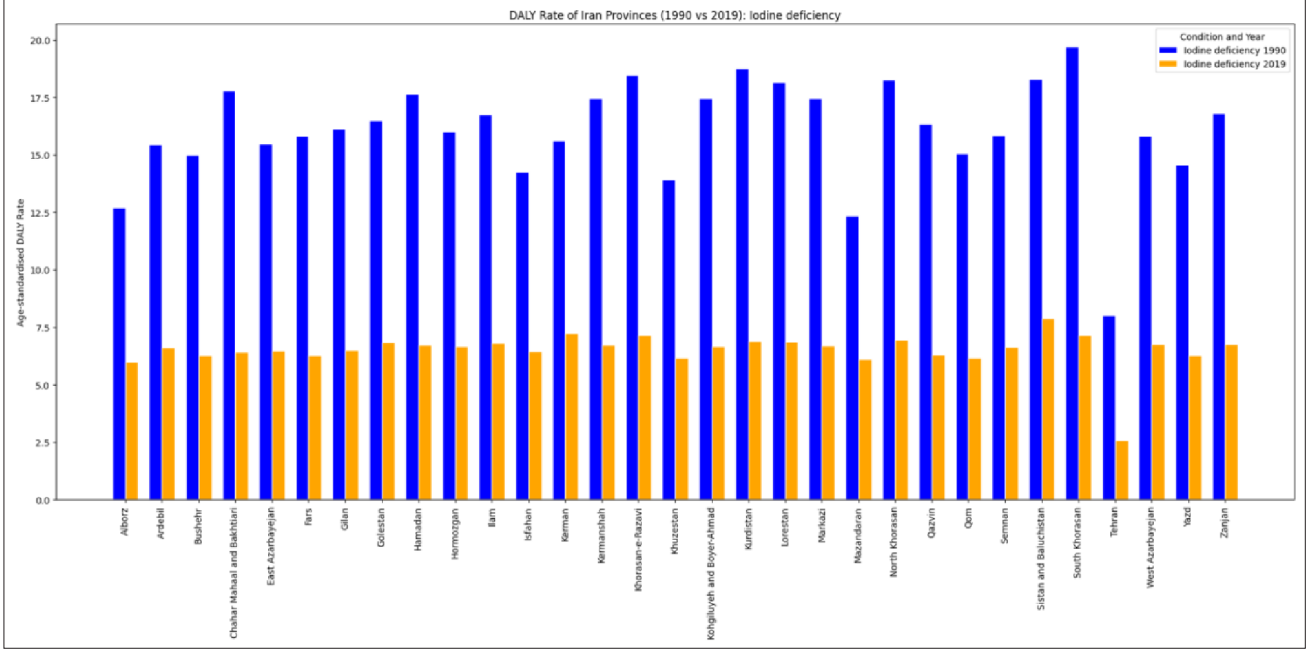
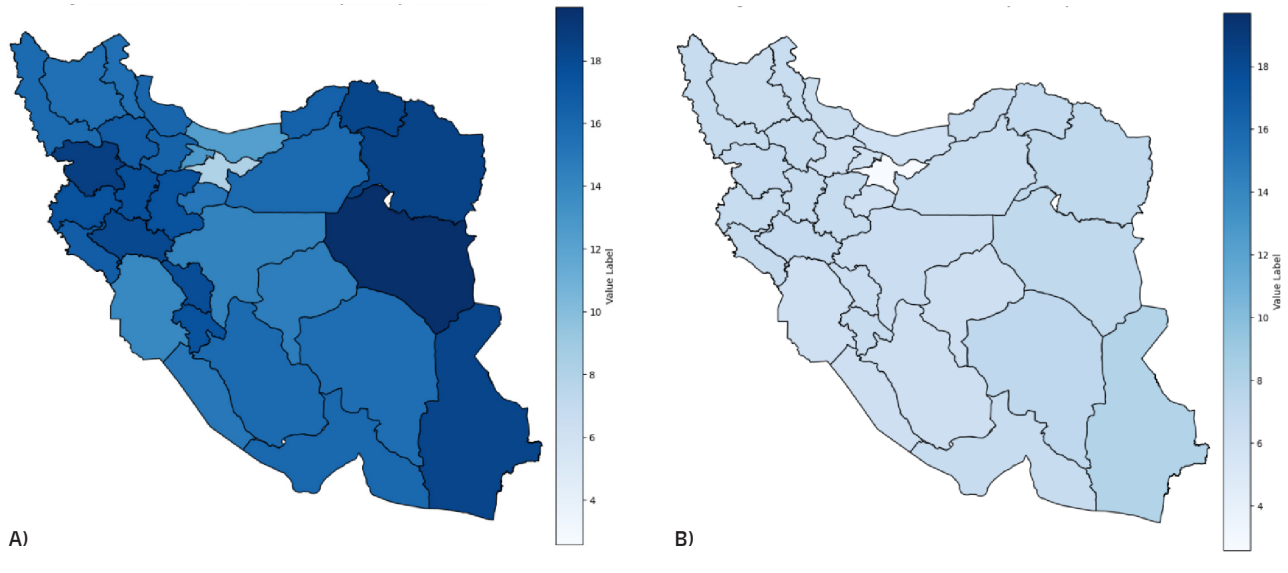


Fig. 3. Age-standardized DALY rate of Iodine deficiency across Iran provinces in A) 1990 and B) 2019.



for developing fetuses, and even higher losses of iodine through breast milk [25].

To our knowledge, this study was the first investigation of the iodine deficiency burden from 1990 to 2019 in Iran as a successful country in the MENA region to mitigate iodine deficiency. We investigate the burden based on gender and different age groups and at national and sub-national levels.

Limitations

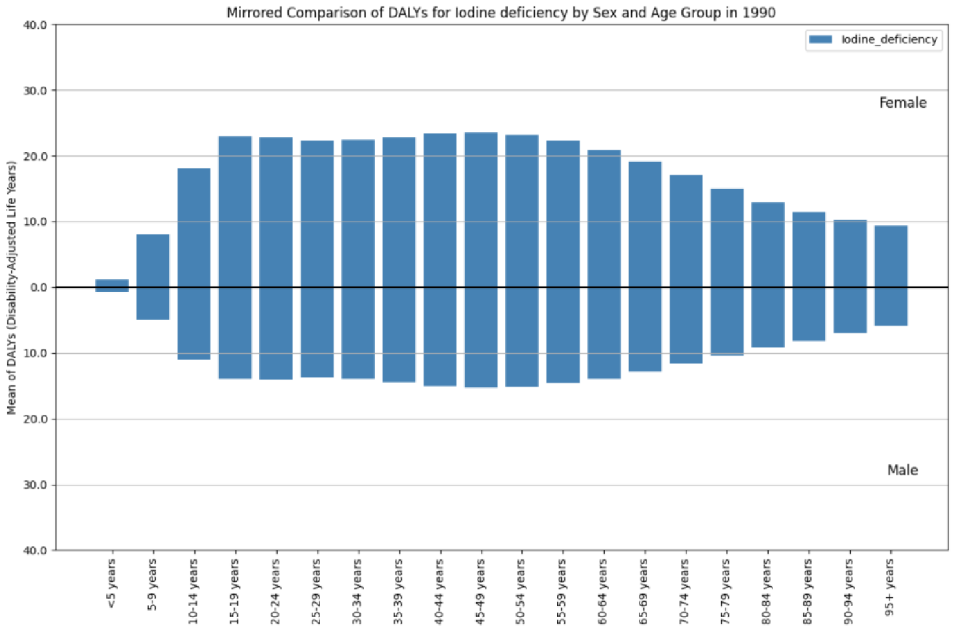
This study, while providing valuable insights into the burden of iodine deficiency in Iran, has several limitations. First, the data were derived from the Global Burden of Disease (GBD) study, which uses the DisMOD-MR 2.1 model for estimation. Although this model is robust, it assumes data uniformity across regions, which can introduce biases, particularly in provinces with smaller populations or inconsistent data collection practices, such as Sistan Baluchistan and Kerman. The wider confidence intervals in these areas reflect greater uncertainty in the data, suggesting that caution is needed when interpreting the results for these regions [26].

Second, this study relies on available data from registries, health surveys, and vital statistics, which may suffer from underreporting or misclassification of iodine deficiency cases, especially in rural and underdeveloped

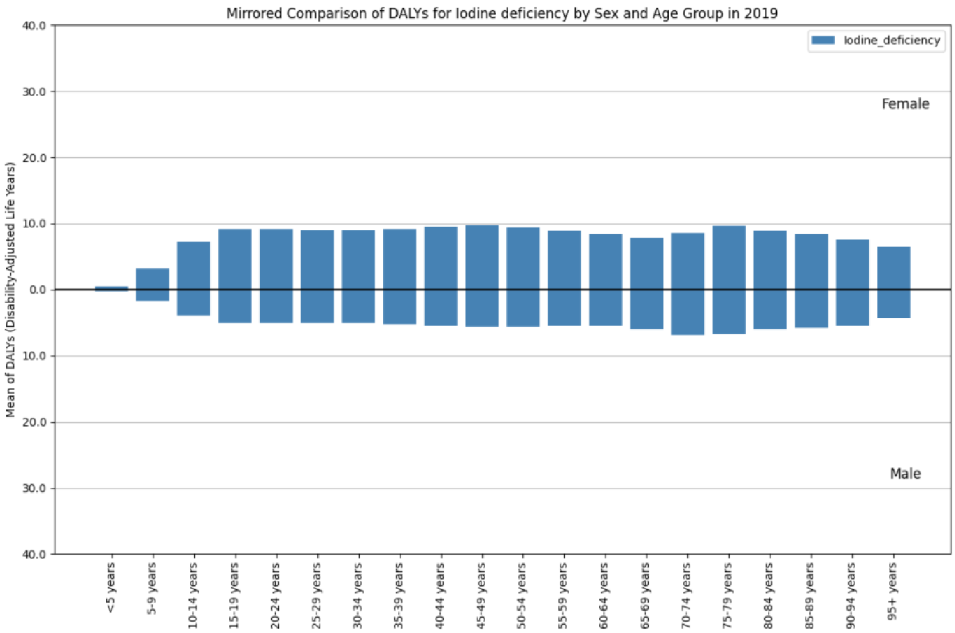
Tab. III. Burden of Iodine deficiency across genders in Iran in 1990 and 2019.

	Prevalence			DALY rate per 100000			Age-standardized DALY rate per 100000		
	1990	2019	Percentage change	1990	2019	Percentage change	1990	2019	Percentage change
Female	545.13	368.61	-32.38	16.29	7.77	-52.30	18.19	7.49	-58.82
Male	329.70	204.03	-38.11	10.16	4.52	-55.51	11.49	4.41	-61.61

Fig. 4. DALY of Iodine deficiency among males and females in Iran in A) 1990 and B) 2019.



A)



B)

regions. This could lead to either overestimation or underestimation of the actual burden of iodine deficiency in some areas [27, 28].

Additionally, while disability-adjusted life years (DALYs) provide a useful measure of disease burden, they may not fully capture the broader, subclinical impacts of iodine deficiency, such as cognitive impairments or developmental issues that may not directly contribute to DALYs but still affect overall public health [28, 29].

Finally, the study does not explicitly model potential confounders such as healthcare access, socio-economic factors, or the effectiveness of public health interventions

over time, which could have influenced trends in iodine deficiency. Further research should explore these factors in more detail, especially at the sub-national level, to provide a more comprehensive understanding of the burden of iodine deficiency [28, 30, 31]

Conclusions

In conclusion, we found that the iodine deficiency disorder burden decreased from 1990 to 2019. Some provinces still require more regulation to mitigate the burden of iodine deficiency. Moreover, the female population aged 45-49 despite the reduction in ASDR, still has the highest burden of disease which requires more robust health policy practices as they have the most critical part in a sustainable health system, especially in child development. Moreover, the elderly male population (aged between 75 and 79) in 2019 had the highest ASDR compared to the highest levels in 45-49 years in 1990.

Conflict of interest statement

The author declares no financial or ethical conflicts of interest for any of the studies described in this manuscript.

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Authors' contributions

PR: conceptualization, study design, data analysis, supervision, project administration and manuscript proofreading; MAK: data collection and manuscript preparation; MAA: literature review and drafting of the manuscript; SG: literature review and drafting of the manuscript; MNA: literature review and drafting of the manuscrip; ZR: data verification and manuscript editing; KD: supervision, project administration, and manuscript review; AF: data acquisition and quality assurance; ED: supervision, project administration and manuscript proofreading.

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Non Comunicable Diseases

Estimation of Dental Caries in Adults coming to a Dental College in Himachal Pradesh (North-West India) using CAST Index: a Cross-Sectional Study

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Keywords

Dental Caries • Caries Assessment Spectrum & Treatment Need Index • DMF • Index and Adults

Summary

Background. *Decayed Missing Filled Index is the universal index of choice to record dental caries however, it is unable to estimate the severity of dental caries. The Caries Assessment Spectrum and treatment (CAST) Index is a new index which can be used to distinguish the intensity of caries.*
Aim. *To ascertain dental caries using CAST index and to compare the association of CAST index with DMF Index values attained using CAST index in adults.*
Materials and Methods. *The cross-sectional survey recorded dental caries using CAST index in adults. 30.6% of adults experienced tooth loss and 32.3% recorded caries lesion advancing to dentin. 29.5% of adults had lesion attacking pulp but the gender predilection was insignificant. Caries severity in adults worsened with increasing age with significant association ($p < 0.00$). Scarcely 7.3% had undergone restorative care owing to dental caries.*
Conclusions. *The CAST index provides all-inclusive knowledge with regard to caries severity and transient shift in oral health in adults.*

Introduction

The global burden of untreated dental caries continues to pose a challenge with India emerging among top five countries and contributing 18.1% of global case-load of dental caries [1]. It is appalling to note that untreated dental caries contracted indirect cost up to 22 US billion dollars. Dental caries problem exacerbates largely due to exposure to sugar-rich food and beverage consumption and to some extent viewing advertisements of sugar-rich foods.
Dental caries influences oral health in all walks of life from infancy, school age, adolescence, adulthood and up to elderly. The consequences of untreated dental caries leads to loss of working hours, loss of productivity and an instance of registered case of blindness [1, 2].There is dose-response relationship between sugar consumption and dental caries such as dental caries worsens with high intake of sugar. High sugar intake precipitates the emergence of non-communicable disease such as diabetes, cardiovascular disease and non-alcoholic fatty-liver disease [3]. Evidence states that dental caries worsens when associated with physical multi morbidity and consuming diet which exacerbates acid-producing and acid-colonizing bacteria promoting the onset of dental caries [4, 5].
There is substantial evidence with pooled data exhibiting the prevalence of dental caries by using the universally applicable DMF Index [6, 7]. However, there is scant evidence pointing to prevalence of dental caries recorded using Caries Assessment Spectrum and Treatment Index CAST index [8]. Although DMF Index is cited to be the most widely used in recording dental caries still it bears constraints resulting in underestimation of caries and its inability to detect enamel lesions. It is unable to distinguish among decayed, missing and filled teeth [9]. CAST Index is a new dental index which is useful in projecting full spectrum of dental caries and in distinguishing severity of dental caries [10]. CAST index is useful in understanding the intensity of dental caries and has demonstrated good face and construct validity [9]. There's dearth of literature concerning dental caries estimation in permanent dentition using CAST index. Hence forth the study was conducted to evaluate dental caries in adults using CAST index and to correlate the association between CAST index values and DMF Index values obtained using CAST index.

Materials and methods

Before commencing the study, ethical clearance was acquired from Institutional ethical committee on 28th October 2022 with reference BDC/BHUD/12361A/28-10-22. The sample size was estimated by considering expected prevalence from previous study be 55% [6], margin of error set at ± 5% and possible attrition of 10% yielded sample size of 424 [11].
The above cross-sectional study duration lasted for 4 months from November 2022 till February 2023. The subjects were clearly explained about the objective of study and only those who were above 18 years of age were enrolled in the study after obtaining written consent while screening from dental out patient department OPD. Convenience sampling was utilized in

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enrolling the participants. Subjects who were physically and mentally incapacitated and minors were excluded from the study. A close-ended questionnaire in English language and translated to Hindi language in accordance with understanding of participants yielded responses for oral hygiene practices. The brushing habits were assessed by asking the type of aid and type of material used for cleaning teeth and the frequency of cleaning teeth by the subjects. Prior to clinical recording intra examiner reliability was assessed by performing calibration on 20 subjects by single examiner. The Cohen's kappa statistics drawn was 0.94 indicating perfect agreement. The subjects were seated on a dental chair and dental caries was recorded using CPI probe, plain mouth mirror and gauze piece using CAST index.

Caries Assessment Spectrum and Treatment Index is a practical and reliable index that provides a broad overview of dental caries. This index is practically useful in recording stages of caries lesions advancing from enamel to dentin and progressing to pulpal tissue [12].

CAST index involves 9 codes in marking dental caries clinically. Code 0, corresponds to sound tooth, followed by Code 1 related to sealed tooth and Code 2 is associated with tooth restored with restorative material. The stages of carious lesions are scored from codes 3 to 7, such that Code 3 corresponds with visual change in enamel, Code 4 affiliated with caries-related discoloration in dentine and Code 5 inter-related with distinct cavitations in dentine.

Codes 6 and 7 relate to caries accelerating to pulp chamber and further deepening into fistula/abscess. Finally tooth lost due to dental caries is classified as 8. Additionally if the recorder is unable to relate with any of the above categories it corresponds with Code 9 [12].

The anonymity and confidentiality of responses obtained was strictly adhered in accordance to Helsinki Declaration of World Medical Association [13].

Statistical Analysis

The derived data was assessed for normality using Shapiro-Wilk Test and due to non-normal distribution of data non-parametric test was performed. Sociodemographic details obtained were age and gender. Mann-Whitney U-Test was performed to differentiate two independent group of samples. Spearman's Rank Correlation coefficient^R was conducted to inspect correlation between DMF index and CAST index. Regression analysis was conducted to associate connection between gender and change of toothbrush with dental caries.

Results

The mean age of the subjects was 36.06 (± 11.11). 60.3% (n = 256) comprised male subjects and 39.7% (n = 168) were females. 50% (n = 212) had caries lesion confined to enamel and just 7.3% (n = 31) underwent restoration of teeth due to dental caries. 4% (n = 17) felt caries related discoloration and one-third (32.3%) experienced progression of caries to dentinal stage. 29.5% perceived pulpal pain with progression of caries and 30.6% (n = 130) reported loss of tooth/ tooth mortality due to dental caries (Tab. I).

Tab. I. Frequency distribution of caries assessment spectrum and treatment codes.

Criteria	Frequency (%)
A cavity is restored with an (in)direct restorative material	30 (7.3%)
Distinct visual change in enamel only; a clear caries-related discolouration is visible, with or without localised enamel breakdown	212 (50%)
Internal caries-related discolouration in dentine; the discoloured dentine is visible through the enamel, which may or may not exhibit a visible localised breakdown	17 (4%)
Distinct cavitation into dentine; the pulp chamber is intact	137 (32.3%)
Involvement of the pulp chamber; distinct cavitation reaching the pulp chamber, only root fragments are present	125 (29.4%)
The tooth has been removed because of dental caries	130 (30.7.%)

Tab. II. Oral Hygiene practices.

Question	Response	Frequency (%)
Type of Aid Used	Toothbrush	408 (96.3%)
	Treestick	3(0.7)
	Toothbrush + Treestick	12(2.8)
	Finger	1(0.2)
Type of Material Used	Toothpaste	382 (90.1%)
	Toothpaste + Toothpowder	33 (7.8%)
	Toothpaste	6 (1.4%)
	Do not Use	3 (0.7%)
Frequency of Cleaning	Once a day	407 (96%)
	Twice a day	17 (4%)

96.3% reported cleaning of their teeth by using toothbrush and dismally 4% had the habit to clean their teeth twice a day. Surprisingly 7.8% used toothpaste and toothpowder to clean their teeth (Tab. II). Regression analysis conveyed that those who changed their toothbrush after 6 months (p = 0.00, OR = 1.538 and CI = .852, 2.225) had higher risk of dental caries as compared with those changing toothbrush within 3 months (p = 0.07, OR = 0.45 and CI = -0.06, 0.94) 7.1% with CAST score of 3 were in reversible premorbidity stage. 6.6% (n = 28) (codes 4 and 5) were in morbidity phase and 1.4% had severe morbidity (Codes 6 and 7). Remaining 1.7% (n = 7) (code 8) had severe mortality of teeth. Differentiating CAST scores with gender was non-significant (Tab. III); however females were slightly predisposed to dental caries in regard to mean DMF 2.26 (± 2.34) when weighed with mean DMF in males 2.10 (± 2.76).

Regression analysis showed females were more plausible to develop dental caries (p = 0.00, OR = 1.957 and CI = 1.204, 2.709) as opposed to males. The CAST scores worsened with age progression (Tab. IV).

Tab. III. Comparing Caries experience association with Gender using Mann-Whitney U Test.

Variable	Gender	Mean Rank	Mean (± SD)	Mann Whitney U (2 Tailed-p value)	Z Value
Cavity is Restored with Restorative Material	Male (n = 256)	213.68	0.14 (± 0.68)	0.586	-.544
	Female (n = 168)	210.70			
Visual Change in Enamel	Male	210.73	1.12 (± 1.65)	0.692	-.396
	Female	215.20			
Internal caries-related discolouration in dentine; the discoloured dentine is visible through the enamel, which may or may not exhibit a visible localised breakdown	Male	213.90	0.04 (± 0.24)	0.393	-.855
	Female	210.37			
Distinct cavitation into dentine; the pulp chamber is intact	Male	216.36	0.56 (± 0.98)	0.333	-.968
	Female	206.62			
Involvement of the pulp chamber; distinct cavitation reaching the pulp chamber, or only root fragments are present	Male	205.51	0.61 (± 1.39)	0.071	-1.804
	Female	223.15			
The tooth has been removed because of dental caries	Male	210.57	0.81 (± 1.96)	0.623	-.492
	Female	215.44			

* p < 0.05. SD: Standard deviation.

Tab. IV. Differentiating caries Experience with Age using Mann-Whitney U Test.

Variable	Age Group	Mean Rank	Mean (± SD)	Mann-Whitney U-(2 Tailed-P Value)	Z Value
Cavity is Restored with Restorative Material	19-44 years	210.18	0.14 (± 0.68)	0.093	-1.679
	45-70 years	221.25			
Visual Change in Enamel	19-44 years	220.99	1.12 (± 1.65)	0.003*	-2.982
	45-70 years	180.54			
Internal caries-related discolouration in dentine; the discoloured dentine is visible through the enamel, which may or may not exhibit a visible localised breakdown	19-44 years	211.62	0.04 (± 0.24)	0.397	-.848
	45-70 years	215.83			
Distinct cavitation into dentine; the pulp chamber is intact	19-44 years	210.80	0.56 (± 0.98)	0.504	-.668
	45-70 years	218.18			
Involvement of the pulp chamber; distinct cavitation reaching the pulp chamber, or only root fragments are present	19-44 years	204.33	0.61 (± 1.39)	0.001*	-3.316
	45-70 years	243.26			
The tooth has been removed because of dental caries	19-44 years	201.31	0.81 (± 1.96)	0.000*	-4.478
	45-70 years	254.62			

* p < 0.05. SD: Standard deviation.

Approximately half of the subjects (54%) had decayed teeth with mean DMF calculated using CAST index as 2.16 (± 2.60). An intriguing observation was that the lower permanent molars were more carious than upper permanent molars with a prevalence of 41.2% and 21.6% involving 1st and 2nd lower right molars. The preponderance of lower left 1st permanent molar being 45% and 25.7% for lower left 2nd permanent molar. The estimated prevalence of caries in upper right permanent molars was 23.8% for 1st molar and 14.8% for 2nd molar and caries prevalence in upper left permanent molars was 21.2% for upper left 1st molar and 12.3% for upper left 2nd molar.

The spread of dental caries in premolars was 26.4% in mandibular arch and 32.2% in maxillary arch. In context to anterior teeth 16% decayed teeth were observed in maxillary arch and in mandibular arch 13.5% had prevalence of dental caries in anterior teeth.

The percentage of decayed teeth in 45-70 year age group was 88.7% and 71.4% had decayed teeth in 19-44 year age group. Similarly percentage of missing teeth in 45-70 year age group was 46% and clinically 26.8% had missing teeth in 19-44 year age group. The Mean number of intact teeth were 29.83 (± 2.54).

The decayed teeth in 45-70 years age were significantly more than 19-44 years (U = 12343)

p = 0.008 and as well as missing teeth in 45-70 years age were significantly higher than 19-44 years (U = 11415), p = 0.000) (Tab. V).

An interesting observation was insignificant association of mean DMF with gender. Spearman's Rank correlation exhibited strong correlation of CAST index scores with DMF index scores (p < 0.000) (Tab. VI).

Discussion

In the above study 50% of subjects had caries lesion confined to enamel (pre morbidity), which

Tab. V. DMFT comparison with Age using Mann-Whitney U Test.

	Age Group	Mean Rank	Mean (± SD)	P Value	Z Value
Decayed Teeth (DT)	19-44 years	204.84	1.19 (± 1.75)	0.008*	-2.653
	45-70 years	241.31			
Missing Teeth (MT)	19-44 years	202.08	0.82 (± 1.96)	0.000*	-4.161
	45-70 years	251.74			
Filled Teeth (FT)	19-44 years	210.43	0.15 (± 0.68)	0.146	-1.452
	45-70 years	220.29			

* $p < 0.05$. SD: Standard deviation.

Tab. VI. Spearman's Rank Correlation Coefficient between DMF Index and CAST index.

Variable	Spearman's correlation coefficient (r)	P Value
Visual Change in Enamel	-.233**	0.000*
Cavity restored with restorative	-.235**	0.000*
Internal caries-related discolouration in dentine the discoloured dentine is visible through the enamel, which may or may not exhibit a visible localised breakdown	-.065	0.182
Distinct cavitation into dentine; the pulp chamber is intact	.359**	0.000*
Involvement of the pulp chamber; distinct cavitation reaching the pulp chamber, or only root fragments are present	.817**	0.000*
The tooth has been removed because of dental caries	-.704**	0.000*

* $p < 0.05$. SD: Standard deviation.

was substantially high in contrast to previous studies [8, 10, 14, 15] which could be due to ignorance and delayed approach in seeking dental care necessitating instant restorative care and promotion of oral health maintenance. One-third (32.3%) were detected with dentinal caries involving pulp which was analogous to similar finding from western India [11] and approximated with a previous research from south India [16]. However, none of the subjects had pus releasing sinus tract which might be due to timely dental intervention and prompt treatment but in disagreement with earlier conclusions [8, 10, 14]. Bleakly only 7.3% availed prompt restorative care which was slightly raised collating with earlier observations obtained in children and adolescents [17, 18].

It was compelling to observe that oral hygiene practices influenced the onset of dental caries as those who changed toothbrush after 6 months were succumbing to dental caries which was in tune with similar study showing a direct association of dental caries with frequency of change of toothbrush [19].

45-70 year age group subjects were predominantly having missing teeth and decayed teeth in contrast to 19-44 year age-group and this observation corresponded with previous literature [7, 15]. Tooth mortality resulting in loss of tooth was marginally high as opposed to previous research [8, 15] and preponderance of tooth mortality was more in females when distinguished with males [15]. Women being homebound are involved in home responsibility as a result are less expressive in conveying their oral health problems which eventually contributes to tooth mortality [15]. Women experienced tooth mortality and as a result mean DMF in females was slightly more than males which could be explained because of the early eruption of teeth in females, vulnerability to dental caries due to hormonal changes, variation in salivary flow rate and laying open to cariogenic microflora [20]. Slightly less than one-tenth were having caries-related discoloration which coincided with earlier observations reported previously using CAST index [14, 16]. Lower First permanent molars accounted for severe morbidity and tooth mortality because of variance in tooth morphology and differences in post-eruptive maturation of enamel [21] which complemented with a study involving adolescents [22] but was in disagreement with previous findings [23]. Inter-arch differentiation revealed distribution of dental caries more in maxillary arch than mandibular arch which was synonymous with previous literature [24, 25] and attributed to poor maintenance of oral hygiene and food-lodgement visible in occlusal surfaces of molars [25]. The overall mean DMF obtained projected to higher side when compared to past studies [8, 16]. There were significant association between DMF index scores and CAST index scores which was in concordance with previous studies [17, 26] drawing similar results because of early recognition of non-cavitated lesions and early cavities discerned using CAST index when correlated with DMF index. DMF Index may cause underestimation of caries [26] and lacks the sensitivity in locating minor deviation in caries advancement [18] when weighed with CAST index showing continuum of dental caries on a single tooth.

Limitations

The cross-sectional design of the study bears several short-comings. We could not assess the incidence of dental caries and it would be difficult to draw casual inference. The study design is inadequate to inspect temporal relation between outcomes and risk factors [27].

One-time measurement of disease of interest in a cross-sectional study poses challenge in generalizing the study findings.

Recommendations

The soaring cost of dental services raises alarm bells to address the social and commercial determinants influencing oral health. Tooth mortality can be avoided if oral health promotion and prevention could be channelized at primary care level [28]. Imposition of tax on sugar-laden items may bring-down the caries-attributed tooth-loss [3]. Alternatives measures shall be laid down for instance counselling the school administrators to educate the school going children about the consequences of sugar intake contributing to dental caries. Create trained workforce who may be useful in disseminating knowledge on untreated dental decay through medium of oral health education. Strengthen the on-going Ayushman Bharat Scheme which involves oral component under comprehensive primary health care to full fill the unmet oral health needs of the population [29].

Conclusions

Therefore, CAST index demonstrates comprehensive measurement of extent and severity of dental caries in detail rather than DMF index. CAST index should be effectively utilized in estimating dental caries comprehensively. Health planners can promulgate oral health promotion and prevention in a better way by employing CAST index in detection of dental caries.

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Conflict of interest statement

None.

Author's contributions

Study conception and Design: AV, BR. Acquisition of Data: AV, BR. Analysis and Interpretation of Data: AV, BR**.** Drafting of Manuscript: AV, BR**.** Critical Revision: AV, BR.

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Non Comunicable Diseases

Awareness of breast self-examination and understanding of breast cancer treatment options among female patients of Lahore, Pakistan: a cross-sectional study

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Keywords

Breast cancer • Cross-sectional • Pakistan • Allopathic • Traditional medicine

Summary

Introduction. *Breast cancer is a major worldwide health concern that affects women in both developed and developing nations. The purpose of the study is to assess Pakistani women with breast cancer's present understanding of breast self-examination (BSE) as well as their choices for traditional and non-conventional breast cancer treatment options.*
Methods. *A cross-sectional study was carried out in two hospitals' cancer departments as well as homeopathic and nutritional clinics in Lahore, Pakistan. The data for the present study was collected from January to June 2023.*
Results. *A total of 296 responses were obtained. The study findings showed that most participants had little knowledge about BSE and were using multiple treatment options without informing their healthcare provider.*
Conclusions. *Breast cancer awareness is crucial for early detection, education about risk factors, and proactive fitness management. Complementary and alternative medicine (CAM) might cause problems when used with allopathic medicines, especially if healthcare professionals are not adequately informed about its concomitant use.*

Introduction

Breast cancer affects women in both developed and developing countries, making it a serious global health concern. Limited resources, inadequate nutrition, and reproductive-related factors exacerbate breast cancer disparities. Restricted healthcare access leads to delayed diagnoses and treatment and higher mortality rates in underserved populations. Inadequate nutrition compromise's immune function, and reproductive factors, like early menstruation, late menopause, or fewer pregnancies, can contribute to these disparities [1]. After overtaking lung cancer in 2020, female breast cancer accounted for 11.7% of all cancer cases and was the world's top cause of cancer incidence. Breast cancer is expected to have a substantial impact on global cancer statistics, accounting for 15.2% of all new cancer cases worldwide by 2023. It also continues to be the world's sixth most common cause of cancer death [2]. There is a significant variation in incidence rates across different countries. High-income countries report rates as high as 90 per 100,00,000 women, while low-income countries report as low as 30 per 100,00,000 women [3, 4]. The majority of incidents of breast cancer are diagnosed in women 50 years of age and older, with around 80% of cases occurring in this age group. With a five-year relative survival rate of roughly 90% for early-stage breast cancer, it drops to about 27% for metastatic cases. Early diagnosis significantly improves outcomes [5].
Based on Khan et al., by 2023, there will be 90 to 100,00 cases of breast cancer for every 100,00,000 women in Pakistan, making it the most common cancer among females. The illness adversely affects people's physical, mental, social, and existential well-being, which substantially negatively impacts their quality of life (QoL) [6]. For example, even after therapy concludes, patients frequently experience ongoing fatigue and discomfort. A study indicated that breast cancer patients report clinical levels of distress after treatment. Mentally, the diagnosis can cause high levels of worry and sadness. As seen in a study where 30% of breast cancer patients reported fewer social connections as a result of their illness, the demands of continuous treatment might socially result in isolation or damaged relationships [7]. According to a study, facing a severe disease prompts introspective thoughts about one's personal beliefs and life's purpose, which can cause existential discomfort. For instance, in the setting of their sickness, patients commonly struggle with worries related to mortality and the purpose of their existence. Common side effects of treatment that worsen physical distress include fatigue, pain and hair loss. Patients may experience emotional problems such as anxiety, depression and body image issues, which can lead to social withdrawal and strained interpersonal relationships. Changes in desire and

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fertility issues can affect one's sexual health, while existential distress is related to facing death and the meaning of life [6]. These particular instances highlight the extensive and significant effects of breast cancer on a person's general health and their QoL [8]. The National Cancer Institute (2022) states that improving the overall quality of life through holistic support catered to individual needs, supportive care, rehabilitation, and survivorship programs are critical in addressing these challenges [9].

There are two types of risk factors for breast cancer: modifiable and non-modifiable. Genetics, family history, age, gender and previous radiation exposure are non-modifiable factors. Genetic mutations like those in the BRCA1 and BRCA2 genes, as well as a family history of the disease, can further increase a person's risk of developing breast cancer. Modifiable factors give intervention opportunities. Prolonged estrogen exposure from early menstruation, late menopause or hormone replacement therapy can raise risk. Reproductive history, such as postponed childbirth or limited breastfeeding, as well as lifestyle decisions like obesity, alcoholism, physical inactivity and eating patterns, all have a significant influence. Exposure to chemicals that disrupt hormones is one example of an environmental variable that may impact risk. It is essential to address these factors through lifestyle modifications, early detection, and preventive measures to reduce the risk of breast cancer [1, 10, 11].

Breast self-examination, or BSE, is crucial for the early diagnosis, monitoring, and detection of breast cancer. During clinical breast exams, medical experts physically examine patients to check for anomalies such as lumps or changes in the size and shape of the breasts. Women without symptoms are encouraged to get screened as early as age 40 because regular screens help find small, treatable tumours early on. Furthermore, mammograms are often recommended before the onset of symptoms and are crucial for diagnosing breast cancer in its early stages. Biopsies are required to confirm and characterize cancer; extra imaging modalities such as ultrasonography and MRI may be employed for further evaluation. By regularly completing BSE, people can recognize changes like lumps or skin changes and seek timely medical intervention. BSE is an adjunct to clinical examinations and mammography, not their substitute. It empowers individuals to actively participate in their breast health by promoting the early diagnosis of potential issues [9, 12, 13].

Complementary and alternative medicine or CAM therapies include nutritional counselling and homeopathic medicine. These therapies usually aim to reduce side effects from conventional treatments, boost immunity, and treat cancer symptoms. However, CAM may occasionally clash with conventional treatments, leading to difficulties if their usage with allopathic treatment is not correctly revealed to healthcare practitioners. The fact that around two-thirds of women utilize complementary and alternative medicine without first talking to their oncologists emphasizes the need for better patient-provider communication [14-16]. In order to augment their treatment strategy, patients with breast cancer often look into several complementary and alternative medicine (CAM) therapies. The goal of nutritional counseling for breast cancer patients is to optimize diet in order to promote therapy, control side effects, and enhance general health. Individualized care lowers the chance of cancer recurrence, increases immunity, and helps patients keep their vigor. Dietary supplements such alpha-factor, high-dose vitamin C, and selenium are used to boost immunity and manage side effects. Herbal drugs such as mistletoe therapy and Chinese herbal remedies are highly sought after due to their potential to enhance both treatment outcomes and quality of life. Moreover, mind-body therapies like qigong, acupuncture, and osteopathy are utilized to reduce stress, ease pain, and enhance overall well-being. These, along with many other complementary and alternative medicine (CAM) modalities, are valued for their ability to complement conventional treatments while addressing many aspects of health and recovery [17].

This study seeks to address important gaps in the understanding and practice of breast self-examination (BSE) and available treatment choices for breast cancer among Pakistani women. The study specifically planned to assess this population's present awareness and comprehension of BSE and investigate their preferences for both conventional and non-traditional breast cancer therapies. By evaluating these factors, the study hopes to pinpoint possible areas in which resources and instruction might be deficient as well as offer insights into how treatment preferences might affect patient decisions and results. The ultimate goal of the research is to improve early identification and treatment efficacy for breast cancer in Pakistani women through focused interventions and support techniques.

Materials and methods

Study design and settings

In the current study, a cross-sectional study plan was implemented. Patients with a diagnosis of breast cancer provided data for the collection. This study assessed breast cancer treatment options and awareness of breast self-examination. The research was carried out in two hospitals' cancer departments as well as homeopathic and nutritional clinics in Lahore, Pakistan. The data was gathered from Anmol Cancer Care Hospital and Shaukat Khanam Cancer Memorial Hospital. The clinics treating women with breast cancer in the township, Dharampura, and Ischra market provided information for homeopathic herbal and nutritional therapy.

Study criteria

This study enrolled all women with breast cancer receiving therapy irrespective of their age, marital status, level of education or ethnic background. Patients receiving nutritional treatment, herbal remedies, or homeopathic medicine were included in this study in addition to those

receiving chemotherapy or other allopathic treatments. To ensure that respondents understand and answer the survey questions openly, minimum criteria of Urdu fluency is necessary. This degree of competence is essential for efficient communication and preserving the accuracy and dependability of the data gathered in Pakistan, where a large number of people live in rural regions and may not know how to read or write English. The study excluded female patients who were not receiving treatment for breast cancer or who still receiving a diagnosis, as well as patients with conditions were other than breast cancer. Furthermore, the study excluded immigrants who were not proficient in Urdu and patients with co-morbidities.

Sample size

The convenience sampling was used to collect the data, and participants were chosen based on their availability and desire to participate. Although this method made data collecting more efficient, it might have introduced biases of its own, including a lack of population representation. Because of this, the results may not be entirely generalizable because the sample may not accurately represent the wide range of traits and experiences that make up the target population. The sample size was calculated using the Solvins formula, which is $n = N / (1 + N e^2)$ where, n = Sample size, N = Estimated population size, e = Margin of error (0.05).
This formula was used to determine the estimated sample size of 320. However, for convenience, a sample of 296 patients receiving breast cancer treatment was gathered.

Data collection tool (DCF)

The data for the present study was collected from January to June 2023. The data was gathered using an extensive structured DCF. The body of existing literature served as the basis for designing the questionnaire [18]. The data collection instrument was divided into four primary sections, including participant consent, demographic information, history of breast cancer, and awareness of breast self-examination and choices for treating breast cancer. In first section, respondents were asked if they gave their approval to take part in the study. In second section, data on age, marital status, educational background, socioeconomic status, menarche and menopause age, number of living kid(s) in case of married female, and occupation were collected. In third section, breast cancer history, including age at onset, family history, signs and symptoms, side effects, surgery, and treatment received, is covered in this section. In fourth section of the survey, participants were asked about their understanding of BSE. In particular, this portion examined their knowledge of potential therapies, such as CAM, their preferred methods of managing their ailment, and whether they had consulted a doctor about their alternatives. The Cronbach's alpha value was found to be 0.71, indicating that the questionnaire is reliable.

Ethical approval

Ethical approval for this study was issued by the Research Ethics Committee of Superior University under reference number 264/01/2023.

Participant's consent statement

Before taking part in the study each participant gave written informed permission. They were made aware of the objectives, methods, possible disadvantages and advantages of the study. Participants could leave at any time without incurring any penalty because participation was entirely voluntary.

Statistical analysis

Using SPSS version 21, data was analyzed. The survey parameters were calculated using frequency distributions and percentages. The association between variables, such as education, family history, awareness of breast self-examination, and therapy choices, was assessed using the Pearson Chi-square test. Using a technique known as Cronbach's alpha, we were able to assess the survey questions' reliability by determining how well they lined up. Experts carried out content assessment to ensure validity of survey tool and verified that they truly understood the questionnaire by determining whether the questions aligned well with the objectives we were investigating. These actions demonstrate the accuracy and strength of the data. The p values less than 0.05 were regarded as significant.

Results

Demographic information

The demographic data of the participants are summarized in Table I. A total of 296 people participated in the survey, with all categories summing to 100,00% that demonstrated accuracy and consistence of the data. The study findings revealed that most participants were 31 to 41 (28.72%) old and married (n = 215, 72.64%). The participants' socioeconomic status showed that most females belonged to the middle class (n = 169, 57.09%). Moreover, most females were illiterate (n = 131, 44.26%) and housewives (n = 244, 82.43%).

Participants' number of children

Table II provides a breakdown of the information pertaining to the participants' number of children. Of the 215 married, divorced, or widowed participants who were expecting to have children, 15 (6.98%) were infertile. Furthermore, the data showed that most females (n = 53, 25.65%) had three children.

Menarche and menopause age of the participants

An overview of the data about the menarche and menopause ages of the individuals is given in Table III. According to the statistics, the majority of females (n = 131, 44.26%) did not yet have menopause, while the majority of females (46.96%) had their menarche between the ages of 16 and 18.

Tab. I. Demographic information of the participants (n = 296).

Variables	Frequency (n)	Percentage (%)
Age distribution (years)		
21-30	25	8.45
31-40	85	28.72
41-50	78	26.35
51-60	73	24.66
61-70	33	11.15
Above 70	2	0.67
Total	296	100.00
Marital status		
Married	215	72.64
Unmarried	19	6.42
Widow	18	6.08
Divorced	44	14.86
Total	296	100.00
Socioeconomic status		
Low	100.00	33.78
Middle	169	57.09
High	27	9.12
Total	296	100.00
Education		
Illiterate	131	44.26
Primary education	39	13.18
Secondary education	73	24.66
Under graduation	29	9.80
Graduation	14	4.73
Post graduation	10	3.37
Total	296	100.00
Occupation		
Working women	40	13.51
Student	12	4.05
Housewife	244	82.43
Total	296	100.00

Tab. II. Information on the participants' living children (n = 215).

Category	Frequency (n)	Percentage (%)
Infertility	15	6.98
1	14	6.51
2	25	11.63
3	53	24.65
4	41	19.07
5	36	16.74
More than 5	31	14.42
Total	215	100.00

The history of breast cancer among participants

Table IV provides the patients' breast cancer history. The results of the study showed that the majority of the symptoms that the patients encountered were painful lumps; however, some also reported painless lumps, changes in breast size and shape, thickening of the skin, and nipple retraction with secretory discharge. The majority of females (28.04%) diagnosed with breast cancer between the ages of 31 and 40 and had

Tab. III. The participants' information on menarche and menopause age (n = 296).

Category	Frequency (n)	Percentage (%)
Menarche age (years)		
Under 12	15	5.07
12-15	134	45.27
16-18	139	46.96
18-20	8	2.70
Total	296	100.00
Menopause age (years)		
Under 40	35	11.82
40-45	30	10.14
46-50	69	23.31
Above 50	31	10.47
Menopause is not present yet	131	44.26
Total	296	100.00

a right-side breast tumor (n = 156, 52.70%). Most of them had stage 3 breast cancer (n = 124, 41.89%), had undergone breast surgery (n = 160, 54.05%) and had been receiving therapy for more than a year (n = 108, 36.49%). According to the study findings, patients with breast cancer had a family history of the disease in their relatives (n = 147, 40.30%), parents (n = 74, 25%), or siblings (n = 60, 20.27%), while few participants had no family history (n = 22, 7.43%).

Awareness of breast cancer self-examination (BSE) among participants

Table V provides information on participants' awareness of BSE. In contrast to (n = 53,17.91%), the majority of participants (n = 243, 82.09%) were unaware of BSE and had not received any education about it. Furthermore, very few females claimed to have conducted BSE (n = 50, 16.89%), to be aware of its process (n = 53, 17.91%), and to have benefited from an early diagnosis of breast cancer (n = 48, 16.22%). Table VI provides information about patients 'counseling. A total of 53 participants out of 296 had received counseling. The patients received counseling from doctors (n = 18, 33.96%), pharmacist (n = 17, 32.08%), friends (n = 4, 7.55%), family members (n = 12, 22.64%) and others (n = 2, 3.775%).

Details about the treatment received by patients

The Table VII provides information on the therapeutic decisions made by participants. In the current study, a variety of treatment modalities were examined that influenced participants therapeutic decisions. While some participants chose to use homeopathic remedies or dietary interventions others only used allopathic treatments. Furthermore a subset of subjects integrated homeopathic, allopathic and nutritional approaches in their therapy. The goal of this combined reporting is to give a thorough picture of the participants' treatment preferences. Participants employed allopathic (n = 152, 51.35%), homeopathic (n = 72, 24.32%), herbal (n = 52,

Tab. IV. Participants' breast cancer history (n = 296).

Variables	Frequency (n)	Percentage (%)
Main symptoms		
Painless lump	81	27.36
Painful lump or pain when touched	101	34.12
Change of shape and size of breast	22	7.43
Discharge of secretion with pain	57	19.26
Skin thickening and nipple retraction	35	11.82
Total	296	100.00
Side of breast tumor		
Right side	156	52.70
Left side	140	47.30
Total	296	100.00
Stage of breast cancer		
Stage 1	5	1.69
Stage 2	113	38.18
Stage 3	124	41.89
Stage 4	54	18.24
Total	296	100.00
Age at which breast cancer was diagnosed		
21-30	29	9.80
31-40	83	28.04
41-50	78	26.35
51-60	75	25.34
61-70	31	10.47
Total	296	100.00
Family history of breast cancer		
Parents	74	25.00
Siblings	60	20.27
Relatives	140	47.30
No family history	22	7.43
Total	296	100.00
Had any surgery for breast cancer?		
Yes	160	54.05
No	136	45.95
Total	296	100.00
Duration of the present therapy		
8 months	22	7.43
9 months	30	10.14
10 months	25	8.45
11 months	47	15.88
12 months	64	21.62
More than a year	108	36.49
Total	296	100.00

Tab. V. Participants' awareness about breast cancer self-examination (BSE) (n = 296).

Questions	Response	
	Yes n (%)	No n (%)
Have you heard of BSE?	53 (17.91)	243 (82.09)
Has anyone educated you about BSE?	53 (17.91)	243 (82.09)
Have you done BSE?	50 (16.89)	246 (83.11)
Has BSE helped you in early diagnosis of the disease?	48 (16.22)	248 (83.78)
Do you know how to perform BSE?	53 (17.91)	243 (82.09)

Tab. VI. Participants' counseling about breast cancer self-examination (BSE) (n = 53).

Who educates the patient about BSE?	Frequency (n)	Percentage (%)
Doctor	18	33.96
Pharmacist	17	32.08
Friends	4	7.55
Family	12	22.64
Any other	2	3.77
Total	53	100.00

Tab. VII. Participants' therapeutic choices (n = 296).

Category	Frequency (n)	Percentage (%)
Therapy used at the early diagnosis		
Allopathic	152	51.35
Homeopathic	72	24.32
Herbal medicines	52	17.57
Food	20	6.76
Total	296	100.00
Are you taking any nutrition supplements?		
Yes	191	64.53
No	105	35.47
Total	296	100.00
Are you using more than one therapy?		
Yes	82	27.70
No	214	72.30
Total	296	100.00
If use CAM or used more than one therapy; then are you informing their therapist or physician?		
Yes	61	20.61
No	164	55.41
NA	71	23.99
Total	296	100.00

17.57%), and nutritional treatment (n = 191, 64.53%) in addition to food (n = 20, 6.76%) after an early diagnosis. The majority of participants (n = 164, 55.41%) did not tell their healthcare practitioner that they were relying on multiple therapeutic choices (n = 214, 72.30%).

The Table VIII provides information on the degree of satisfaction that accompanies them. Out of the 152 participants who had allopathic treatment, the majority expressed satisfaction with it (n = 110, 72.37%) when compared to other groups. Out of the 72 subjects who were receiving homeopathic treatment, 28 (38.89%) found homeopathic medicine satisfactory while 44 (61.11%) did not. Out of 52 participants who were relaying on herbal medicines, 37% (71.15%) people expressed dissatisfaction with their herbal treatment while 15 people (28.85%) said they were satisfied. Of the 20 patients receiving food-based therapies, 5 (25.00%) reported being satisfied and 15 (75.00%) reporting being dissatisfied.

Tab. VIII. Participants' satisfaction level with the current therapeutic choices.

Category	Frequency (n)	Percentage (%)
Overall level of satisfaction with present therapy (n = 296)		
Yes	141	47.64
No	155	52.36
Total	296	100.00
Patient satisfaction among those receiving allopathic medicine treatment (n = 152)		
Yes	110	72.37
No	42	27.63
Total	152	100.00
Patient satisfaction among those receiving homeopathic medicine treatment (n = 72)		
Yes	28	38.89
No	44	61.11
Total	72	100.00
Patient satisfaction among those receiving herbal treatment (n = 52)		
Yes	15	28.85
No	37	71.15
Total	52	100.00
Satisfaction with food (n = 20)		
Yes	5	25
No	15	75
Total	20	100.00

Current allopathic treatment and related adverse effects

Tables IX and X provide information about allopathic treatment and associated adverse effects. 110 (37.16%) respondents out of 296 provides information on their drug (s) used in chemotherapy. Out of 110, when compared to docetaxel (n = 20, 18.18%), trastuzumab (n = 22, 20.00%), doxorubicin (n = 14, 12.73%), and 5FU + docetaxel (n = 14, 12.73%), the therapy with cyclophosphamide + 5FU + doxorubicin was found to be more common (n = 28, 25.45%). Participants (n = 296) listed severe GIT problems (n = 149, 50.34%), joint issues (n = 5 9, 19.93%), nausea and vomiting (n = 34, 11.49%), and liver concerns (n = 8, 2.70%) as adverse effects.

Tab. IX. Allopathic drugs used in chemotherapy (n = 110).

Drug(s)	Frequency (n)	Percentage (%)
Cyclophosphamide+5FU+doxorubicin	28	25.4
Docetaxel	20	18.18
Trastuzumab	22	20.00
Docetaxel+trastuzumab	12	10.91
Doxorubicin	14	12.73
5FU+docetaxel	14	12.73
Total	110	100.00

Tab. X. Treatment side effects reported by participants (n = 296).

Side effects	Frequency (n)	Percentage (%)
Joint problem	59	19.93
Severe GIT issues	149	50.34
Nausea and vomiting	34	11.49
Liver problem	8	2.70
No side effects	16	5.41
More than one above mentioned side effects	30	10.13
Total	296	100.00

Decisions on breast self-examination and treatment are influenced by education and family history

Education and family history are related to breast self-examination and treatment decisions, and results are presented in Table XI. The results of the study indicated that BSE and treatment decisions were significantly influenced by education and family history of breast cancer ($p < 0.05$).

Discussion

In this current study, different stages and symptoms of breast cancer are discussed. It showed that most of the women (42%) considered in this study had stage 3, and 38.3% had stage 2. According to the Nadem Bilani et al. stated that 42% females were diagnosed at the stage 1 and 25% at stage 2 [19]. In the context of symptoms, this study suggested that 34.12% of patients had a painful lump or pain when touched, and 27% had a painless lump. In contrast, others showed different symptoms like nipple retraction, skin thickening, change of shape or size of breast, discharge of secretion, *etc*. Caroline Burgess et al. (2001) found out that the majority of the patients had breast lump and felt pain when touched. According to the WE Barlow et al., women with a diagnosed breast cancer were more likely to report a breast lump (72.2%) than those without (47.4%) [20].

A recent study found that 38.3% of patients acquired breast

Tab. XI. Association of education and family history with breast self-examination and therapeutic choices (n = 296).

Variables	Education	Family history
Have you heard of BSE?	0.001	0.031
Have you done BSE?	0.020	0.009
BSE helps you in the early diagnosis of cancer.	0.013	0.028
Do you know how to perform BSE?	0.040	0.036
Which type of treatment was used?	0.020	0.032
Which type of therapy is used at the early diagnosis of breast cancer?	0.006	0.011
Are you using more than one therapy?	0.023	0.002
If you use CAM, then are you informing their physician?	0.04	0.034

$p > 0.05$ = non-significant and $p < 0.05$ = significant.

cancer from their parents, siblings, or other relatives. 9.3% of breast cancer cases were passed down from parents and 9.3% from siblings. However, the medical reports of 61.7% of patients revealed no family history of breast cancer, because even when they experience symptoms, patients without a family history may not consider themselves as being at high risk and may be less likely to seek early medical assistance. But, according to Richard W. Sattin et al., most breast cancer is inherited from first-degree relatives like mother and siblings [21].

Breast self-examination is an essential technique for the early detection of breast cancer. However, it will be beneficial to patients if it is done appropriately. Compared to uneducated or rural areas, the females at the higher learning institution were well aware of self-breast inspection and practiced it [22]. According to the current study, the majority of patients (82.3%) had not heard about breast self-examination, while just 17.91% of women had. Only 16% of female patients had performed this, and BSE helped her in the early diagnosis. In Turkey, 68% of females had heard about breast self-examination, but only 34% of female patients had performed this before their diagnosis. Our research, however, revealed considerably lower awareness and practice rates. These variations could be ascribed to regional variations in healthcare resources available, cultural perspectives on preventive health, or differing degrees of public health education. The primary sources of this information and knowledge were television and different programs on TV channels [23, 24].

This study examined allopathic (chemotherapy), homeopathic, herbal, and diet treatments. When it came to the early diagnosis of breast cancer, 51.35% of patients underwent allopathic therapy, 24.32% used homeopathic therapy, 17.57% used herbal treatment, and 6.7% used dietary treatment. The data indicate that 48% of women have used complementary and alternative therapies, such as herbal, homeopathic, and nutritional. However, according to this, the majority of the women, 66% of patients, had at least one CAM therapy after the completion of allopathic treatment of disease, and most of them felt that their physician did not authorize their use of complementary and alternative medicine [25]. According to Grayson A. et al., 84% of female patients who used CAM as side therapy for their disease did not disclose this to their respective allopathic practitioner [26], and the same way in this current study also, 55.41% of female patients did not inform the usage of alternative therapies to their oncologist.

Recent research revealed that 47.7% of them were satisfied with the therapy they were receiving at the time, while 52.3% were not. It also demonstrated the level of patient satisfaction with various treatment approaches. While 27.63% of patients were dissatisfied with the existing chemotherapy, 72% of patients were satisfied with allopathic therapy. Merely 38.89% of patients expressed satisfaction with homeopathic treatment, whilst 53% of women expressed dissatisfaction. Of the patients, 71.15% were unsatisfied with herbal or dietary therapy, whereas just 28.85% of women were satisfied. The results of this study are nearly comparable to those of a different study carried out by A research by H. Boon et al. (2000) found that 24.4% of patients were satisfied with alternative therapies, while 62.6% were content with conventional treatments or believed that conventional treatments would cure their illness. These findings are fairly similar to our study, which found that allopathic therapy had the highest satisfaction rating when compared to alternative therapies. However, the use of CAM is expanding significantly [27]. In a related vein, H. Boon et al. stated in a 2007 article that these alternative therapies will no longer be referred to as "alternative and complementary therapies", owing to the growing prevalence of complementary and alternative medicine (CAM), the label "alternative" is losing use as these treatments are more thoroughly incorporated into traditional healthcare [28].

The current study discovered that the patient's education and family history had a statistically positive relationship with the knowledge of breast self-examination, the type of therapy used in the early diagnosis of disease and their compliance or relation with their allopathic practitioner. The present investigation discovered a statistically significant positive link between patients' educational attainment. More specifically, people with more educational attainment were more likely to identify symptoms and seek medical attention as soon as possible. The Pearson correlation coefficient revealed a correlation coefficient of 0.45 ($p < 0.01$). The study also found that patients were more likely to undergo screening and diagnostic treatments if there was a family history of breast cancer. Analysis was used to evaluate this, and the results indicated that patients with a family history had an increased likelihood of participating in early screening programs by ($p < 0.05$) compared to those without such data.

Conclusions

This research offers significant perspectives on how education and awareness affect the treatment of breast cancer. More specifically the current findings suggested that a sizable percentage of participants do not know enough about breast self-examination. This disparity emphasizes the need for more strong awareness-raising efforts, such as community-based workshops and instructional initiatives designed to address these issues. The significance of pursuing the advancement of allopathic treatment is highlighted by our results which also show a notable improvement in patient outcomes. Additionally, the integration of conventional treatments with complementary approaches, such as nutritional and lifestyle modifications, has shown promise in enhancing overall therapeutic efficacy. Future studies ought to concentrate on assessing the integrated therapies long-term efficacy and investigating novel approaches to improve patient education and early detection. Also, the study found that common side effects of current treatments like nausea, joint problems, fatigue, and GIT issues have a major negative influence on patients'

quality of life. Addressing these side effects through supportive care and symptom management is necessary to improve overall patient satisfaction and treatment adherence.

Conflict of interest statement

The authors declared no conflict of interest among them.

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Authors' contributions

NM: conceptualized and designed the study; KA, MZ: compiled the data. EM and SA drafted the final manuscript. All the authors read and approved the final manuscript.

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NURSING

Basing patient safety education on real student experience: development of a multinational simulation scenario

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Keywords

Emotional safety • Undergraduate nursing education • Simulation • Patient safety

Summary

Introduction. *Implicit learning during clinical placements includes patient safety issues. Simulation scenarios offer ways to improve the learning process and students' awareness of patient safety. The aim of this study was to develop a prototype simulation scenario based on real student experiences.*
Methods. *This was a mixed-method study using a multi-phase design. Nursing students' experiences of workplace events they identified as possible threats to patient safety were collected between 2017 and 2019. These experiences were used to develop an interprofessional scenario about patient safety.*
Results. *A range of scenario materials were produced including a video. Participation in the scenario video had positive impacts including: "feeling safer" while performing nursing activities and more timely detection and reporting of errors. Nursing students reported that participation in the scenario taught important lessons about patient safety, communication, listening to patients and healthcare collaboration.*
Conclusions. *The role-playing methodology of the scenario provided opportunities for reflection on patient safety and improved interprofessional understanding and communication in an emotionally safe environment.*

Introduction

Nurses play a key role in ensuring patient safety [1]. Nurse education occurs in both academic and clinical settings and European law (Directive 2013/55/EU) requires at least half of a nursing education programme be delivered in clinical practice. Educating student nurses about patient safety from both academic and clinical perspectives is important [2]. Implicit learning occurring in the workplace [2, 3] can influence patient safety. Disparities between clinical practice and 'classroom' teaching may have a negative impact on students [4]. Therefore, it is important to create emotionally safe environments for learning [4, 5] and ensure close relationships between academic theory and clinical practice.
During clinical placements students may see and adopt unsafe practices that are not evidence-based. Undertaking clinical placements where there is a poor patient safety culture hinders the learning process and creates emotional dissonance in students [4]. Students often recognize poor practice but may keep quiet, influenced by a need to be accepted by colleagues [6-8]. They may be reluctant to raise concerns because of their perceived role and position [7, 9].
Innovation in patient safety education requires collaboration between healthcare faculty members, clinical practice leaders and staff at all levels and across professions [4]. Interprofessional and interdisciplinary learning offers students new understandings and alternative perspectives, encouraging the development of a broader range of reactions to patient-safety issues. New tools to improve learning processes are needed as adjuncts to traditional teaching [4].
Interdisciplinary, evidence-based simulation is one approach used as a learning instrument. Scenarios based on real events offer students the possibility to develop new skills outside the workplace [10, 11]. An essential element of simulation is debriefing, to reduce the gap between theory and practice [1-14]. Debriefing helps students solidify their relational, psychomotor, and cognitive skills [14-16]. Simulation scenarios also offer opportunity to share situations across countries with varying healthcare systems and approaches to care [17].
Jeffs et al. (2022) [32] emphasize the need for healthcare organizations, including academic institutions, to adopt proactive strategies to enhance patient safety. Academic institutions, in particular, should lead efforts to improve patient-centered, team-based care. This can be achieved by incorporating interprofessional education into curricula, providing explicit training on roles and responsibilities, fostering effective communication skills, and ensuring seamless transfer of care [33].
From a recent review of literature regarding educational

interventions to improve patient safety, Jiang et al. (2024) [34] found that a range of simulation strategies were proven to be effective, furthermore learning strategies in which real-world experiences and safety issues were discussed and addressed were important.

The European Project 'Shared Learning from Practice to Improve Patient Safety' (SLIPPS) focused on developing resources for patient safety education, that are based on real student experience, multidisciplinary and standardized [1, 3] The project supports formal and informal learning by promoting reflection on significant events experienced by students in clinical practice [1, 3]. This paper describes the methodology and process used in developing the first SLIPPs scenario, which formed the basis for development of a range of subsequent scenarios. All resulting materials are available on the SLIPPs website (https://www.SLIPPs.eu).

Methods

Aim

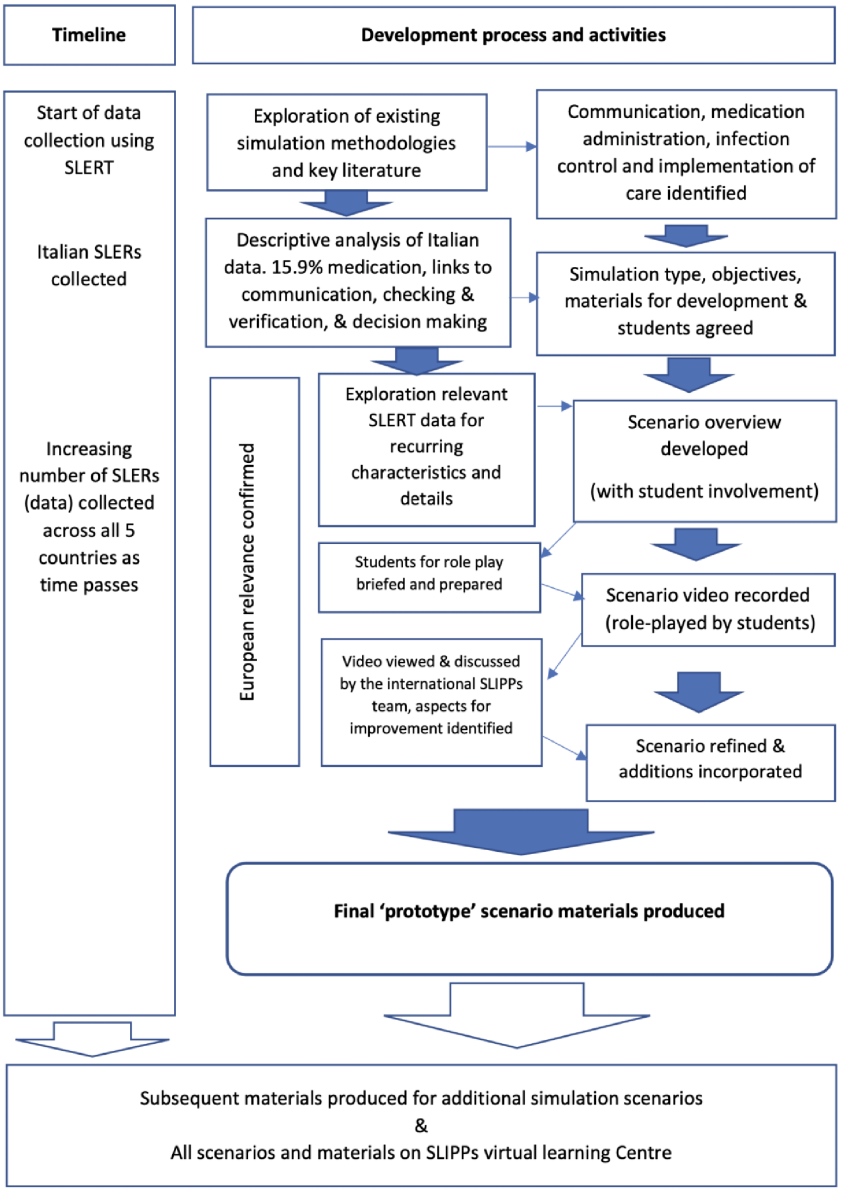
To develop a prototype scenario to facilitate learning about patient safety that:

- Is based on real experiences;
- Has a focus on medication administration;
- Includes a range of different materials (documents, guides, scripts, and a videoed version) allowing flexible use;
- Can be used with students across various stages of their education;
- Has multinational relevance.

Study design

This mixed-method study used a multi-phase design (Fig. 1). Scenario development was underpinned by the

Fig. 1. Scenario development process.



Tab. I. SLERT reports gathered.

Profession	Country					Total
	Finland	Italy	Norway	Spain	UK	
Midwifery	2	21	0	0	7	30
Nursing	59	67	29	54	87	296
Total	76	88	29	54	94	326

Nursing Education Simulation Framework (NESF) [11]. Standards and guidelines for best practice in the development and conduction of simulation scenarios were followed [18]. Materials including a video version of the scenario, were planned to allow flexibility of use (*e.g.* from live enactment of the scenario to viewing the video). After the production of the first simulation scenario, a similar methodology was followed in developing further patient safety learning scenarios (see: SLIPPs.eu).

Ethical approval

The study was approved by Liguria Regional Ethics Committee (Reg. N. 300REG2017). Appropriate ethical procedures were followed in all participating countries. Participation was voluntary and informed consent was obtained from all participants before every phase. Data confidentiality was assured, as was the option to withdraw at any time.

Data collection, analysis, and scenario development

The SLIPPs Learning Event Recording Tool (SLERT) [19] collects narrative and demographic data about students' learning experiences related to patient safety whilst in clinical placements. The tool prompts students to describe, consider, and reflect on events they feel have been important for their learning. This includes both what they learned, and the emotional investment involved (see [19] for details). The SLERT tool was used to gather 326 student reports over 18 months between 2017 and 2019 (Tab. I) from a convenience sample of nursing (n = 296) and midwifery students (n = 30) from five European countries (Italy, England, Finland, Spain, and Norway).

Data were analysed on an ongoing, iterative basis. Communication, medication administration, infection control and implementation of care emerged as topics with wide-ranging relevance. Early descriptive analysis of the Italian data (n = 88) identified 15.9% of reports (n = 14) related to medication issues. Of these, 50% (n = 7) were also identified as relating to checking and verification, 42.8% (n = 6) communication, and 35.7% (n = 5) decision making. Given the potential to incorporate multiple aspects of professional practice into a scenario focused on medication administration, this was chosen as the topic for prototype development. Subsequent ongoing analysis of data confirmed the relevance of this topic.

Scenario development

Italian nurses with expertise in clinical practice, research and education developed the prototype scenario supported by multinational SLIPPs sub-group meetings. At the outset, it was necessary:

- to define the simulation type (live participant role play), objectives, and materials to be developed (documents and video recording);
- to identify the type of students to be involved;
- to describe the proposed scene [11, 20].

Narrative exploration of a selection of relevant SLERT data enabled the identification of recurrent characteristics that were included in the scenario to ensure authenticity. Consideration was given to the type of event (*i.e.* near miss, hazard, good practice, adverse event), the complexity involved, and the year of the degree course during which the event occurred [11].

A scenario overview and general synthesis document were developed covering principal scenario elements (context, students' involvement, learning objectives, roles). Simultaneously, a script was produced outlining the role-play. This included details of the resources needed to ensure fidelity. Preparation and participation in role-play enabled students to experiment with different situations, understand what it is like to be in the situation of the patient, or another health professional, and engage in reconceptualization through picturing themselves in possible future scenarios [21, 22].

The presence of a skilled, knowledgeable nurse facilitator was also a key consideration. Facilitators orientate the students in the learning environment, conduct pre-simulation meetings to explain the objectives expected from participation and clarify the overall aim of the simulation [21]. This helps the students to act the roles to the best of their potential and work towards achieving the specific learning objectives. During the scenario, facilitators make suggestions, guide the students in their specific roles, and encourage corrections if necessary. They also play an important part in creating a sense of emotional safety for the students during their learning [4, 23]. Debriefing was planned and undertaken at end of the prototype simulation based on the '3D Model of Debriefing' [24] which involves four phases (Tab. II).

Tab. II. Guide for Debriefing.

Key questions	
1.	How are you feeling now?
2.	What were the positive actions? What went well?
3.	What do you want to improve? Would you do something differently?
4.	Have you ever been in the same situation?
5.	Take home message: what did you learn from this scenario?

First use and scenario improvement

The prototype scenario included six roles: one physician, two patients, one nursing student, one nursing assistant, and one nurse supervisor. The setting is a room with two beds on a medical ward, and while the focus is on medication administration, other elements are also included (see Box 1: scenario outline). Members of the Italian nursing team facilitated the role play, assigning roles to the students involved, explaining the scenario, and discussing participation and learning outcomes. The scenario lasted for 10 minutes, and was video recorded in its entirety. At the end of the role-play debriefing was undertaken. The video was discussed by the international SLIPPs team and aspects for improvement were identified which included adding 'pause and reflect' points and showing the text of the debriefing questions in the video (Tab. III).

Results

Following first use of the role play scenario, debriefing was undertaken with the students involved. Facilitators encouraged discussion of strengths and areas for improvement in the care portrayed. They reflected on participants emotions, and on expected and unexpected outcomes of the simulation experience. The care delivered by the role play characters (as per the script) was reviewed against best-practice. The debriefing was videotaped (with consent) and transcribed verbatim. Drawing on thematic analysis principles [25], the transcript was read by the research sub-group members, and independently coded using debriefing questions and temporal codes (before, during, after) as heuristics to help understand the formative nature of the experience.

Debriefing findings

Four themes emerged from analysis of the debriefing:

- the simulation experience itself;
- similar situations in practice;
- the emotions involved;
- the learning obtained.

When asked how they felt during the simulation performance, all felt they had been able to interpret the role assigned to them and especially reported experiencing the scenario at the emotional level:

> *"I was able to immerse myself in the simulation and this sincerely made me feel every uncomfortable as a patient; because I was the patient no one considered…I saw everything, but I understood only a part of the dynamics that were unfolding… so I felt very uncomfortable"* (PhD Student playing Mrs Taylor, one of the patients)

One issue highlighted was the difficulty of completely immersing oneself in one specific role, when that participant had in real life experienced several of the scenario roles (*e.g.*, nursing student, nurse, and patient) and identified with all of them. Those who interpreted a role they had never personally experienced were able to gain insights into the distinguishing features of that role and the differences from their own 'real' role.

> *"It was useful because it showed me that there are moments or activities that we undervalue [or give little attention to], like giving out meals, perhaps because they are not part of our[nursing] remit we do not perceive the criticality/importance of them*

Tab. III. Scenario synthesis.

Background Johanna Smith was admitted to a medical ward for hyperthyroidism. She has no clinical complications. She is awake in her bed and waiting for her morning medications. The patient is affected by other chronic diseases; therefore, she has multiple therapy and medication charts. The scenario is happening in the morning, at the beginning of the morning shift, during the medication administration round.
Scene 1: It is handover time in the medical room. The physician tells the nurse (who is starting her shift) that during the morning he will change the prescription of some medications for Mrs. Smith, but he cannot do it straight away. He tells the nurse to go ahead and administer the medications to the patients, specifying that he will see her later.
Scene 2: Mrs. Smith wants to know what kind of medicines she is going to take, because she wants to know if she must take them before or after her breakfast, which the support worker is distributing in the meantime. Meanwhile, Mrs Taylor– lying in the bed next to Mrs Smith, insistently asks the student if she can take her medication, which was left on her bedside table and that she usually takes by herself. The nursing student tells the patient that she needs to check the prescriptions with the nurse who is on duty. The nurse reminds the student to focus on the medications pertaining to Mrs Smith. While the nurse and the student check the pharmacological prescription, the physician enters the room and tells the student and the nurse supervisor that they must immediately change the dosage of Thiamazol for Mrs Smith. The student tries to remain concentrated, but the continuing distractors and the therapy spread across several sheets, do not facilitate this activity and the student is visibly in difficulty. Given the situation of risk of error, the supervisor interrupts the administration of the medicines and asks to the physician to rewrite Mrs Smith's therapy, to avoid any mistakes. After the therapy's adjustment, the nursing assistant enters the room calling for the nurse with a sense of urgency as there has been an emergency in the ward. The student, remains alone, and continues with the administration of Mrs. Smith's medicines but makes a mistake giving the patient the wrong medication. The patient, after having taken the pill, realizes that the pill had a different colour from that she was given on previous days, and asks for an explanation.
Scene 3: The student runs into the nurses' room and says to the nurse supervisor that she has made a mistake.

for the patient." (PhD Nursing Student playing a Healthcare Assistant)

When asked if they had already experienced the situation played out in the scenario in their professional lives, most of the participants said that they had all experienced something similar and recalled the emotions involved.

"Something similar has happened to me, not as a patient but as a relative...therefore I felt from the patient's position the anxiety of not knowing [what was happening], not being at the centre of things. In this situation [the simulation] I drew on that personal experience" (PhD Nursing Student playing Mrs Taylor, one of the patients)

Feelings of uncertainty or anxiety were described by students when they were unsure of their own knowledge about the medications they were administering. One participant described how a lack of communication between nurse and patient on key issues could result in feelings of discomfort and disorientation.

"It has happened to me once, or actually several times, when a patient would come to me asking why he/she had those pills in their hand, and I have had that same feeling of having made a mistake [as is portrayed in the scenario]" (Third-year Nursing Student playing the role of Manuela, nursing student)

The students stressed the power of the emotional impact of a situation whether real or simulated, and how that could serve to activate learning.

"Therefore, when the professional or student recognises the emotional impact, and above all has time afterwards to reflect and to understand why the event happened and what happened- then it can become a learning situation, a discussion or reflection. Such as is happening here now [in the debriefing], as could have happened between the student and supervisor [in the scenario]… Therefore that is the fundamental thing, to talk and say what has happened, why it has happened and what could have happened" (PhD Nursing Student playing the role of Johanna, patient receiving the wrong treatment)

Learning from the Simulation experience

Students were also asked to describe positive aspects of participating in the simulation. They were also asked to reflect on the timeliness with which the nursing student portrayed in the scenario recognised the medication administration error and communicated it to the nurse supervisor.

The character of the nurse supervisor, and the attention that she paid to the student during the role play, were reported to demonstrate positive supervisory behaviours. The depiction of teamwork and collaboration across the various professions was also identified as an important element of the scenario.

When asked if they would have done anything else, or done something differently, in a similar real situation, communication was seen as a key aspect for improvement.

Reflecting on the scenario the participants underlined the importance of ensuring that nurses have sufficient time to dedicate to each phase of the care process, without being distracted. Care delivery (including medication administration) should occur without interruptions from other people (*e.g.*, patients or healthcare professionals), which could potentially lead to errors.

"For me a fundamental thing that emerges from this simulation is the need to dedicate the right [amount of] time to each moment of activity ... to find a 'structured space' in which to undertake care delivery so that the care and clinical processes have their desired effect." (PhD Nursing Student playing the role of a Healthcare Assistant)

Finally, participants were asked to identify if they had identified a 'take home' message from the simulation experience. All agreed that the experience offered something additional to their usual activities.

"…. no matter which role we found ourselves in [in the scenario], everyone took a little piece home, whether tomorrow we return to be nurses, or in the case during our lives we end up being patients, or we return to be students…I think I can speak on behalf of everyone… Each of us has learned something." (PhD Student playing the role of Johanna, patient receiving the wrong treatment).

Development of further scenarios and SLIPPs' online learning centre

The development of the first scenario prototype resulted in a range of materials (Tab. IV) and formed the basis for the creation of a series of subsequent scenarios.

Thanks to the large number of SLERTs collected, there was a broad variety of student accounts to draw upon. Other scenarios concerned issues such as: infection control and aseptic technique in midwifery, communication, transfer of care, and hospital discharge. Suitable materials were developed to accompany each simulation scenario. These materials formed a 'library' of resources, which can be accessed on the project's website: https://www.slipps.eu/simulation-scenarios/.

Discussion

This paper outlines the development of the first SLIPPs simulation scenario for patient safety education based on real student experiences [26]. There are many reports of the advantages of using authentic (high-fidelity) scenarios to teach technical and communication skills, teamwork, interprofessional collaboration, and patient education [12, 27, 28].

The innovation in this scenario development was the extrapolation of storylines and events directly from descriptive and reflective accounts of real patient safety related events. These were drawn from the experiences of students on placement across five European countries. While scenario development was informed by 'expert' knowledge, theory, and opinion, it was situated in the real

Tab. IV. Materials relating to the scenario.

1. Guidelines for scenario development, a theoretical summary. *These guidelines offer background information providing the theoretical basis for scenario development. This offers faculty the foundations for developing new scenarios of pertinence to their context (e.g. country, clinical setting, student group, educational level required).*
2. The Scenario overview, a document giving an overview of the scenario requirements and the educational potential of the scenarios. *This outlines the topic and envisaged location and gives an overview of the simulation: design, considerations for assigning roles, approximate timings, responsibilities, potential areas of learning and learning objectives, debriefing structure etc. This document is an important resource facilitating faculty/educators to clearly identify and consider the areas of learning that can be addressed through the scenario (for example, knowledge, skills, critical thinking, decision making, student self-confidence etc).*
3. The 'Teacher template', containing the operational and technical details of each scenario. *This provides a framework for faculty/educators to plan and prepare for scenario use in their particular context. Once completed this framework also acts as a valuable record of the various elements, structure and considerations relevant to the scenario, who worked on it and what literature and theory it is based upon.*
4. The Slide deck includes a graphical synthesis of what is in the "teacher template", with the extra addition of literature insights on every theme covered in the specific scenario, available through hyperlinks to the scientific papers.
5. Where there are Scenario videos, these show (with an oral explanation) the scenario acted out. *These allow viewers to watch the scenario in action, to pause and replay elements as required., This enables faculty to tailor use of the scenarios to the students' needs (i.e. by varying time spent on reflection, or through replaying sections to allow for greater observation and analysis). The videos also offer a solution in situations where the students/faculty do not have the facilities or resources to 'act out' the situations, thus increasing accessibility to these multi-nationally developed educational resources.*
6. The Debriefing sheet contains questions to be asked during a debriefing. *Debriefing is a crucially important element of simulation use [1] which is sometimes not given sufficient attention. Based on an established model of debriefing [2] this sheet assists faculty/ educators to structure the debriefing session and prompts them to consider the functions of debriefing in order to optimise the learning that occurs.*
7. The Feedback sheet is a form to collect comments and suggestions from the scenario users (students or educators). *These enable the collection of feedback to allow ongoing development and updating of the scenarios and further tailoring to future health care practice and technology developments.*

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lived undergraduate students' experiences, reflections, and emotions.

Simulation can trigger a range of emotions for those involved. The emotional dimension of learning through experience (practice or simulation based), is important and should not be overlooked [4, 5]. The creation of an emotionally safe context in which to learn how to be a healthcare professional is also important [4, 5, 29]. The use of simulation-based scenarios allows the education of future professionals in a safe and protected environment [30].

Simulation-based education is reported as an effective strategy for improving communication skills and understanding professional roles. This was supported by the debriefing undertaken during development of the SLIPPs scenario, which enabled students to become more aware of the roles and scope of practice of other healthcare professionals. Such learning through experience, including vicarious learning as in simulation, may enhance self-efficacy. Therefore, simulation education can act as an important adjunct to practice learning by offering a rehearsal of situations and roles, fostering the internalisation of evidence-based practices, and enhancing reflection. This lays the foundations for safer healthcare delivery [3, 30].

The international character of this development, and the accessibility of the materials produced allows the creation of direct links between educators, universities, students, and, consequently, European healthcare professionals [31]. This creates new opportunities for learning. Addressing common issues linked to patient safety in different healthcare contexts allows the development of shared educational strategies. This improves patient safety in the current context of global health workforce migration.

Limitations

The principal limitation of this study is the difficulty inherent in creating a scenario with as much transferability as possible to the different European healthcare contexts. This has undoubtedly resulted in the loss of features linked to specific national healthcare contexts and cultures. Notwithstanding the production of materials in English, communication used in the scenario (*i.e.*, between healthcare professionals and patients) was specific to the care context and therefore has some transferability. 'Props' (*i.e.*, uniforms, devices, machines, equipment, *etc.*) used in the scenario can be substituted to suit a particular national context and infrastructure, thus enhancing realism and usability. We addressed limitations linked to international relevance and to ensuring that all the teaching materials were developed with rigour, by constantly sharing the study phases with the five partner countries.

Concusions

This study reported the innovative development of a prototype simulation scenario based on students' real life placement experiences of patient safety. The scenario drew on existing patient safety and simulation literature, data from the SLIPPS project, student involvement and discussions between project partners. The prototype

formed the basis for development of further scenarios.
The overall purpose of these scenarios is to act as flexible educational resources to improve student learning and ultimately the safe provision of care. The scenario materials produced can be used 'of the shelf' or tailored to fit specific needs, and in the creation of new scenarios. The use of scenarios that involve different healthcare professionals give participants opportunities for reflection on other roles and on communication between team members. This lays the foundations of high-quality future interprofessional practice. Using role play methodology in simulation also offers students the opportunity to rehearse nursing activities and interprofessional situations in an emotionally safe environment.
Involving students in an active way in the development of educational resources such as simulation scenarios offers additional learning opportunities both for the students directly involved and for the future generations. Building scenarios on students' experiences and involving them in the development of the scenario resources (videos and materials), allows them to see that the lessons possess currency, relevance and authenticity.

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Conflicts of interest statement

None.

Authors' contributions

Conceptualization, Methodology, Analysis, and overall supervision. SR: Conceptualization, Analysis, Writing-Original draft preparation. ND: Data curation, Writing-Original draft preparation. RC: Data curation, Investigation. FN: Data curation, Analysis, Writing-Original draft preparation. GA: Methodology, Data curation, Reviewing and editing final draft. GC: Reviewing and editing final draft. LS: Conceptualization, Methodology, and overall supervision. MZ: Data curation and overall supervision. PJG: Data curation, Reviewing and editing final draft. AS: Conceptualization, Methodology, Analysis, Writing-Original draft preparation and overall supervision

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NURSING

Quality of Life and non-motor symptoms Improvement in Parkinson's Disease through Nutritional Intervention: a Case Study

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Keywords

Parkinson's disease • Non-motor symptomatology • Nutritional challenge • Sarcopenia • Quality of life

Summary

Non-motor symptomatology in Parkinson's disease (PD) is related to patients' quality of life (QoL). The Non-Motor Symptoms Scale (NNMS) assesses QoL by investigating numerous domains including nutritional status, which is represented by domain 6. Patients with PD commonly suffer from dysphagia, and consequently malnutrition, leading to sarcopenia and increasing motor deficits in relation to loss of muscle mass and energy deficit. The impact of dysphagia on PD patients' health status, makes it necessary to study the effectiveness of specific nutritional programs in addressing feeding needs, with the goal to improve clinical outcomes and the patient's perception of their QoL. The 'Weancare' Program was trialed on an 84-year-old PD patient suffering from dysphagia and the Tower of Pisa Syndrome. The first assessment of the patient showed an early overall deteriorating condition, particularly under a nutritional point of view. The patient was assessed before and after the intervention considering serological tests, and the QoL through the New Non-Motor Symptoms Scale (NNMS). We found a beneficial impact of the 'Weancare' program on the patient significantly improving the non-motor symptomatology and QoL and the investigated outcomes, enhancing a better subjective experience of mealtime lived by the patient.

Introduction

Parkinson's disease (PD) is the most widespread neurodegenerative disease, after Alzheimer's disease, with a global prevalence of six million people. Considering the last generation, the trend of incidence has grown by 2.5 times, making this affection one of the main causes of neurological disability [1]. PD predominantly affects individuals between the age of 50 and 60. Men have a slightly increased risk of developing the disease compared to women with a prevalence ratio of about 3:2. Additional risk factors include familiarity and exposure to pesticides [2].

PD is a degenerative disease of the Central Nervous System (CNS) mainly characterized by muscular rigidity and other motor and non-motor symptoms, such as cognitive, behavioral and dysautonomia symptoms. The onset of the disease is characterized by a prodromal phase that may precede motor symptoms even for several years. Usually, this phase may include constipation, hyposmia, sleep disorders, orthostatic hypotension, mood depression, urination disorders, and erectile dysfunction [3, 4]. On the other hand, motor symptoms, include tremor at rest, bradykinesia, stiffness, and postural instability [5]. In patients with PD, non-motor symptoms are related to the quality of life [4, 6]. This link could be observed through the Non-Motor Symptoms Scale (NNMS), especially in domain 6 on gastrointestinal tract and associated disorders [7].

Malnutrition in patients affected by PD is still a relevant variable that results in sarcopenia and increased motor deficits due to the loss of muscle mass and energy deficit. Indeed, European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend monitoring weight loss and implementing interventions to manage patients' weight or body mass loss [8].

Dysphagia is a common syndrome in patients with PD, even in early stages of the disease. The prevalence of dysphagia varies between 11% and 97% of the patients during the disease [9]. This condition impacts both the safety of feeding and the nutrition and hydration status of the patient, with the risk of affecting the patient's overall survival [10, 11]. Malnutrition can thus be caused by dysphagia as a result of reduced daily food intake, increased requirements related to a health condition or a preexisting state of malabsorption and excessive nutrient loss, or as a combination of these conditions. The consequences of these disorders on patients may vary and include increased infections, increased functional tissue loss (sarcopenia), increased comorbidities and mortality [11, 12]. Sarcopenia prevalence related to PD disease severity is recognized and this fact highlights the importance of screening for sarcopenia [13]. This type of clinical picture of

PD patients can be assessed thanks to specific scales, which enable, for example, to identify the syndromic dimension of the disease and the components that impact the patient's overall quality of life [7, 14] and, even, detect individuals with cognitive deficits [15]. Moreover, the application of a specific nutritional program for patients with swallowing-related problems is recommended in the prevention of malnutrition in patients with PD. Indeed, previous studies have demonstrated a rapid reversibility of malnutrition in hospitalized older patients with cognitive and functional decline enrolled in a specific nutritional program [16, 17]. Moreover Di Nitto et al. (2022) [18] have found that an Effective self-care behaviors, including adherence to medications, health surveillance, and seeking help, have been shown to improve outcomes in patients with chronic conditions, underscoring the importance of comprehensive care plans.

Case description

In April 2021, an 82-year-old-male presented to the Day Hospital service at the La Colletta hospital in Arenzano (Genoa, Italy). The patient had been affected by Parkinson's Disease for 2 years, with consequent dysphagia assessed using Fiberoptic endoscopic evaluation of swallowing (FEES). Additionally, the patient suffered from the Pisa Tower Syndrome [19]. The European Working Group on Sarcopenia in Older People (EGWSOP) Assessment tool confirmed the presence of sarcopenia in the patient, which included physical performance by measuring gait speed, muscle mass by assessing mass indices via vector impedance testing performed with Bioelectrical Impedance Vector Analysis (BIVA), and muscle strength using prehensile hand strength. The Walk Analysis parameters were mostly altered from normal ranges (Tab. I). Cadence (measured in steps per minute) and speed (measured in meters per second) showed higher average values than normal average values. These data show a slowing down of gait speed compared to physiological gait.

Materials and methods

To treat malnutrition and the related symptoms, the patient was offered a diet intervention, called the Weancare Domus food plan based on the Dhysphameal product line that is developed specifically for individuals with dysphagia, offers a nutritionally balanced range of foods designed to support safe and adequate nutrient intake while minimizing the risks associated with swallowing difficulties. These products are tailored to ensure appropriate texture and consistency according to the severity of dysphagia, thereby facilitating ingestion and digestion while preventing aspiration or choking risks.

Tab. I. Walk Analysis data.

Space-time parameters	Patient's values (mean ± standard deviation)	Normal values (mean ± standard deviation)
Test duration (s)	126.0	//
Cadence (steps/min)	131.89 ± 19.34	114.60 ± 8.40
Speed (m/s)	1.39 ± 0.11	1.19 ± 0.16

One of the critical features of Dysphameal products is their enhanced protein-energy density, aimed at mitigating muscle deterioration (sarcopenia) and nutritional deficiencies often observed in patients with dysphagia. The formulations provide a full spectrum of macronutrients and micronutrients necessary for daily intake, supporting overall health without reliance on pharmacological supplements.

In terms of formulation, these foods are crafted to maintain smooth consistency, stability in storage, and natural flavours, thereby catering to the specific dietary and sensory needs of patients. This approach is designed not only to fulfil nutritional requirements but also to improve compliance and quality of life for individuals with compromised swallowing functions. This was prepared with the collaboration of a nutritionist and consisted of lyophilized recipes to be rehydrated autonomously to constitute the serving dish, which, during the experimental period, would be the patient's prevalent nutritional intake. Everything that was needed for the meals was delivered to the patient's home, according to his personal preferences.

To observe the developments and results achieved by the Weancare domus diet program, the patient included in the study was followed-up. This involved the use of non-invasive, inexpensive and user-friendly devices, to measure body parameters, which have been used over the last ten years and have the potential to be used in future clinical health [21].

The study develops in two different phases: at the beginning of the study (Time 0, T0) and after 6 months (Time 1, T1).

At T0 the following anthropometric indexes were assessed: age, height, weight, arm circumference, Body Mass Index (BMI), the blood chemistry data, including cell blood counts, nutritional and inflammatory indexes and the Bioelectrical Impedance Vector Analysis (BIVA). BIVA versatility across various fields highlights its usefulness in assessing body composition and hydration status without relying on body weight, making it a valuable tool for healthcare and nutritional assessment. This analysis method uses a plot of resistance (Rz) and reactance (Xc) standardized by the subject's height to assess body composition and hydration status. It is particularly useful because it does not rely on population-specific formulas and can be applied across different groups, including patients with various health conditions and comorbidities, but also healthy individuals. The BIVA graphical representation, typically an RXc graph, features ellipses that represent different levels of hydration and body composition (Fig. 3). These ellipses serve as reference intervals to evaluate an individual's or group's bioelectrical impedance

against a healthy reference population [20]. The BIA 101 BIVA® PRO device was employed for analysis. The instrument runs at a frequency of 50 hertz and presents a resolution value of 0.1 ohm and an accuracy value of 1% for resistance (Rz) and reactance (Xc); it was used for these assessments, with data plotted to represent hydration levels and body composition. Monthly BIVA assessments provided non-invasive, bioelectrical measurements of body composition, capturing parameters such as Skeletal Muscle Mass (SMM), Skeletal Muscle Mass Index (SMI), Appendicular Skeletal Muscle Mass (ASMM), Total Body Water (TBW), Extra Cellular Water (ECW), and Phase Angle (PhA). All assessments were performed by trained professionals in a controlled setting, adhering to standardized protocols to ensure accuracy and consistency across data collection points.

The patient's non-motor symptoms (NMS) were assessed using the Italian version of the Non-Motor Symptoms Scale for Parkinson's Disease (NNMS). Also this scale was administered at baseline (T0) to evaluate the patient's initial quality of life (QoL) and again six months after starting the intervention (T1).

The NNMS assesses the impact of symptoms across nine domains: cardiovascular, falls, sleep and asthenia, mood and cognition, misperception and hallucinations, attention and memory, gastrointestinal function, urinary function, and sexual activity. Each domain score reflects the frequency and severity of symptoms, with higher scores indicating greater impairment in QoL.

To support adherence to the dietary plan, the patient was also monitored through regular phone consultations, which provided an opportunity to address any challenges related to the 'Weancare Domus' diet and maintain dietary compliance. These phone sessions complemented in-person evaluations, ensuring consistent support.

The patient's nutritional status was assessed using the Mini Nutritional Assessment scale (MNA).

Results

Treatment was started in September 2022 (Covid-19 pandemic invariably postponed the start of the trial).

At the beginning of the study (T0), the patient involved presented the following anthropometric parameters: age 82 years old, height 175 cm, weight 58 kg, right arm circumference 23 cm, BMI 18.94 (on the threshold of underweight), blood chemistry data including blood count, nutritional and inflammatory indices were generally in the normal range.

In T0 the patient had a MNA score of 18 points, confirming a real risk of malnutrition. At the end of the intervention, the patient completed the MNA scale again, and the total score improved from 18 points to 22.5 points (+4.5).

In T0 the NNMS total score was 93 points, so 26.7% of NNMS domains were compromised. In T1 the percentage of compromised domains drops to 10.1% (35 points) (Fig. 1).

After the intervention (T1), the score changes in various domains: in the cardiovascular domain it dropped from 1 to 0, in the second one (sleep/fatigue) from 13 to 4, in the third one (mood/cognition) from 28 to 2, in the fifth one (attention/memory) from 3 to 0, in the sixth one (gastrointestinal) from 6 to 1, in the seventh one (urinary) from 13 to 4, and in the ninth one (miscellaneous) from 5 to 0 (Fig. 2.).

At the beginning (T0) and at the end (T1) of the project, the patient underwent bioimpedance measurements, and the parameters of interest were compared before, during and after the intervention.

The parameters taken into account are shown below: the Skeletal Muscle Mass (SMM), shown in Figure 4, includes the total metabolically active lean body mass; the Skeletal Muscle Mass Index (SMI), is shown in Figure 5; the Appendicular Skeletal Muscle Mass (ASMM), shown in Figure 6, is the metabolically active lean body mass of arms and legs; Total Body Water (TBW) and the Extra Cellular Water (ECW), are shown

Fig. 1. Total score of the patient NNMS scale in relation to the percentage of impairment of quality of life. (a) Total score of the NNMS scale completed during the interview with the patient at the beginning (T0) and at the end of the intervention (T1); (b) percentage of impairment in quality of life compared to the NNMS scale score at the beginning and at the end of the intervention.

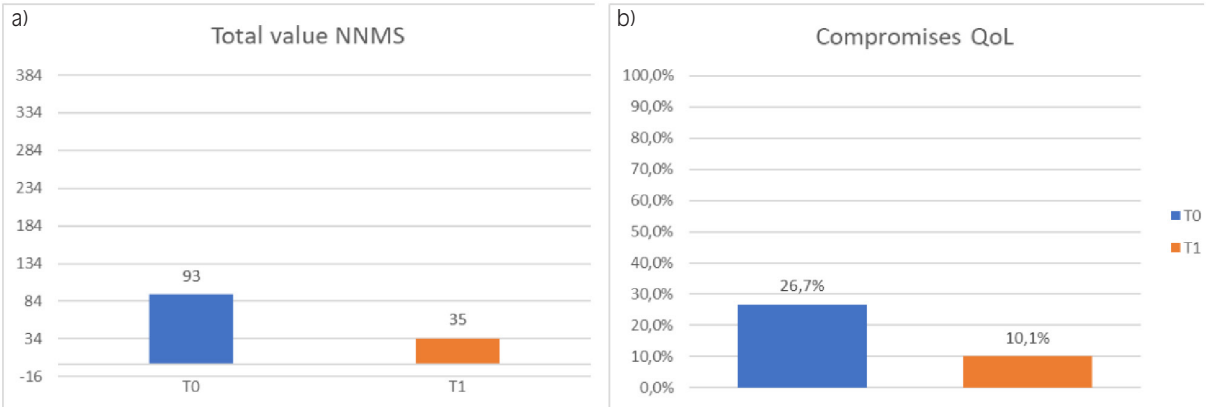


Fig. 2. NNMS Scale domains: pre- and post-intervention scores.

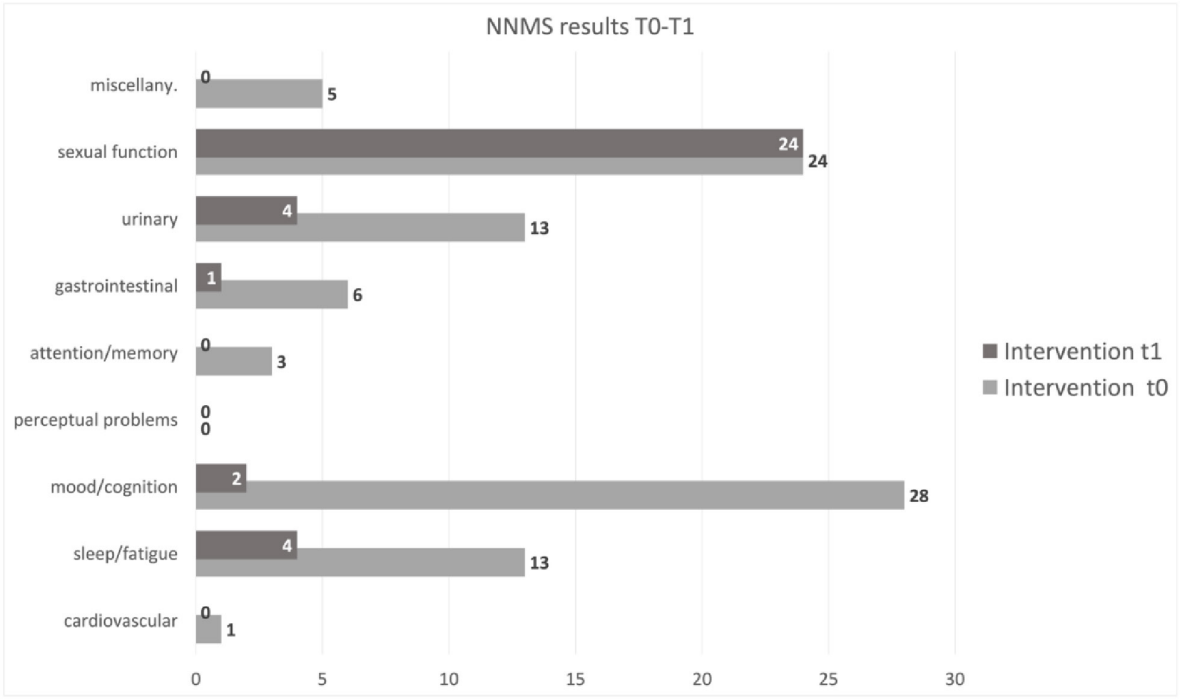


Fig. 3. Graphical representation: vector analysis of bioelectric parameters. The graph shows the measurements taken at T0 (red star, pre-intervention) and T1 (black dot, post-intervention).

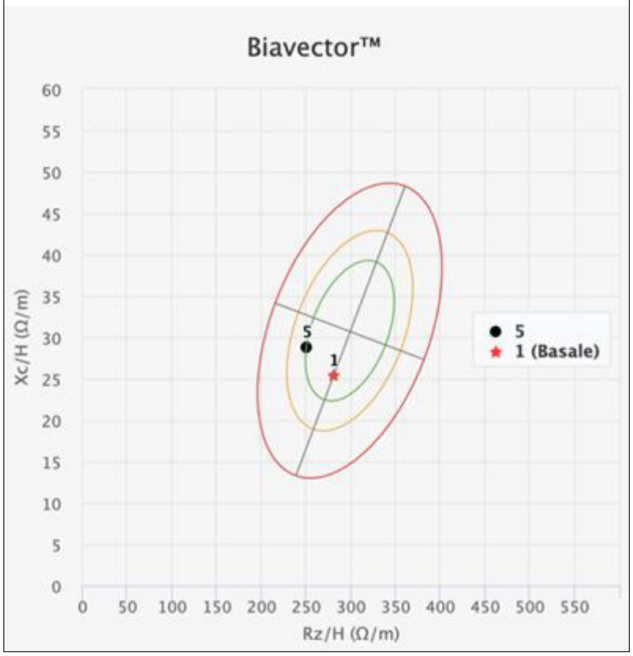
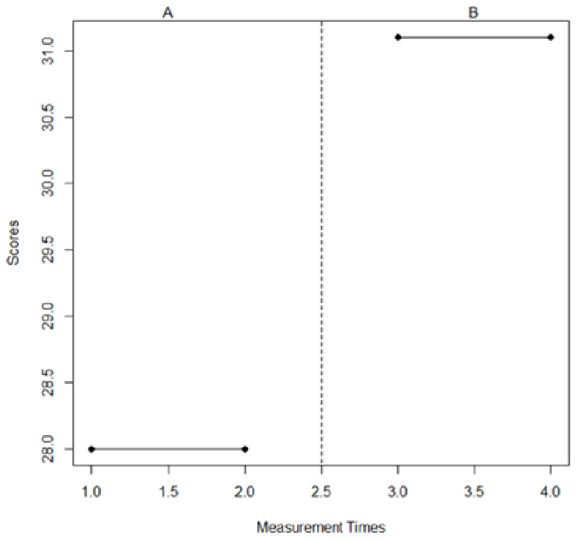


Fig. 4. Skeletal Muscle Mass: pre- and post-intervention scores.



in Figure 7; Phase Angle (PhA), shown in Figure 8, which highlights the relationship between Rz and Xc, so it indicates intra- and extra-cellular proportions. Other parameters included body cell mass (BCM), body cell mass index (BCMI), Free Fat Mass (FFM), and Fat Mass (FM).

Discussion

This study basically reflects the state of the art. The patient examined in the present study was affected by PD and suffered from dysphagia. The initial assessment confirmed an early condition of overall deterioration, impacting also on the nutritional aspects, confirmed by age-related changes in the patient's body composition, showing a higher risk of disease exacerbation and disability.

The overall data analysis enabled to identify the effects

Fig. 5. Skeletal Muscle Mass Index: pre- and post-intervention scores.

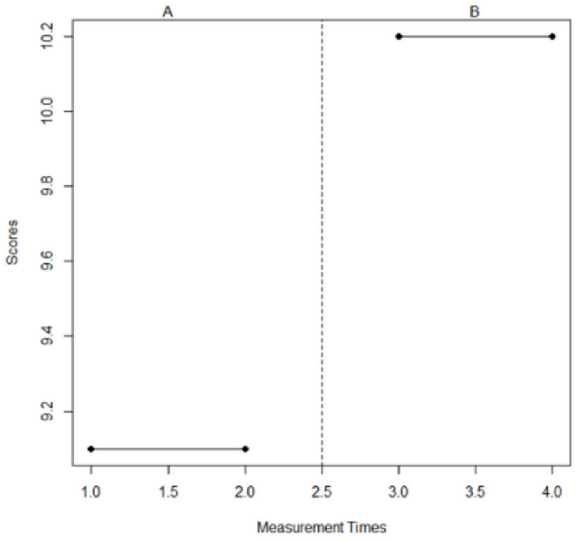


Fig. 6. Appendicular Skeletal Muscle Mass: pre- and post-intervention scores.

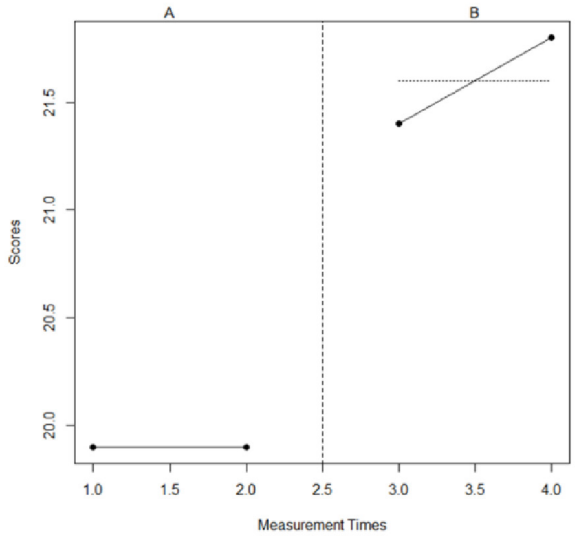


Fig. 7. Pre- and post-intervention scores: (a) Total Body Water; (b) Extra cellular Water.

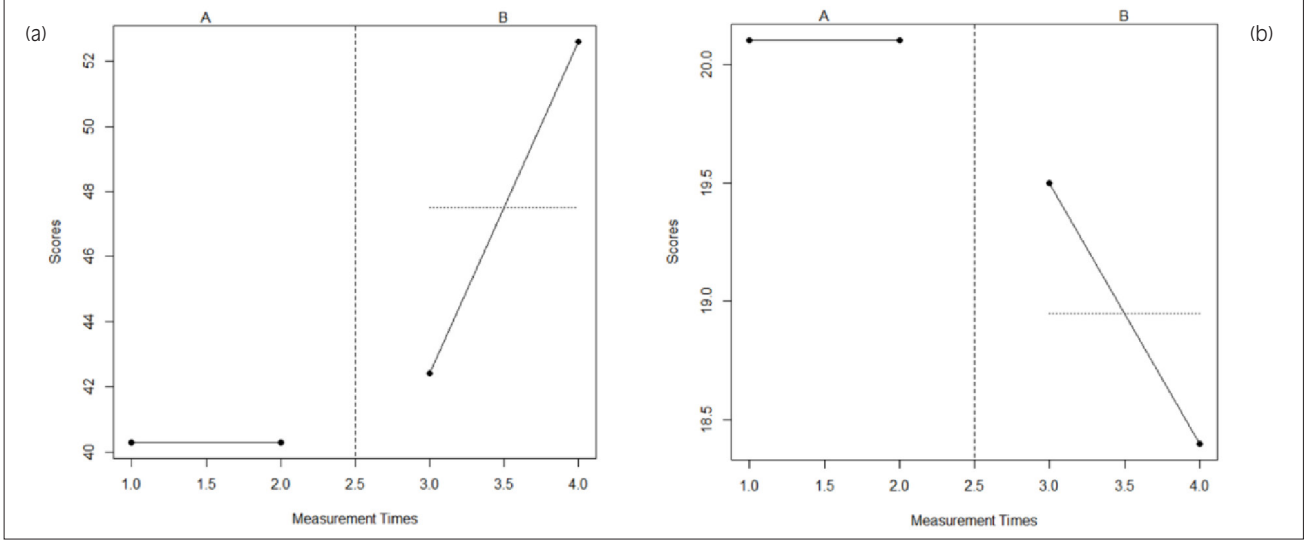
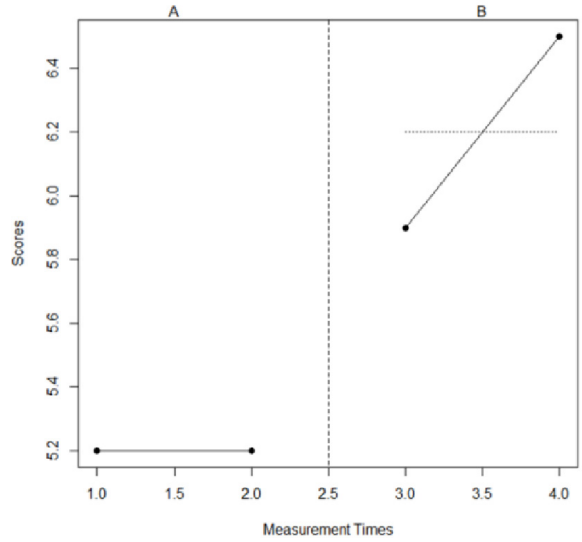


Fig. 8. Phase Angle: pre- and post-intervention scores.



of our intervention on the patient's body mass. In fact, BIVA's analysis showed a change in the comparative parameter, with an evident increase in SMM and consequently SMI. ASMM was also investigated because of its correlation with muscle strength and consequently QoL, and it increased considerably compared to its initial values. Concerning the patient's water component, an increase in TBW and a decrease in ECW was seen. This showed an improvement in the state of hydration with a consequent reduction of oedema.

Among all the parameters assessed, one of the most relevant ones was the PhA variable, which tends to decline with age and is highly predictive of a variety of adverse clinical outcomes and mortality [22, 23]. PhA is calculated through bioimpedance spectroscopy, which is free of calculation errors, and is known to reflect cellular integrity and health to assess the impact of sarcopenia on mortality risk in older people [23]. It is associated with muscle mass and power and has been

linked to geriatric syndromes, such as malnutrition, sarcopenia and frailty [23]. Therefore, PhA may be used to predict mortality risk in older people. In other words, a low PhA value may indicate an increased risk of mortality, instead a high value may correspond to a reduced risk [23]. Several previous studies have reported that PhA is associated with clinical and predictive indices such as muscle mass quality, nutritional and functional status [25, 26]. The proposed intervention aimed to improve both the physical indicators, and the subjective experience of mealtime, since it is considered to impact clinical outcomes and consequently patients' and caregivers' QoL.

Considering the patient's QoL, the NNMS was reassessed after the intervention. The overall score dropped to 35 (101,1%), with a significant improvement in all domains, except for the sexual activity and misperception/hallucinations domains, which remained stable, at 24 and 0 respectively. Considering the focus of the intervention, the improvement of the scoring of the gastrointestinal tract domain from 6 to 1, was particularly interesting and noticeable.

Consistently with the NNMS results, the patient reported a substantial improvement of QoL in the conclusive interview. In fact, in this final interview he reported that he could do some light walking for up to two hours a day, as well as resuming home rehabilitation sessions with the physiotherapist for the Pisa Tower syndrome with benefit. In addition to this, during the study the patient completed a food diary, in which he described the meals he ate and the various sensations he considered useful to report. He reported statements such as: "Before I started the feedings my evacuations were solid and took about a quarter of an hour at different times during the day. Now they happen in the morning from 9 to 10 am every day, but the consistency in the first part is formed and quite firm while the remaining part is broken, it lasts 5'-10'. While before it was forced now it is natural".

This can be related to domain 6 of the NNMS scale (gastrointestinal) and also confirms an improvement in the correlated QoL.

At the end of the intervention, the patient completed the MNA scale again with an improvement in the total score from 18 points to 22.5 points. This score does not confirm the move from malnutrition risk to normal nutritional status but does highlight some improvements such as motor skills. In fact, at the beginning of the study the patient assessed himself as autonomous at home while at the end of the study the patient was able to go outdoors for a walk. In addition, problems related to the reduction of food intake due to loss of appetite, digestion problems and chewing/swallowing difficulties ceased. The patient considered his state of health to be the same that of other people of his age, whereas before he could not make a judgement.

With these goals in mind, the patient was offered the 'Weancare Domus' food plan, which consists of modified texture foods processed in a way that makes them both tasty and nourishing. The focus is mainly on the patient's personal experience of the meal, which should be addressed to ensure complete and appropriate meals. The results of the intervention impacted on all the investigated outcomes. Moreover, the patient's personal experience confirmed the findings of the study, including a better QoL due to improved energy and nutritional intake, the information received during the study, and the health education provided to him, all of which enabled him to solve many problems linked to the management of daily activities. The results were satisfying also for the patient's caregiver, who reported an improved quality of family life, mood, and overall autonomy.

Conclusions

The reported case highlights the fundamental role played by nutrition, especially in patients with conditions that may lead to malnutrition and sarcopenia. As in the case of our patient, an appropriate diet, used as a preventive and therapeutic intervention, has the potential to have a positive impact on specific clinical outcomes and perceived QoL for patients and their caregivers.

Limitations

This case study is limited by its single-subject design, focusing on an 84-year-old patient with Parkinson's disease (PD) and specific conditions like dysphagia and Tower of Pisa Syndrome. The generalizability of the results to the broader PD population is constrained. Additionally, the intervention period coincided with the COVID-19 pandemic, potentially influencing both the implementation and the outcomes of the 'Weancare' program. Future studies should include larger, more diverse samples and control groups to validate and extend these findings.

Future Development

Future research should explore the long-term effects of the 'Weancare' program and similar nutritional interventions on a larger cohort of PD patients. Investigating the program's impact on different stages of PD and in patients with varying degrees of dysphagia could provide more comprehensive insights. Additionally, integrating advanced nutritional assessments and personalized dietary plans based on individual metabolic needs could further enhance clinical outcomes and quality of life for PD patients. Exploring the role of interdisciplinary approaches involving nutritionists, neurologists, and speech therapists may also yield significant improvements in managing non-motor symptoms in PD.

Acknowledgements

None.

Informed consent statement

Not applicable.

Conflicts of interest statement

"The authors declare no conflicts of interest." "The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results".

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Authors' contributions

Conceptualization, MZ, GC, MS, AG and AB; methodology, MZ, GC and AB; software, MZ, LD; validation, MZ, GC and AB; formal analysis, MZ, GC and AB; investigation, MZ, LD; resources, MZ, GC, MS, AG and AB; data curation, MZ, LD; writing-original draft preparation, MZ, LD, GA; writing-review and editing, MZ, LD, GA; supervision, MZ, LS, AB; All authors have read and agreed to the published version of the manuscript.

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NURSING

The influencing factors of nurses' well-being in critical care during pandemic era: a systematic review protocol

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Keywords

Intensive care nurses • Well-being • Systematic review protocol • Nursing

Summary

Purpose. *To review, identify and disclose predictive and hindering factors of critical care nurse well-being in the COVID-19 era.*
Design. *Systematic review protocol based on the Joanna Briggs Institute (JBI) guidelines.*
Review Methods. *All quantitative primary studies focused on factors influencing the well-being of critical care nurses and the relationships among these factors will be included. Based on the review question, six databases will be searched: MEDLINE, The Cochrane Library, SCOPUS, CINAHL, Web on Science, PsycINFO. Time limits will be set according to the COVID-19 pandemic era. To establish the quality of studies JBI tools will be used. Where possible, data will be summarised quantitatively through meta-analysis.*
Expected Results. *We anticipate that this systematic review will provide an overview of the factors that impacted the professional well-being of critical care nurses during the pandemic period from COVID-19.*
Conclusions. *This study will be the first to reveal factors that impact intensive care nurses' well-being during the COVID-19 pandemic era. Furthermore, it will provide updated and valid evidence of which factors should be considered predictive of intensive care nurses' well-being and which hinder it.*
Implication for the profession. *Enhancing the professional well-being of nurses is crucial in addressing the growing trend of their intention to leave the profession. Understanding the factors that positively or negatively impact the well-being of critical care nurses during the pandemic is key to developing effective retention strategies within the nursing field. The results of the review will support managers and leaders in direct health policies toward the implementation of interventions to promote the well-being of healthcare workers and to contrast the intention to leave.*

Introduction

Critical care nurses are regularly exposed to high levels of stress, as they manage emotionally challenging situations involving critically ill patients and their families [1-3].
The nature of their work often demands rapid and effective responses in complex and uncertain scenarios, making them vulnerable to psychological challenges such as burnout, compassion fatigue, moral distress, and anxiety, all of which significantly affect their quality of life [4-7]. Ensuring the well-being of critical care nurses is therefore essential to sustain high-quality healthcare delivery and safeguard their professional longevity.
Research has predominantly focused on the negative psychological effects experienced by healthcare workers, particularly in emergency and intensive care settings [8]. However, recent shifts influenced by positive psychology emphasize the importance of balancing this focus on distress with efforts to foster resilience, empowerment, and mindfulness [9-11].
These concepts underline the importance of supporting well-being as "the balance between an individual's resources and the challenges they face," highlighting the potential of workplace wellness initiatives [12]. The well-being of nurses is closely tied to the quality of their work environment. Studies demonstrate that poor working conditions are associated with job dissatisfaction, burnout, and an increased intention to leave the profession [13-15].
Positive workplace factors, such as empowerment, supportive relationships, and effective communication, have been linked to improved performance, patient satisfaction, and reduced turnover intentions [16]. Additionally, practices such as mindfulness and spirituality have been identified as beneficial tools to enhance well-being and foster resilience in critical care settings [17-20].
The COVID-19 pandemic has further underscored the critical importance of addressing nurse well-being. Intensive care nurses faced unprecedented challenges, including increased workloads, shortages of personal protective equipment (PPE), and prolonged exposure to traumatic events, such as high patient mortality rates [21, 22].
The pandemic intensified pre-existing issues, such as staff shortages and burnout, and introduced new stressors, including isolation from family, fear of infection, and moral distress due to suboptimal care or inequitable resource distribution [23-26].
The psychological toll of the pandemic on nurses has been profound, with increased rates of anxiety,

depression, post-traumatic stress, and other psychological comorbidities being widely reported [27].

Addressing these challenges requires early assessment and targeted interventions to meet the psychological needs of healthcare workers. Failing to do so could not only compromise nurses' health and immunity but also negatively impact the safety and quality of healthcare delivery [28].

The global financial crisis of 2008 led to widespread cuts in healthcare spending [29], resulting in nursing shortages and unfavorable working conditions, which placed significant pressure on nurses and negatively impacted patient care, with higher mortality and readmission rates, complications, longer hospital stays, and dissatisfaction among patients [30, 31].

The SARS-CoV-2 pandemic intensified these challenges, creating new working and living conditions for healthcare professionals. Nurses faced unprecedented psychological burdens from factors such as PPE use, departmental reallocation, increased workloads, and high patient mortality rates [32]. Anxiety and fear among healthcare workers, particularly nurses in COVID-19 units, were heightened by isolation from family and difficult working conditions [33, 34].

ICU nurses, in particular, experienced profound psychological impacts, dealing with increased workloads, long hours, insufficient resources, fear of infection, and moral distress from end-of-life decisions and suboptimal care [35, 36]. These stressors exacerbated existing issues like burnout, depression, and post-traumatic stress, with the pandemic worsening workforce shortages in specialized settings such as intensive care [37, 38].

Unaddressed psychological challenges can lead to a decline in nurses' immunity, increasing their susceptibility to infection and compromising healthcare quality and safety [39]. Moral distress during the pandemic arose from situations such as inadequate nursing care [40], patients dying alone [41], unsafe behaviors by colleagues [42], and poor team collaboration [40-43]. Resource shortages, inequities in resource distribution, and staff deficits further compounded these issues [41, 42].

In emergency and out-of-hospital settings, where rapid clinical decision-making is critical, nurses' emotional well-being is particularly vital [44, 45]. Recognizing the critical role of nurse well-being in maintaining a resilient healthcare workforce, this systematic review aims to identify the factors that predict and hinder the well-being of critical care nurses during the COVID-19 pandemic. The findings will provide actionable insights to inform strategies for fostering a supportive work environment, mitigating psychological distress, and ultimately enhancing nurse retention and healthcare outcomes.

Occupational well-being, therefore, has emerged as a critical focus area for developing effective strategies to address these challenges. It is also a key political strategy to combat the growing intention to leave the profession and to support recruitment and retention efforts.

Review aim

To identify predictive and hindering factors of critical care nurse well-being in the COVID-19 era.

Review questions

Based on the purpose of the study, this literature review will try to answer the following research questions:

- What are the predictors of critical care nurse well-being in the COVID-19 era?
- Which factors hinder the well-being of the critical care nurse in the COVID-19 era?

Methods and analysis

Study design

A systematic review of the literature on factors influencing the well-being of the critical care nurse in the COVID-19 era will be conducted, based on a protocol drawn up according to the recommendations of the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis [46, 48], which was registered on the International Prospective Register of Systematic Reviews (PROSPERO).

This protocol was developed in April 2023. We started data analysis in May 2023 and completed the review at the end of November 2023. In the review, the transparency of the selection process of the studies will be based on the GRADE approach for the reporting of the strength of evidence, including the summary table [48]. The GRADE approach will be applied in this review to assess the certainty of evidence across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each outcome will be graded into one of four levels of certainty (high, moderate, low, very low). A Summary of Findings (SoF) table will be generated, summarizing the number of studies, effect estimates, and the certainty of evidence for each outcome, along with justifications for any downgrading or upgrading decisions. This process will guide the narrative synthesis and inform conclusions by emphasizing high-certainty evidence and identifying areas for future research.

To build the research question for this systematic review, we will use the PEOT (Population, Exposure, Outcome, and Type of studies) format was used to identify the significant components of the review's question [49]. Subsequently, we used the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines to comprehensively display the identified records' selection process and report the findings [47].

Inclusion criteria

All quantitative primary studies that examine factors influencing the well-being of critical care nurses, as well as the relationships between these factors, will be considered eligible based on their abstracts.

Population

The review will include all studies involving critical

care nurses employed in critical care settings during the COVID pandemic.
Studies that compare critical care nurses with nurses employed in other clinical settings, or other healthcare workers, will be included if they present data separately.

Exposure

To conduct this review, studies that addressed factors that influence in professional well-being of the critical care nurse were included. The findings from these studies were categorized into favoring factors and hindering factors.

Outcomes

All the studies included argue the professional well-being of critical care nurses during the pandemic covid highlighting what factors are protective and what factors hinder.

Timing

Only studies conducted during the pandemic period, defined from 2020 to 2023, were included.

Type of studies

Our pursuit of a comprehensive systematic review necessitates the inclusion of specific types of studies that meet the following criteria.
The study must be a quantitative primary study, and its abstract should focus on factors influencing the well-being of critical care nurses and the relationships among these factors. Additionally, for inclusion in the review, manuscripts must be primary observational or experimental studies, being published in either English or Italian, being conducted in the critical care setting during the COVID-19 era and providing descriptions of factors that either promote or hinder the well-being of nurses.
Conversely, studies conducted in the pediatric critical care area, editorials, case reports and dissertations, or qualitative studies are to be excluded. Therefore, mixed methods studies are to be included utilizing exclusively quantitative data. However, only primary studies will be included in the review.

Theoretical Framework

This study adopts the "Three Levels Systems Model of Clinician Burnout and Professional Well-being", proposed in 2019 by the Committee on Systems Approaches to Improve Patient Care by Supporting Clinician Well-Being [27]. This framework integrates principles from human factors, systems engineering, occupational safety, and work design to conceptualize professional well-being and burnout as systemic issues. It identifies key work demands and resources affecting healthcare professionals across three interconnected levels: frontline care delivery, healthcare organization, and the external environment [56-59].
Burnout, defined as a syndrome of emotional exhaustion, depersonalization, and reduced personal accomplishment, arises from workplace stress and affects professional behavior and attitudes [51-54]. The framework views burnout as a systemic, work-related issue rather than an individual mental health diagnosis, emphasizing risk reduction and well-being promotion through organizational and systemic changes [55].

Principal variables definitions

For this literature review, the following definitions will be used for the main variables:

- ***Professional wellbeing***: is related to the broader concept of psychological wellbeing, or subjective wellbeing, which is derived from various sources of life and non-work satisfaction enjoyed by individuals [60]. Professional well-being is defined "as an integrative concept that characterizes the quality of life concerning an individual's health and work-related environmental, organizational, and psychosocial factors. Well-being is the experience of positive perceptions and the presence of constructive conditions at work and outside work that enable workers to thrive and reach their full potential" [61]. Occupational well-being is further conceptualized as work-related and is a function of being satisfied in one's work, finding meaning in one's work, feeling engaged while working, having a quality work life, and finding professional fulfillment in one's work [62, 63]. Although occupational well-being can be measured by different indicators [61], work engagement, which is related to the motivational aspects of work, has been a common indicator of occupational well-being. Work engagement is a positive and fulfilling state of mind characterized by "vigour, dedication and absorption" in work [52].
  Occupational well-being is, therefore, a function of the complex interaction of physical, emotional, mental, social, and spiritual factors that interact with the ecosystem in which the person resides [63].
- ***Intensive care medicine or critical care medicine:*** is a medical specialty that deals with critically or seriously ill patients who have, are at risk of, or are recovering from life-threatening conditions. Clinicians in this specialty are often called intensive care, critical care, or intensivist professionals.
  Intensive care relies on multidisciplinary teams composed of many different healthcare professionals. Such teams often include physicians, nurses, physiotherapists, respiratory therapists, and pharmacists, among others. They usually work together in intensive care units [65].
- ***Pandemic era:*** According to the WHO definition, a pandemic is the worldwide spread of a new disease and generally indicates the involvement of at least two continents, with sustained human-to-human transmission. The severity of a disease is not the decisive parameter for a pandemic to be declared, which instead relates to how effectively a disease spreads. Most pandemics (and particularly influenza pandemics) have often originated from disease-ridden animal populations, which then infected

humans with agents that, with subsequent mutations, are capable of being transmitted from human to human [55].

According to the framework "Three Levels Systems Model of Clinician Burnout and Professional Well-being" [27], when framing work system factors that influence Burnout and professional well-being, it is useful to also define the following variables:

- ***Workload:*** Nursing workload is defined as the necessary level of basic clinical skills required in the performance of daily nursing activities [66]. The required skills vary depending on the type of clinical performance in which nurses are employed within a specific hospital setting [67]. Workload includes physical and mental elements, which combine and contribute together to an individual's level of performance in the work environment [68, 69]. The physical workload is determined by physical skills such as moving and handling patients and administering medication [69]. Mental workload includes receiving, understanding, and interpreting information, making decisions, focusing, and interacting with patients and their families [68]. In the literature, physical and mental workload characteristics can impact and influence each other [68].
- ***Workflow:*** A workflow consists of an orchestrated and repeatable pattern of activities made possible by the systematic organization of resources into processes that transform materials, provide services, or process information. It can be represented as a sequence of operations, the work of a person or group, the work of an organization of personnel, or one or more simple or complex mechanisms. From a more abstract or higher-level perspective, the workflow can be considered a vision or representation of real work. The flow described may refer to a document, service, or product that is transferred from one stage to another [70].
- ***Health workforce:*** encompasses a range of professions, including health workers "such as licensed nurses, physicians" and support health professionals, "as well as individuals in health care support roles, such as community health workers", public health workers, "direct support professionals and caregivers" [71]. The term "health workers" is used to encompass the whole range of health professionals and, when necessary, more specific language is used.
- ***Staffing levels:*** Nursing staff make up half of the health workforce worldwide [54]. Providing staffing levels of nurses that match patient demand is key to providing cost-effective healthcare services [72]. Improved nursing staffing levels and a higher proportion of nurses with degrees have been shown to reduce the likelihood of a hospitalized patient dying within 30 days of admission [30]. The literature increasingly suggests that adequate nursing staffing can influence the quality of patient supervision by allowing nurses to spend more time on direct care [73].
- ***Missed care:*** "Missed care" refers to those activities deemed necessary by nurses that were missed or omitted in the last shift due to lack of time [74]. These have a direct impact on variables such as quality of care, safety, and mortality rates [30].
- ***Engagement:*** Schaufeli et al. defined engagement as 'a positive, fulfilling, work-related state of mind' and proposed that an engaged employee has a strong sense of vigour towards, dedication to and absorption in work activities. This refined conceptualisation has similarities to Kahn's [75] in that engagement is concerned with a psychological experience, while at work, that is highly positive and self-fulfilling. Moreover Schaufeli et al. [52] also support Kahn's view that engagement is a psychological state that leads to positive personal and organisational beaviours. nurse involvement may involve participation in advisory committees, unit councils, and a range of hospital committees. High levels of nurse involvement have been linked to better workforce outcomes, including lower staff turnover, lower burnout, and higher job satisfaction ratios [76];
- ***Moral distress:*** occurs when an individual is faced with the dilemma of knowing their ethical responsibility (*e.g.*, appropriate care for their patients) but is unable to act on it due to circumstances beyond their control. Moral injury is related and occurs when individuals are repeatedly engaged, fail to prevent, or witness such dilemmas [77];
- ***Leadership:*** Leadership has been defined as the relationship between the individual who leads and those who choose to follow him/her; it refers to the behaviour of directing and coordinating the activities of a team or group of people towards a common goal [78]. Numerous publications recognize leadership style as a key element in the quality of healthcare. Effective leadership is among the most critical components that lead an organization to effective and successful results. Significant positive associations have been reported between effective leadership styles and high levels of patient satisfaction and reduced adverse effects [78].
- ***Nurses' Practice Environment:*** A good quality nursing practice environment is an environment that promotes nurses' professional autonomy by providing them with sufficient control over their environment. Good relationships between nurses and physicians result in better outcomes for both nurses and patients [79]. Positive work and learning environments are safe and healthy, support the well-being of health workers and learners, and foster ethical and meaningful training and practice [27].
- ***Workplace stress:*** the "harmful physical and emotional response that occurs when job requirements do not match the worker's skills, resources or needs. Workplace stress can lead to health problems or even injury' [27].
- ***Job satisfaction:*** is a pleasant or positive emotional state resulting from the evaluation of one's job or work experiences" [80] or "the extent to which people like (satisfaction) or dislike (dissatisfaction) their jobs" [81] (Tab. I).

Tab. I. Considered variables explanation.

Professional well-being	Critical care settings	Critical care nurse	Factors	Timing
Wellbeing Well-being Burnout	Critical care Intensive care Intensive care unit* Emergency Emergency Medical Service* Emergency Service Hospital Trauma Center* Triage Emergency Department* ICU* Intensive Therapy* Emergency Room ER	Nurse Nurses Nursing staff Nursing personnel Critical care nurse Emergency nurses	Workload Workflow Health workforce Staffing levels Missed care Engagement Moral distress Leadership Nurses practice environment Workplace stress Job satisfaction	COVID era Pandemic era

Search strategies

Electronic search

To answer the research questions, the following electronic databases will be explored: PubMed, CINAHL, Scopus, Cochrane, PsycINFO, and Web on Science. Considering the elements of the main research question, a pilot search enabled the identification of keywords consistent with the proposed research questions for the electronic database search (Tab. II).

The keywords were combined with the Boolean operators 'AND' and 'OR' to obtain the search strategy for the databases considered (Tab. III).

Tab. II. Research Question.

Population	Critical care nurses
Exposure	Influencing factors
Outcome	Wellbeing or Burnout
Timing	COVID-19 Pandemic era

Since no similar systematic reviews are present in the literature, time limits will be set according to define the COVID-19 pandemic era. Language restrictions will be applied by including only studies in English and Italian. The search terms will be identified based on the theoretical framework "Three levels systems model of clinician burnout and professional well-being" proposed in 2019 by the Committee on Systems Approaches to Improve Patient Care by Supporting Clinician Well-Being [27[, and further searches conducted in the literature. Care services identified by the following terms will be considered: "Intensive Care Unit (ICU)", "intensive therapy", "emergency department (ED)", "Emergency Service Hospital", "Emergency Medical Services", "Trauma Centres", "Triage", "critical care", "intensive care", "emergency", "emergency room (ER)". In the event of a terminological mismatch, alternative terms used in the international literature will be considered provided they express some correspondence in meaning.

To maximize the identification of potentially relevant manuscripts for inclusion, bibliographic references of the included articles will be screened (reference lists scanning), and sources that have cited the included articles will be searched on the Scopus database (citation searching).Specific search strategies will be adopted for each database.

All identified bibliographic sources will be managed with EndNote 21.2 for Windows software.

The search terms

The terminology employed will encompass synonyms or precise expressions as dictated by the respective database (Tab. I). These terms will be matched in various formats, such as MESH and TEXT WORDS in MEDLINE, Thesaurus terms in PsycINFO, and natural language in Cochrane Library, CINAHL, and SCOPUS. The study selection process consists of two distinct phases. In the initial phase, titles, abstracts, and keywords will be scrutinized based on predefined inclusion and exclusion criteria. This initial screening aims to identify pertinent documents for inclusion while excluding irrelevant ones. Before commencing the first phase, a meticulous evaluation of duplicate publications or multiple reports stemming from the same study will be conducted using EndNote version 20, with oversight by an external researcher.

The papers will be assessed by four independent reviewers, with determinations of "YES" for inclusion, "NO" for exclusion, or "U" signifying an inability to determine eligibility. In cases where any single criterion is not met, studies will be excluded. Full texts of articles classified as relevant or suitable for our review will undergo comprehensive reading and analysis. Similarly, studies that cannot be adequately assessed based solely on their abstracts will be scrutinized, guided by the established inclusion and exclusion criteria.

An external researcher with expertise in systematic reviews will oversee the entire selection process and ensure the quality of the review and analysis. Both phases will entail separate examination of documents by two researchers, adhering to predefined criteria. In instances of disagreement between these two researchers, a third party will be engaged for resolution. If study information is missing or full-text access is unavailable, authors will be contacted, and if no response is received within two

Tab. III. Search concepts and keywords used combined with appropriate Boolean operators.

Database	Population (critical care nurses)	Setting (critical care settings)	Outcome (well-being or burnout)	Timing (Covid pandemic)
PubMed	AND ("nurse s"[All Fields] OR "nurses"[MeSH Terms] OR "nurses"[All Fields] OR "nurse"[All Fields] OR "nurses s"[All Fields] OR ("nurse s"[All Fields] OR "nurses"[MeSH Terms] OR "nurses"[All Fields] OR "nurse"[All Fields] OR "nurses s"[All Fields]) OR ("nursing staff"[MeSH Terms] OR ("nursing"[All Fields] AND "staff"[All Fields]) OR "nursing staff"[All Fields]) OR ("nursing staff"[MeSH Terms] OR ("nursing"[All Fields] AND "staff"[All Fields]) OR "nursing staff"[All Fields] OR ("nursing"[All Fields] AND "personnel"[All Fields]) OR "nursing personnel"[All Fields] OR "nurses"[MeSH Terms] OR "nurses"[All Fields] OR ("nursing"[All Fields] AND "personnel"[All Fields])) OR ("crit care nurse"[Journal] OR ("critical"[All Fields] AND "care"[All Fields] AND "nurse"[All Fields]) OR "critical care nurse"[All Fields]) OR (("emerge"[All Fields] OR "emerged"[All Fields] OR "emergence"[All Fields] OR "emergences"[All Fields] OR "emergencies"[MeSH Terms] OR "emergencies"[All Fields] OR "emergency"[All Fields] OR "emergent"[All Fields] OR "emergently"[All Fields] OR "emergents"[All Fields] OR "emerges"[All Fields] OR "emerging"[All Fields]) AND ("nurse s"[All Fields] OR "nurses"[MeSH Terms] OR "nurses"[All Fields] OR "nurse"[All Fields] OR "nurses s"[All Fields])))))	("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields] OR ("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields] OR ("intensive"[All Fields] AND "care"[All Fields]) OR "intensive care"[All Fields]) OR ("intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields]) OR ("emerge"[All Fields] OR "emerged"[All Fields] OR "emergence"[All Fields] OR "emergences"[All Fields] OR "emergencies"[MeSH Terms] OR "emergencies"[All Fields] OR "emergency"[All Fields] OR "emergent"[All Fields] OR "emergently"[All Fields] OR "emergents"[All Fields] OR "emerges"[All Fields] OR "emerging"[All Fields]) OR ("emergency medical services"[MeSH Terms] OR ("emergency"[All Fields] AND "medical"[All Fields] AND "services"[All Fields]) OR "emergency medical services"[All Fields]) OR ("emergency service, hospital"[MeSH Terms] OR ("emergency"[All Fields] AND "service"[All Fields] AND "hospital"[All Fields]) OR "hospital emergency service"[All Fields] OR ("emergency"[All Fields] AND "service"[All Fields] AND "hospital"[All Fields]) OR "emergency service hospital"[All Fields]) OR ("trauma centers"[MeSH Terms] OR ("trauma"[All Fields] AND "centers"[All Fields]) OR "trauma centers"[All Fields]) OR ("triage"[MeSH Terms] OR "triage"[All Fields] OR "triages"[All Fields] OR "triaged"[All Fields] OR "triaging"[All Fields]) OR ("emergency service, hospital"[MeSH Terms] OR ("emergency"[All Fields] AND "service"[All Fields] AND "hospital"[All Fields]) OR "hospital emergency service"[All Fields] OR ("emergency"[All Fields] AND "department"[All Fields]) OR "emergency department"[All Fields]) OR ("intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields] OR "icu"[All Fields]) OR "ICUs"[All Fields] OR (("intensive"[All Fields] OR "intensives"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields])) OR ("emergency service, hospital"[MeSH Terms] OR ("emergency"[All Fields] AND "service"[All Fields] AND "hospital"[All Fields]) OR "hospital emergency service"[All Fields] OR ("emergency"[All Fields] AND "room"[All Fields]) OR "emergency room"[All Fields]) OR "ER"[All Fields]))	(("wellbeing"[All Fields] OR ("health"[MeSH Terms] OR "health"[All Fields] OR "well"[All Fields] OR "well being"[All Fields]) OR ("burnout s"[All Fields] OR "burnout, psychological"[MeSH Terms] OR ("burnout"[All Fields] AND "psychological"[All Fields]) OR "psychological burnout"[All Fields] OR "burnout"[All Fields] OR "burnouts"[All Fields]))	("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "covid"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19"[All Fields] OR ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) OR "Sars-Cov2"[All Fields] OR ("pandemia"[All Fields] OR "pandemias"[All Fields]) OR (("pandemic s"[All Fields] OR "pandemically"[All Fields] OR "pandemicity"[All Fields] OR "pandemics"[MeSH Terms] OR "pandemics"[All Fields] OR "pandemic"[All Fields])))
Scopus	(nurse OR nurses OR "nursing staff" OR "nursing personnel" OR "critical care nurse" OR "emergency nurses")	("critical care" OR "intensive care" OR "intensive care units" OR emergency OR "Emergency Medical Services" OR "Emergency Service Hospital" OR "Trauma centers" OR triage OR "Emergency Department" OR icu OR icus OR "intensive therapy" OR "Emergency room" OR ER)	(wellbeing OR well-being OR burnout)	(covid OR covid-19 OR sars-cov2 OR pandemic)

Tab. III *(follows)*. Search concepts and keywords used combined with appropriate Boolean operators.

Database	Population (critical care nurses)	Setting (critical care settings)	Outcome (well-being or burnout)	Timing (Covid pandemic)
CINAHL	(nurse OR nurses OR "nursing staff" OR "nursing personnel" OR "critical care nurse" OR "emergency nurses")	("critical care" OR "intensive care" OR "intensive care units" OR emergency OR "Emergency Medical Services" OR "Emergency Service Hospital" OR "Trauma centers" OR triage OR "Emergency Department" OR icu OR icus OR "intensive therapy" OR "Emergency room" OR ER)	(wellbeing OR well-being OR burnout)	(covid OR covid-19 OR sars-cov2 OR pandemic)
Cochrane	(nurse OR nurses OR nursing staff OR nursing personnel OR critical care nurse OR emergency nurses) in All Text	(critical care OR intensive care OR intensive care units OR emergency OR Emergency Medical Services OR Emergency Service Hospital OR Trauma centers OR Triage OR Emergency Department OR ICU OR ICUs OR intensive therapy OR Emergency room OR ER) in All Text	(wellbeing OR well-being OR burnout) in All Text	(Covid OR Covid-19 OR Sars-Cov2 OR pandemia OR pandemic) in All Text
Web on Science	(nurse OR nurses OR nursing staff OR nursing personnel OR critical care nurse OR emergency nurses)	(critical care OR intensive care OR intensive care units OR emergency OR Emergency Medical Services OR Emergency Service Hospital OR Trauma centers OR Triage OR Emergency Department OR ICU OR ICUs OR intensive therapy OR Emergency room OR ER)	(wellbeing OR well-being OR burnout)	(Covid OR Covid-19 OR Sars-Cov2 OR pandemia OR pandemic)
PsycINFO	(nurse OR nurses OR nursing staff OR nursing personnel OR critical care nurse OR emergency nurses)	(critical care OR intensive care OR intensive care units OR emergency OR Emergency Medical Services OR Emergency Service Hospital OR Trauma centers OR Triage OR Emergency Department OR ICU OR ICUs OR intensive therapy OR Emergency room OR ER)	(wellbeing OR well-being OR burnout)	(Covid OR Covid-19 OR Sars-Cov2 OR pandemia OR pandemic)

weeks, the respective article will be excluded from the review. Detailed records will be maintained to document the reasons for excluding full-text articles.

Methodological quality assessment

The assessment of the methodological quality of the included studies will be carried out, by the research design, with the standardized tools made available in the JBI Manual for Evidence Synthesis [46, 48]. In particular: JBI Critical Appraisal Checklist for Cohort Studies; JBI Critical Appraisal Checklist for Case-Control Studies; JBI Critical Appraisal Checklist for Case Series; JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies; JBI Critical Appraisal Checklist for Randomized Controlled Trials; JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies). The results of the risk of bias assessment of the included studies will be reported in tabular form in the data extraction table and in narrative form in the results and discussion section. The risk of bias assessment will be carried out independently by two researchers and disagreement resolved through a discussion with the team leader G.C.. Considering the exploratory nature of the review, the methodological quality of the included studies will not be considered an exclusion criterion for the narrative synthesis of the results. Conversely, the reduced methodological quality of the study will be considered as an exclusion criterion for any meta-analytic synthesis of the results.

Data extraction

The extracted data will be reported in a structured and previously tested spreadsheet, according to guidelines provided by the Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research [82].

The data will be extracted independently by at least two researchers. Any discrepancies in the extracted data will be resolved by a third researcher. The following data will be extracted: author, year of publication, country, research design, population, sample, socio-demographic characteristics of the sample, purpose of the study, care intervention(s), outcome(s), measurement instruments, influencing factors, results, and quality of the study.

It will be possible to extract additional data not foreseen in the protocol consistent with the research objectives.

Data synthesis and analysis

The information extracted from the studies will first be described in narrative and tabular form. The framework "Three Levels Systems Model of clinician burnout and Professional Well-being" [27] will guide us in the presentation of the results. The results will be categorized according to the three levels of the system (frontline care delivery, healthcare organization and external environment). The influencing factors resulting from the results of the review will similarly be categorized according to the needs/resources categorization. Possible

influencing factors on occupational well-being and any significant associations will also be described.
Where possible, data will be summarised quantitatively through meta-analysis, using Jamovi free software [83]. Additional variables will be considered after analysing possible factors influencing occupational well-being. Furthermore, to detect the impact of each study on the meta-analytical results, a sensitivity analysis will be conducted by removing one study at a time.
Data that cannot be included in the meta-analysis will be summarised narratively.

Implication and relevance

We anticipate that this systematic review will provide an overview of the factors that impacted the professional well-being of critical care nurses during the pandemic period from Covid-19. Knowing these factors will be able to direct health policies toward the implementation of interventions to promote the well-being of healthcare workers. Attending to the level of professional well-being of nurses becomes imperative if we aim to counter the emerging phenomenon of intention to leave that is increasingly affecting the profession.

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Protocol registration

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Authorship statement

All listed authors meet the authorship criteria and all authors agree with the content of the manuscript. All authors have: 1) Made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. 2) Been involved in drafting the manuscript or revising it critically for important intellectual content. 3) Given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content; and 4) Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. And in particular: MEM, MR and GC made a substantial contribution to the conception of this paper. MEM, MR, MB and AM were substantially involved in the design, data acquisition, analysis, and interpretation. MEM, MR were mainly involved in drafting and editing the manuscript. GC, MZ, LS and AB contributed to revising it critically for important intellectual content.

Conflicts of interest statement

All the other authors declare that they have no conflicts of interest concerning the research, authorship, and/or publication of this article.

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Occupationa Medicine and Hygiene

Epidemiology of smoking habits among healthcare workers employed in a regional reference teaching hospital in Northern Italy: a cross-sectional study

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Keywords

Tobacco-based products • Occupational health • Health promotion

Summary

Introduction. *Tobacco consumption is one of the most significant avoidable health risks and cause of premature death globally. Smoking in the workplace represents a potential combination of health risks due to the interactions of tobacco use and professional exposure. Occupational Health Professionals can aid in health promotion of workers and improvement of workplace environment. This study aims to analyze the prevalence of smoking and its determinants among healthcare workers and equated subjects at the Ospedale Policlinico San Martino IRCCS of Genoa, Italy.*

Methods. *An observational, cross-sectional study was performed using demographic and clinical data. It involved a total workforce of 1561 Health Care Workers (HCW), medical residents and healthcare students. We focused on the medical visits performed from July 1 to December 31, 2023. All statistical analyses were performed using SPSS statistical software vers. 26.0 (IBM Corp.).*

Results. *In the studied population, 24.7% of participants reported being current smokers. The univariate analysis showed an association between smoking and several demographic and occupational variables such as different professional categories and occupational risks. At the multivariate analysis physicians (OR 0.39, 95 CI 0.24-0.61, p < 0.001) and professions with exposure to chemical hazards (OR 0.26, 95 CI 0.09-0.80, p = 0.018) showed reduced odds of smoking, while increases in alcohol consumption were associated with increased probability of smoking (OR 1.79, 95 CI 1.19-2.71, p = 0.006).*

Conclusions. *These results highlight a concerning prevalence of smokers among HCW. An up-to-date epidemiological picture on health habits and behaviors may provide a baseline on which targeted interventions can be implemented, considering not only modifiable lifestyle factors but also work-related risk factors to effectively tackle the magnitude of the phenomenon.*

Introduction

Tobacco consumption is one of the most significant avoidable health risks and cause of premature death globally, causing 8 million deaths each year, including close to 1.3 million people exposed to second-hand smoke [1]. Smoking is a well-known risk factor for preventable disease and disability, including respiratory illness, heart disease, and cancer. Although the vast majority of smokers live in low- and middle-income countries, in highly developed regions such as the European Union, annual mortality due to tobacco still reaches nearly 700,000, with an average reduction in lifespan of 14 years [2].

Although considerable progress has been made, one fourth of the overall population in Europe is still a consumer of tobacco products, particularly among the young working age population [3, 4].

Moreover, passive smoking is recognized as an increasing source of indoor air pollution. This is particularly relevant in the occupational setting, where the National Institute for Occupational Safety and Health (NIOSH) determined environmental tobacco smoke (ETS) as potentially carcinogenic to occupationally exposed workers. Epidemiologic studies estimated the relative risk of lung cancer to be increased by 30% for a non-smoker exposed to second-hand smoke [5].

Smoking in the workplace represents a potential combination of health risks due to the interactions of tobacco use and professional exposure, such as to chemical and physical agents, contributing to the development of adverse health effects in the workplace [6].

In this perspective, evidence shows that smoke-free workplaces not only prevent ETS but also reduce total cigarette consumption per smoker by nearly 30%, contributing to the overall health promotion of workers [7]. For this reason, in many developed countries specific legislation has been introduced to reduce or outright ban smoking in workplaces [8].

In Italy, the legislative framework prohibits smoking in all indoor workplaces, extending this ban to outdoor areas for hospitals [9]. Indeed, healthcare professionals represent key actors in the promotion of smoke reduction in patients and the general public in order to achieve

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public health goals. Recent studies performed on this population, within the framework of the "*Progressi delle Aziende Sanitarie per la Salute in Italia* (PASSI)" project, showed a prevalence of current tobacco smoking between 2014 and 2018 of 23.0%, with an average declining trend from 2014 to 2018 [10].

Occupational Health Professionals can aid in health promotion of workers and improvement of workplace environment, as stated by the objectives put forward by ILO and WHO defined as the maintenance and promotion of health and work capacity, as well as the improvement of the work environment and the work itself to make them compatible with safety and health requirements [11]. Moreover, in the Italian context, the Occupational Physician acts in compliance with the obligations mentioned in Article 25 of the Italian Legislative Decree 81/2008, collaborates with the employer in the assessment of risks, for the purpose of planning health surveillance, but also collaborates in the implementation and enhancement of voluntary health promotion programs [12].

Within this framework, and as highlighted by the Italian National Prevention Plan 2020-2025 [13], it is necessary to continue to implement a comprehensive and interdisciplinary approach to promote smoking cessation and smoke-free environments, integrating effective policies and actions to monitor consumption habits, as well as to prevent and protect the population, such as providing support for cessation, updated information on the dangers of tobacco, as well as strengthening the ban of tobacco.

In this context, *Ospedale Policlinico San Martino* IRCCS of Genoa, Italy, is a full member of the Organization of European Cancer Institutes (OECI) as a "Comprehensive cancer centre". The Occupational Health Unit, as part of the Improvement Action Plan, promotes activities to prevent cancer through early detection and counseling, aiming to a reduction of active and passive smoking among the working population.

Despite the growing recognition that both smoking and workplace exposures are associated with the development of several morbidities, few investigators have explored the potential interactions between these two factors and their impact on disease in workers.

In line with these objectives, this study aims to analyze the prevalence of smoking and its determinants among healthcare workers and equated subjects at the *Ospedale Policlinico San Martino* IRCCS of Genoa, Italy.

Materials and methods

The present study was developed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [14].

Study design and population

An observational, cross-sectional study was performed using demographic and clinical data.

The study was carried out on March 14-May 14, 2024. It involved a total workforce of 1561 Health Care Workers (HCW), medical residents and healthcare students attending at the *Ospedale Policlinico San Martino* IRCCS of Genoa, Italy, the regional tertiary adult acute care reference hospital. This population routinely undergoes occupational health surveillance programs performed by the Occupational Health Service (OHS) in accordance with Italian Law. We focused on the medical visits performed from July 1 to December 31, 2023.

Trained occupational physicians and medical residents of the OHS collected data and information from the examinations during the study period. All the information were obtained with a retrospective review of the electronic medical records routinely registered on Canopo–HSE Software (vers. 23.12) during medical visits performed for health surveillance of workers and equated subjects exposed to professional risks. All data for each person, were collected at one point in time, and were extracted in an *ad hoc* Microsoft Excel (version 2402) dataset created for the statistical analysis.

Information concerning the following variables were extracted:

- demographic information (age, gender);
- occupational category (physicians, nurses, administrative healthcare technicians, non-healthcare technicians, coordinators);
- department (clinical areas, surgical areas, technical areas, service areas);
- professional risk factors (biological agents, manual handling of loads/patients, visual display unit, night shift work, anesthetic gases, chemical agents, cancerogenic/mutagenic agents, animal allergens, electromagnetic fields, ionizing radiation, laser);
- smoking habits (including typology, quantity per day and duration);
- alcohol consumption (regular consumption, AUDIT <Alcohol Use Disorders Identification Test>);
- coffee consumption (regular consumption, quantity per day);
- sleep quality;
- physical activity;
- allergies.

The study was approved by the Ethics Committee of the Liguria Region (administrative reference number: N. 111/2024 - DB id 13697). All the activities were performed in compliance with the Declaration of Helsinki and current healthcare standards, according to the recommendations of the Italian Ministry of Health and World Health Organization. All HCWs included in the study signed written informed consent for data collection according to routine healthcare procedures of the Occupational Health Surveillance Program at *Ospedale Policlinico San Martino* IRCCS of Genoa, Italy. Data were anonymized before the analysis. Personal information regarding all the subjects included in the investigation was protected according to Italian law.

Statistical analysis

Continuous numerical variables were summarized as means and standard deviations (SDs) or, when

appropriate, medians and interquartile ranges (IQRs). Nominal and ordinal categorical variables were summarized and described as frequency and percentages. The Mann-Whitney U test, the χ_2 test, and Fisher's exact test were used, according to the variable type, for a univariate analysis of the association between professional and clinical characteristics and smoke, the main outcome of interest. Multivariate analyses were performed for variables with probability (p) values of < 0.20 in the univariate analysis. Differences were considered significant when $p < 0.05$. A backward stepwise logistic regression was used to calculate the odds ratio (OR) and the 95% confidence intervals (CI). A 2-tailed $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS statistical software vers. 26.0 (IBM Corp.).

Results

Overall, health surveillance data on 1561 workers were included. The mean age was 36.9 (14.1) years, 72.6% of participants were female, and the most frequent work categories were physicians (35.5%), nurses (33.4%) and administrative employees (12.8%). Concerning the type of ward or department, 44.0% comprised clinical areas, 26.6% surgical areas and 16.7% technical department. Most common professional risk factors were biological agents (89.6%), manual handling of loads/patients (31.7%) and night shift work (14.5%).

Concerning relevant healthy behaviors and habits, 65.6% reported performing regular physical activities, whereas regarding unhealthy habits, 55.7% reported regularly drinking alcohol, with an average AUDIT-C score of 1.7 (0.6), 84.3% reported commonly drinking coffee an average of 2.0 (1.1) cups a day, with 8.6% of individuals reporting sleep disturbance.

Regarding smoking habits, 24.7% of participants (n=385) reported being current smokers, of whom 77.9% reported using traditional cigarettes, 21.0% reported using e-cigarettes, and only 4 (1.0%) reported smoking cigars. Among users of traditional cigarettes, an average smoking history of 11.9 (12.1) years and an average daily consumption of 8.0 (6.4) cigarettes was reported.

The comprehensive demographic characteristics of the included sample are summarized in Table I.

Univariate and multivariate analyses of the variables associated with smoking are outlined in Table II. As revealed by the univariate analysis, the probability of being a smoker was associated with several demographic and occupational variables such as different professional categories (*e.g.,* physicians OR 0.62, 95 CI 0.45-0.86; nurses OR 1.73, 95 CI 1.28-2.34), occupational risks (*e.g.,* manual handling of loads/patients OR 1.68, 95 CI 1.32-2.14; night shift work OR 1.94, 95 CI 1.44-2.62), while concerning workers' behaviors and habits, alcohol (regular alcohol use OR 1.57, 95 CI 1.24-1.99; AUDIT-C OR 1.88, 95 CI 1.43-2.45) and coffee consumption (regular coffee use OR 2.50, 95 CI 1.67-3.74; number of cups per day OR 1.19, 95 CI 1.07-1.33) showed increased probability of smoking, with physical activity demonstrating reduced odds of smoking (OR 0.76, 95 CI 0.60-0.97).

Assessing factors independently associated with the outcome of interest, the multivariate logistic regression model resulted in physicians and professions with exposure to chemical hazards showing reduced odds of smoking, while increases in alcohol consumption were associated with increased probability of this habit.

Tab. I. Demographic characteristics of the included sample of workers at IRCCS Ospedale Policlinico San Martino of Genoa, Italy, stratified by smoking status.

Variable	Smoker	Non-smoker	Total
Demographic characteristics			
Age [years] M (SD)	37.6 (14.1)	36.8 (14.1)	37.0 (14.1)
Female [n (%)]	265 (23.4)	868 (76.6)	1133 (100.0)
Male [n (%)]	120 (28.0)	308 (72.0)	428 (100.0)
Work category [n (%)]			
Physician	64 (17.8)	295 (82.2)	359 (100.0)
Nurse	100 (29.7)	237 (70.3)	337 (100.0)
Administrative	25 (19.4)	104 (80.6)	129 (100.0)
Healthcare technician	6 (11.3)	47 (88.7)	53 (100.0)
Non-healthcare technician	21 (33.3)	42 (66.7)	63 (100.0)
Coordinator	5 (25.0)	15 (75.0)	20 (100.0)
Occupational setting [n (%)]			
Clinical area	130 (25.2)	385 (74.8)	515 (100.0)
Surgical area	78 (25.1)	233 (74.9)	311 (100.0)
Technical area	54 (27.6)	142 (72.4)	196 (100.0)
Services	31 (20.8)	118 (79.2)	149 (100.0)
Exposure to occupational risks [n (%)]			
Biological	344 (24.6)	1055 (75.4)	1399 (100.0)
Manual handling of loads/patients	156 (31.5)	339 (68.5)	495 (100.0)
Visual Display Unit	49 (25.1)	146 (74.9)	195 (100.0)
Night shift	82 (36.3)	144 (63.7)	226 (100.0)
Anesthetic gases	24 (18.6)	105 (81.4)	129 (100.0)
Chemical	12 (14.6)	70 (85.4)	82 (100.0)
Cancerogenic/ mutagenic	7 (17.9)	32 (82.1)	39 (100.0)
Animal allergens	1 (16.7)	5 (83.3)	6 (100.0)
Electromagnetic fields	0 (0.0)	5 (100.0)	5 (100.0)
Ionizing radiation	6 (22.2)	21 (77.8)	27 (100.0)
Laser	3 (23.1)	10 (76.9)	13 (100.0)
Healthy and unhealthy behaviors and habits			
Regular alcohol consumption [n (%)]	246 (28.3)	623 (71.7)	869 (100.0)
AUDIT-C [M (SD)]	1.8 (0.6)	1.6 (0.3)	1.7 (0.6)
Impaired sleep [n (%)]	25 (20.2)	99 (79.8)	124 (100.0)
Regular physical activity [n (%)]	227 (22.6)	777 (77.4)	1004 (100.0)
Coffee consumption [n (%)]	339 (26.6)	935 (73.4)	1274 (100.0)
Daily cups of coffee [M (SD)]	2.2 (1.3)	1.9 (1.1)	2.0 (1.1)

Tab. II. Univariate and multivariate analyses of demographic, professional and health habits characteristics associated with smoking in the included sample of workers at IRCCS Ospedale Policlinico San Martino of Genoa, Italy.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Demographic characteristics				
Age (per 1 year increase)	1.00 (0.99-1.01)	0.328		
Gender	0.78 (0.61-1.01)	0.058		
Work category				
Physician	0.62 (0.45-0.86)	0.004	0.39 (0.24-0.61)	< 0.001
Nurse	1.73 (1.28-2.34)	< 0.001		
Administrative	0.78 (0.49-1.24)	0.300		
Healthcare technician	0.41 (0.17-0.98)	0.044		
Non-healthcare technician	1.74 (1.01-3.01)	0.046		
Coordinator	1.12 (0.40-3.12)	0.828		
Occupational setting				
Clinical area	1.02 (0.78-1.33)	0.877		
Surgical area	1.00 (0.75-1.36)	0.978		
Technical area	1.17 (0.83-1.66)	0.371		
Services	0.76 (0.50-1.16)	0.205		
Exposure to occupational risks				
Biological	0.96 (0.66-1.40)	0.841		
Manual handling of loads/patients	1.68 (1.32-2.14)	< 0.001		
Visual Display Unit	1.03 (0.73-1.45)	0.872		
Night shift	1.94 (1.44-2.62)	< 0.001		
Anesthetic gases	0.68 (0.43-1.07)	0.097		
Chemical	0.51 (0.27-0.95)	0.033	0.26 (0.09-0.80)	0.018
Cancerogenic/mutagenic	0.66 (0.29-1.51)	0.328		
Animal allergens	0.61 (0.07-5.24)	0.652		
Ionizing radiation	0.87 (0.35-2.17)	0.767		
Laser	0.92 (0.25-3.34)	0.894		
Healthy and unhealthy behaviors and habits				
Regular alcohol consumption	1.57 (1.24-1.99)	< 0.001		
AUDIT-C (per 1 score increase)	1.88 (1.43-2.45)	< 0.001	1.79 (1.19-2.71)	0.006
Impaired sleep	0.75 (0.47-1.18)	0.208		
Regular physical activity	0.76 (0.60-0.97)	0.026		
Coffee consumption	2.50 (1.67-3.74)	< 0.001		
Daily cups of coffee (per 1 cup increase)	1.19 (1.07-1.33)	0.002		

Discussion

The present study suggests the existence of an association between occupational factors and smoking habits.

In particular, we found out that being a physician showed an independent association with smoking, demonstrating an almost 10% lower prevalence (17.8%) compared to the overall proportion of smokers. This result is in line with the PASSI surveillance system data from Minardi et al. which considered smoking prevalence among healthcare workers in Italy from 2014 to 2018 [10], in which they observed a prevalence of smokers among physicians between 20.8% in 2014 and 11.5% in 2018, from 10 to 15% lower than the proportion among other healthcare workers.

Moreover, workers exposed to chemical agents demonstrated a significative lower prevalence of smoking compared to other working exposures. This could, at least in part, be explained by strictly regulated no-smoking policies in laboratories. Indeed, Hong et al. suggest that workers with greater concern about their exposure to chemical hazards were less likely to smoke [15]. A further possible explanation could be a positive collateral effect of training and information campaigns enacted for specific inhalatory chemical risk prevention. However, this hypothesis requires additional investigations to better understand and confirm this association.

Other work categories and professional exposures that showed significant, albeit non independent, associations were working as a nurse, manual handling of loads/patients and night shift work. Concerning the first, previous studies in literature have shown similar elevated proportions [16]. Regarding workers who perform manual handling of loads or patients during their occupational activity, epidemiological data from the UK have suggested that nearly one in four employees in routine manual occupations smoke tobacco, over three times more than workers in other roles [17]. The latter

association between night shift work and smoking habit was considered by Peplonska et al. and their results are in accordance with the current study, assessing that the majority of current smokers investigated (40.6%) were night shift workers [18]. Our findings are also confirmed by Knutson et al. who observed a higher proportion of shift workers as current smokers (shift workers, 54% *vs* day workers, 39% - p = 0.001) [19]. Bae et al. assessed that workers may be more prone to smoking during shift work to relieve stress sleepiness [20]. In the present study, this association was particularly relevant as active smokers showed an almost double probability of smoking compared to day workers.

Other modifiable lifestyle factors associated with smoking were coffee and alcohol consumption and physical activity. Health-care workers who regularly consume coffee and alcohol had a higher probability of being smokers. Treolar et al. widely analyzed the relationship between caffeine consumption and smoking habits [21]. The association between smoking and alcohol consumption was also confirmed at the multivariate analysis. This is not surprising since many studies in literature consistently confirm this association. Ho et al. highlighted an almost double prevalence of tobacco and alcohol co-users compared to tobacco-only users [22].

On the other hand, practicing regular physical activity was associated with a protective effect toward smoking. A recently published paper by Tie et al. observed a significant negative association between physical exercise and smoking behavior among residents [23].

The findings of our study are strengthened by the application of a rigorous methodological approach. However, this study presents some limitations, particularly due to the self-reporting of data, with the possible introduction of selection and recall bias, as well as a lack of effective and precise assessment of health habits and behaviors as well as occupational exposures. Furthermore, the limited number and homogeneity among individual cases might include some confounders that could not be factored into the analysis. For these reasons, further quality research is required in order to confirm the validity of these findings.

Conclusions

The results of our study highlight a concerning prevalence of smokers among HCW, a professional category for which European and Italian regulations prohibit extensively smoking in all healthcare facilities and work environments. An up-to-date epidemiological picture on health habits and behaviors may provide a necessary baseline on which targeted *ad-hoc* interventions can be implemented, considering not only modifiable lifestyle factors but also work-related risk factors, and developing information and educational policies, with the aim of effectively tackle the magnitude of the phenomenon.

This preventive approach, from a Total Worker Health perspective, can bring together occupational health and public health goals, paving the way for a Global Health evidence-based practice.

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Conflicts of interest statement

The authors declare no conflicts of interest.

Author's contributions

Conceptualization, L.P., A.Mo. and G.D.; methodology, A.R., A.Ma. and L.P.; software, A.R., A.Ma., C.B. and L.P.; formal analysis, A.R., A.Mo., L.P. and G.D.; data curation, L.P., C.B., A.Ma. and L.M.; writing—original draft preparation, L.P., A.R., A.Mo. and G.D.; writing—review and editing, A.R., A.Mo., G.D., L.M., M.G.M., N.D. and P.D.; supervision, A.R., A.M., G.D. and P.D.; project administration, G.D. and P.D. All authors have read and agreed to the published version of the manuscript.

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History of Medicine and Ethics

Tetanus: historical and palaeopathological aspects considering its current health impact

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Keywords

Clostridium tetani • History of medicine • Infectious diseases • Palaeopathology • Vaccination • Tetanus • Toxin

Summary

The present article summarises the historical and palaeopathological evidence of tetanus, an ineradicable yet vaccine-preventable infectious disease caused by Clostridium tetani. The antiquity of the disease is described thanks to historical written sources, artistic references and very recent palaeogenetic data. A recollection of now long-supplanted therapies is offered together with a focus on the introduction of an effective vaccine. Moreover, a potential identification of tetanus in the Bible is analysed and general considerations on the current health relevance of tetanus are presented.

Introduction

The soil provides a biologically active medium rich in microorganisms [1]. Worthy of note is the bacillus *Clostridium tetani*. It is classified as an obligate anaerobic bacterium, which forms spores that can survive in unfavorable environmental circumstances, such as the presence of oxygen. When spores find appropriate conditions for their development, typically an anaerobic environment, they germinate. A wound that is sufficiently deep, as small as that caused by the puncture of a thorn, or a metal spike located in the ground, are sufficient for the tetanus spores to enter the host. Meanwhile, other aerobic bacteria consume the oxygen present in the tissues adjacent to the wound, creating ideal conditions for spore germination. The multiplication of *C. tetani* remains localised in the area of the wound. It is at this stage that the very potent tetanus toxin, also known as tetanospasmin (TeNT, literally the toxin that causes muscle spasms), is released [2]. TeNT binds to the membranes of motor nerve neurons. The nerve impulse that allows voluntary muscles to move is normally regulated by an inhibition phase. The tetanus toxin alters the ability to inhibit the electrical signal, which therefore continues to reach the muscle without any modification. The resulting spasmodic contractions are impressive. The muscles of the jaw contract by tightening the mouth (lockjaw), the forehead is typically wrinkled (tetanic *facies*), and the characteristic sardonic laugh appears on the face [3]. Strychnine poisoning can mimic the contraction of the muscles that gives the impression of a smile [4]. The muscles of the back and the rest of the body, then, contract very conspicuously: one of the most typical postures is *opisthotonos* (Grek ὀπισθεν + τόνος; 'behind'+'tension'), a state of hyperextension where the head, neck, and spine assumes a very arched position [5]. This bodily response was accurately depicted by the famous Scottish neurologist Sir Charles Bell (1774-1842), in 1809 in a patient suffering from this specific tetanic manifestation (Fig. 1). The early form of the disease, the most insidious, leads to premature death, within 5-10 days, usually from asphyxia and heart failure [2].

The Antiquity of Tetanus

Limitations of osteological sources

In the past, and in many less developed regions of the world, tetanus is a real scourge. Besides the typical case of infection contracted following contamination with spores in the soil, two other forms of tetanus should be noted: neonatal, and post-traumatic in soldiers. Neonatal tetanus occurs when the umbilical cord is severed with unsterilised instruments [6]. Estimates from the World Health Organization report 49,000 newborns died in 2013 from neonatal tetanus, a figure that is still staggering, although there has been a substantial reduction since the 1988 picture, when newborn deaths amounted to nearly 800,000 [7]. Post-traumatic tetanus in soldiers is historically well-documented. The death of soldiers caused by traumatic tetanus resulted from a wound sustained in battle. The Roman historian Livy (59 BCE

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Fig. 1. The image depicts a case of tetanic opisthotonos, a condition characterised by a fully arched spinal column, forming a bridge-like conformation. This is caused by a significant contraction of the dorsal muscles, with the extensor muscles of the spine being more prominent than the flexor muscles - 1809, painting by British physician Sir Charles Bell (1774-1842) (Wikipedia Commons – Public Domain).

- 17 CE) remarked on the siege of Sutrium in 309 BCE, during the war between the Romans and the Etruscans (*Ab Urbe Condita Libri*, IX.32): *apud Romanos tantum volnerum fuit ut plures post proelium decesserint quam ceciderant in acie* ("the Romans had so many wounded that more died of their hurts after the battle than had fallen on the field") [8, 9]. Not all battle wounds at the time (as well as in previous and subsequent conflicts) were infected with tetanus spores, but the picture offered by Livius' sentence is quite vivid: the phase *after* the actual battle, not *before* or *during* it, can prove the most problematic for survival.

From a palaepathological perspective, unlike with other infectious diseases leaving pathognomonic traces in the skeleton (*e.g.* tuberculosis, leprosy, and syphilis) it is extremely difficult to diagnose tetanus from bone lesions because they are non-specific [10]. They consist of rib fractures, exacerbated by an individual's bone fragility (either in young individuals or old ones) and compression vertebral fractures, with the spinal segment T4-T6 being the most commonly affected [11, 12]. Compression fractures of vertebral bodies can result in post-tetanic hyperkyphosis [13], yet this is often difficult to distinguish in paediatric patients from Scheuermann's juvenile kyphosis, an idiopathic spinal condition [13]. The only potentially pathognomonic sign could be the division of some vertebrae, as reported in the literature, in two fragments as a result of the tetanic contractions [12], yet these can also be caused by other forms of trauma such as an impact with an object or surface.

Attestations in historical written sources

Referring to ancient texts, the history of medicine and palaeopathological analysis of sources gives interesting clues. One of the earliest descriptions of the disease, particularly of its risus sardonicus and trismus (lockjaw) manifestations, dates back to Ancient Egypt, and is found in the surgical section of the Edwin Smith Papyrus (ca. 1500 BC), in *Case 7* [14, 15, 16]:

> *One who has a gaping wound in his head, which has penetrated to the bone and violated the sutures of his skull, who has a toothache, whose mouth is clenched, who suffers from stiffness in his neck: an ailment for which nothing is done* [15].

Much more accurate expositions are found in Hippocrates' (460 BCE - ca. 370 B.C.E.) work *Epidemics*:

> *The commander of the large ship; the anchor crushed his forefinger and the bone below it on the right hand. Inflammation developed, gangrene, and fever. Her was purged moderately. Mild fevers and pain. Part of the finger fell away. After the seventh day satisfactory serum came out. After that, problems with the tongue: he said he could not articulate everything. Prediction made: that opisthotonos would come. His jaws became fixed together, then it went to the neck, on the third day he was entirely convulsed backward, with sweating. On the sixth day after the prediction he died* [17].

The Roman author Aulus Cornelius Celsus (fl. 1st cent. CE) offered another description of tetanus in his work *On Medicine* (*De medicina*, IV.6):

> *There is, however, no disease more distressing, and more acute, than that which by a sort of rigor of the sinews, now draws down the head to the shoulder-blades, now the chin to the chest, now stretches out the neck straight and immobile. The Greeks call the first opisthotonus, the next emprosthotonus, and the last tetanus, although some with less exactitude use these terms indiscriminately. These diseases are often fatal within four days. If the patients survive this period, they are no longer in danger. They are all treated by the same method and this is agreed upon, but Asclepiades in particular believed in bloodletting […]* [18].

In the above passage, it is worth mentioning how the report that some patients could survive the disease can considered critical since untreated tetanus is *de facto* associated with 100% mortaly. For this reason, it cannot be excluded that cases of spontaneous recovery [19] were observed in antiquity or that, in some instances, tetanus was mistaken for other neurological conditions.

Subsequently, Areteus of Cappadocia (1st cent. CE) in his work *Of the causes and signs of acute diseases* (*De causis et signis acutorum morborum*, I.VI) called tetanus an incurable disease to the point that he went on to write that it is a blessing for the sick person, when the respiratory complications of tetanus arise, they are freed from the pains, the distortion of the limbs and the resulting deformity, a harrowing spectacle especially for family members who witness the scene. Areteus added that the limbs of the tetanus patient are so rigid that even if a doctor wanted to try to loosen them, he or she would have to cut and break them off a person who is still alive. He concluded that the doctor shares the pain and anguish

with his or her patient, being able to assist him or her but not freeing him or her from suffering. For Areteus this condition of helplessness is "the great misfortune of the physician" [20].

The celebrated French surgeon Ambroise Paré (1510-1590) studied trismus and introduced a device to keep a patient's mouth open despite the abnormal contracture: this demonstrate how no-one understood the correct aetiology despite trying to find empirical solutions and how someone could only describe the clinical presentations and outcome with some accuracy.

Finally, regarding the antiquity of tetanus, additional data have recently emerged thanks to palaeogenetic analyses, capable of recovering ancient *Clostridium* DNA from archaeological material; phylogenetic analyses revealed the presence of known clades of *C. tetani*, as well as the identification of new, closely related lineages. Furthermore, 13 variants of the tetanus neurotoxin (TeNT) were identified, including some that were exclusively present in ancient samples from South America. One of these variants was subjected to experimental analysis on mice, which demonstrated that it was capable of causing tetanus muscle paralysis with the same efficacy as modern variants. This finding suggests that ancient DNA may not only serve to confirm the presence of neurotoxigenic *C. tetani* in human archaeological samples, but also to identify new variants of TeNT with the potential to cause disease in mammals. In conclusion, the study of ancient DNA provides insights into the historical evolution of pathogenic bacteria and the possible origin of modern infectious diseases [21].

Tetanus In The Holy Bible?

In the Gospel of Matthew (Matthew 8:5-8 NIV), the following parable is recounted:

> *When Jesus had entered Capernaum, a centurion came to him, asking for help. "Lord," he said, "my servant lies at home paralyzed, suffering terribly." Jesus said to him, "Shall I come and heal him?" The centurion replied, "Lord, I do not deserve to have you come under my roof. But just say the word, and my servant will be healed* [22].

This case was briefly discussed by Kaufamann in a 1964 article [22] who considered the "unusual combination of paralysis with pain" as pointing to tetanus as the illness affecting the centurion's servant. Among Kaufmann's arguments was that strychnine poisoning was not known to have been used at that time, hence making tetanus – or potentially rabies as an alternative – the more likely explanation for the servant's affection [22]. Indeed, as pointed out by Cilliers and Retief [23], strychnine, a toxic alkaloid deriving from the seeds of the small tree *Strychnos nux vomica*, native to India, was discovered only in the 17th century AD. Kaufmann, quoting a 1937 work by Grier dates back knowledge (and/or) usage of strychnine to the 9th century AD, yet still much later than the facts narrated in the Gospels [22, 24]. Rabies, although existing in ancient times, appears less likely a diagnosis because its anxiety, confusion and agitation would have been described by the source (with a potential interpretation as a demonic possession). However, no data are available in this biblical case about previous traumatic injuries sustained by the servant to support tetanus. If one were to consider this a genuine tetanus case and look at it purely in biological terms, he could speculate that it could be an instance of spontaneous recovery from the disease.

Although a rare occurrence, if the tetanus toxin is produced slowly in small amounts, there is time for the host's immune system to produce the antitoxin, which could partly explain cases of spontaneous recovery [19].

One needs to be cautious when reading the Gospels, which shall never beinterpreted as biographies of Jesus Christ. The Gospels are not suitable for palaeopathography since the fil rouge of the entire narrative is the faith in God. In all Gospels, the crucial point is the faith in God. In this case, thanks to the exceptional faith of the pagan centurion, Jesus Christ manifests God's mercy through a miraculous healing (*Then Jesus said to the centurion, "Go! Let it be done just as you believed it would." And his servant was healed at that moment* - [Matthew 8:13 NIV]).

The scientific advances: from *Clostridium tetani* to the first vaccine

The early decades of the 19th century were still far from a significant progress in the medical knowledge on tetanus. On the 8th of October 1838, at a packed session of the Medico-Chirurgical Society of Bologna, the celebrated physician and patriot Luigi Carlo Farini (1812-1866) read a memoir on the use of electricity in the treatment of tetanus [25]. While the treatises on the supposed origin (rheumatic, inflammatory, gastric, *etc*.) of this disease, responsible for an unstoppable muscular contraction almost invariably resulting in the death of the patient, multiplied, the only certainty was the total impotence of the physician.

Inspired by Carlo Matteucci's (1811-1868) experiments on the use of electricity in frogs, Farini had decided to apply a direct current to a patient suffering from tetanus following infection from a gunshot wound. The electric current "giving rise to a kind of paralysis" could "make the tetanic phenomena disappear", leading to a relaxation of the patient, whose muscles finally ended up loosening, including the resolution of lockjaw, as well as the resumption of capillary circulation.

The beneficial effects, unfortunately, were short-lived (about 30 minutes), and the deadly spasmodic contraction returned to take possession of the patient's exhausted limbs. Before long, the unhappy man expired. A disconsolate Farini admitted the defeat of this new therapeutic approach. Nevertheless, animated by a sincere spirit of research and emphasising albeit partial benefits of his method (which nowadays would be called "palliative"), he proudly affirmed:

And let me be told whether other means and drugs give birth to similar advantages, or whether sooner

many are not clearly useless or harmful, and others are worthwhile in dampening sensitiveness for an instant by giving rise to engorgement and thus worsening morbid complications [25, authors' own translation].
Unable to discover the cause of the disease, Farini tried to rationalise the prescribed therapy and spare the sufferer whose fate is sealed from an unnecessary ordeal. The study had a resounding international reach, even appearing in the pages of the British journal *The Lancet*, where 10 years earlier, a similar case had been reported, in which apparently a combination of rectal opium and electricity had saved a woman's life from tetanus secondary to an iatrogenic blisterover the chest [26].
The cause of the disease was not understood until 1884 when Giorgio Rattone (1857-1929) and Antonio Carle (1854-1927), demonstrated the infectious nature of tetanus and its transmissibility in rabbits. Meanwhile the internist Arthur Nicolaier (1862-1942) identified the causative agent as *C. tetani* bacilli. In contrast, the credit for isolating the tetanus germ in the laboratory belongs to Japanese physician Kitasato Shibasaburo (1853-1931). Shibasaburo was also the co-discoverer (with Alexandre Yersin) of the causative agent of bubonic plague (*Yersinia pestis*) during the 1894 epidemic in Hong Kong, which gave rise to the Third Plague Pandemic [27].
With his German colleague Emil von Behring (1854-1917) they actively collaborated [28, 29]. In 1890 they were able to produce the first serum capable of counteracting tetanus toxins. Unfairly, the discovery won the Nobel Prize in 1901 for the German scientist alone.
Passively transferred antitoxin was developed in 1897 by Edmond Nocard (1850-1903) and was used throughout the First World War [28, 29]. However, the first effective active tetanus vaccine was not successfully developed until 1923 by bacteriologist Gaston Ramon (1866-1963). He succeeded inactivating the tetanus toxin obtaining the so-called toxoid or anatoxin and immunitiy in the vaccinated. The gradual development and steady use of large-scale vaccines then allowed a gradual reduction in tetanus mortality.

Tetanus Today

If vaccinations are admnistered, tetanus does not pose a threat today. However, unlike many viruses, tetanus is not eradicable because the spores are prevalent in the environment. News of a case of tetanus in a little girl hospitalised in Turin in October 2017 caused great public apprehension and inflamed the vaccine diatribe [30]. Around the same time, another case was reported in specialist medical literature in France. Interestingly, sometimes a single episode generates stronger emotional reactions than one would expect compared mulitple cases reported all at once. For example, although little has been reported in the press in recent years, there is another, much more extreme scenario in which the importance of tetanus vaccination is decisive: that of natural disasters [31]. Also wars (the current Russo-Ukraine war and the Israelo-Palestinian conflict) are potential conditions for the spread of tetanus (as it was during WWI) and shall be taken into consideration.
Tetanus, along with other infectious diseases, is a major threat following events such as earthquakes, tsunamis, hurricanes, and nuclear disasters. There is no need to go too far back. In 2004, a combination of earthquake and tsunami devastated Aceh in Indonesia over 8 minutes and even reached Thailand, India, Sri Lanka, and all the way to the coast of East Africa claiming the lives of 127,000 people (more by other estimates) and left about half a million injured. Another smaller event in 2006 with around 6,000 dead, and 37,000 injured) followed an earthquake in Yogyakarta, Indonesia. In both these events, tetanus readily manifested itself, with 106 cases documented in Aceh in the months following the earthquake that initiated the tidal wave, and 71 in Yogyakarta [32, 33].
Very significant is one additional case of tetanus reported in the international scientific literature, that of a 66-year-old Hispanic-American gardener who developed tetanus and risked death because the site of entry of the *C. tetani* spores was not obvious to the physicians, other clinical diagnoses initially being considered. The clinic, however, included, quite classically, lockjaw (spastic contracture of the masseter muscles), opisthotonos (spasm of the back muscles along the spine), sardonic laughter (spasm of the facial muscles mimicking a smile), and a boat-shaped abdomen (conformation due to contracture of the abdominal muscles). Once diagnosed with the disease, the patient was saved by a cocktail of drugs: benzodiazepines administered intravenously (anxiolytic action), neuromuscular blockers (to block nerve impulse transmission at the neuromuscular junction), mechanical ventilation (supporting patient breathing by ensuring adequate air volume to the lungs), metronidazole antibiotic therapy (active against vegetative forms of *C. tetani*), tetanus anti-toxin (antibodies that directly counteract the pathogen) [34].
In earlier times this patient would almost certainly have died, while today science has saved him.

Conclusions

Tetanus has been a constant companion of humankind, as evidenced by its presence in ancient texts and recent palaeogenetic discoveries. From a purely palaeopathological perspective, the ancient skeletal remains so far analysed are not particularly helpful in identifying tetanus in the ancient world. The effects of the strong contraction of the back muscles may manifest themselves at the level of the spine as an hyperkyphosis (severe curvature of the vertebral column). However, such condition would not be pathognomonic of tetanus infection, since other diseases manifest a similar skeletal alteration. In contrast, palaeomolecular analyses have identified ancient neurotoxigenic clostridia in samples derived from archaeological contexts.
Notwithstanding notable advancements in medical

science, tetanus persists as a significant public health concern, particularly in regions with limited access to vaccines, with cases emerging in unvaccinated individuals or during natural disasters. In such instances, injuries and a lack of timely medical intervention allow the spores of the bacterium to take hold. The history of tetanus also emphasises the continued importance of vaccination.

Despite the unwarranted scepticism surrounding vaccines, the practice of vaccination remains a pivotal strategy for the control of numerous epidemic diseases, including smallpox (which was eradicated in 1980 as a direct consequence of extensive vaccination programs).

It is regrettable that, as evidenced by the recent SARS-CoV-2 pandemic, mistrust of vaccines has once again become prevalent. This is due to the rapid transmission of disinformation campaigns and fake news via the Internet, and on occasion, the endorsement of misleading information by celebrities.

Vaccine hesitancy and anti-vaccine movements have a long history [35, 36]. The first anti-vaccine league was established in the mid-1850s in the United Kingdom, when there was considerable opposition to a law requiring smallpox vaccination [37]. One notable example of endorsement of vaccine hesitancy can be attributed to the poet and politician and leading exponent of Romanticism, Lord Byron (1788-1824), was openly sceptical of the smallpox immunisation method developed by Jenner in 1749. He went so far as to compare it to questionable medical practices and quackery prevalent at the time [38].

Although tetanus is now uncommon in resource-rich settings, the disease remains a threat to all unvaccinated people, particularly in resource-limited countries where the continued existence of *C. tetani* in the environment indicates that while the disease can be controlled, it cannot be eradicated. Since *C. tetani* spores cannot be removed from the environment, immunization and suitable treatment of wounds and traumatic injuries are necessary for tetanus prevention.

Consequently, ongoing vigilance and vaccination efforts are essential.

Informed consent statement

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Data availability statement

Not applicable.

Conflicts of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

FMG, EV: designed the study; FMG, EV: conceived the manuscript; FMG, EV: drafted the manuscript; RB, STD, VV, AN, MM, EV: revised the manuscript; FMG, EV, RB, STD, VV, AN, MM, EV: performed a search of the literature; RB, STD, VV, AN, MM: critically revised the manuscript; FMG, EV, RB, STD, VV, AN, MM, EV: conceptualization, and methodology; FMG, EV, RB, STD, VV, AN, MM, EV: investigation and data curation; FMG, EV: original draft preparation; MM: editing. All authors have read and approved the latest version of the paper for publication.

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History of Medicine and Ethics

Policy brief: addressing the shortage of human resources in the Iranian health system

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Keywords

Policy brief • Healthcare workforce • Human resource shortage • Equity • Health policy

Summary

This policy brief highlights the critical shortage of healthcare workers in Iran, which hinders access, quality, and patient outcomes. The growing demand from population increases and chronic diseases, coupled with issues like geographic maldistribution, workforce migration, inadequate training, and limited support systems, exacerbates the crisis. Urban areas benefit disproportionately, leaving rural communities underserved and healthcare quality compromised. Evidence-based recommendations include incentivizing rural placements, improving workforce management systems, enhancing salaries and working conditions, expanding education and training, and leveraging digital health tools and task-shifting models. A phased implementation strategy is proposed, combining short-term pilot projects with long-term reforms to build a resilient healthcare workforce.

Introduction

Problem Statement

The Iranian health system is grappling with a critical shortage of healthcare professionals, encompassing doctors, nurses, specialists, and other key healthcare workers [1]. This deficit in human resources has emerged as a significant barrier to the effective delivery of healthcare services across the country. The issue is multifaceted and stems from an imbalance between the supply of healthcare professionals and the growing demands of the population [2]. Rapid population growth, increased life expectancy, and the rising prevalence of chronic diseases are straining the healthcare system's capacity to meet these demands [3].

The current shortage of healthcare workers has led to several negative consequences. It has adversely affected the quality of care provided to patients; increased waiting times, and created an uneven distribution of health services, particularly in rural and underserved areas [4]. The rural-urban disparity in the distribution of healthcare professionals further complicates the situation. Major urban centers like Tehran, Isfahan, and Shiraz attract a disproportionate number of healthcare workers due to better working conditions, facilities, and career advancement opportunities [5]. In contrast, rural and underserved areas face significant challenges in recruiting and retaining qualified staff. As a result, healthcare access in these regions remains severely limited, causing inequalities in service delivery and patient outcomes [6].

In addition to geographic imbalances, Iran's health sector is also affected by the migration of skilled healthcare workers to other countries. Better financial incentives, professional development opportunities, and improved working conditions abroad have contributed to a steady outflow of healthcare professionals from Iran [7]. This "brain drain" further exacerbates the domestic shortage and poses a significant threat to the country's healthcare system [8]. Another factor contributing to the shortage is the insufficient capacity of the country's educational and training institutions [9]. The medical education system is unable to keep up with the growing demand for healthcare services. Limited seats in medical and nursing schools, inadequate training facilities, and insufficient opportunities for specialization have resulted in a lack of skilled personnel. Furthermore, there is a need for more robust residency and fellowship programs to address gaps in specialized care [10].

The current healthcare workforce is also experiencing high levels of burnout, partly due to an overwhelming workload [11]. The COVID-19 pandemic has only intensified these challenges, revealing the fragility of the healthcare system and highlighting the urgent need for reforms. Health professionals have faced increased mental and physical strain during the pandemic, leading to high turnover rates and exacerbating the existing workforce shortages [12]. Addressing this critical issue requires a holistic approach that targets both immediate and long-term challenges. The shortage of healthcare workers poses a threat not only to healthcare access but also to the overall sustainability of the health

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system [13]. Without adequate and equitable human resource distribution, the health system's ability to deliver essential services and respond to future health crises remains compromised [14].

Objective

The purpose of this policy brief is to provide an evidence-based analysis of the current shortage of healthcare professionals in Iran and propose actionable solutions to address this pressing issue. By examining the root causes, consequences, and key challenges related to the shortage, this policy brief aims to guide policymakers in formulating strategies to mitigate the impact of the human resource deficit on the health system. The primary objective of this policy brief is to highlight the need for a comprehensive and strategic approach to strengthen the healthcare workforce in Iran. This includes enhancing workforce planning, improving geographic distribution, reducing outmigration, and expanding training and development opportunities. The brief seeks to emphasize the importance of equitable access to healthcare services for all populations, particularly those in underserved areas. Furthermore, this policy brief aims to promote sustainable workforce policies that can address both immediate and long-term needs. Short-term measures such as providing incentives for rural placement, implementing retention strategies, and task-shifting initiatives can help mitigate the current shortage. At the same time, long-term strategies, including investments in education and training, workforce planning, and capacity building, are essential to ensure a stable and resilient healthcare system in the future. To achieve these goals, the policy brief outlines a series of recommendations that focus on addressing geographic imbalances, enhancing retention efforts, expanding education and training programs, promoting new workforce models, and utilizing digital health technologies. The solutions presented aim to build a more robust and equitable healthcare system that can effectively meet the evolving needs of Iran's population. By providing a detailed analysis of the current challenges and proposing evidence-based solutions, this policy brief aims to inform policymakers, stakeholders, and healthcare leaders about the urgent need for reform in the Iranian health system. Strengthening human resources for health is crucial to improving the quality, accessibility, and equity of healthcare services in Iran. Addressing the shortage of healthcare professionals is not only a matter of increasing workforce numbers but also ensuring that these professionals are adequately distributed, well-trained, and motivated to provide quality care. It is imperative to implement policies that create an enabling environment for healthcare workers, promote sustainable development of human resources, and improve the overall performance of the health system. Through these efforts, Iran can build a resilient and responsive healthcare workforce capable of delivering high-quality services to all citizens.

Background, context and current situation

The Iranian health system is currently facing a critical shortage in its healthcare workforce. This includes not only doctors and nurses but also specialists, paramedics, and support staff [15]. According to recent data, the number of healthcare professionals per capita in Iran remains below global standards, which presents a significant barrier to achieving equitable healthcare access. The country's health workforce is unevenly distributed, with a stark contrast between urban and rural areas [16]. While major cities such as Tehran, Isfahan, and Shiraz have a relatively higher concentration of healthcare workers, rural and underserved areas continue to struggle with acute shortages. This geographic imbalance is a key contributor to inequitable access to healthcare services across the country [17].

One of the prominent challenges is the outmigration of skilled healthcare professionals. In recent years, many Iranian doctors, nurses, and specialists have left the country in pursuit of better career prospects, higher salaries, and improved working conditions abroad [18]. This trend of "brain drain" has intensified the human resource crisis in the health sector. The lack of competitive compensation, limited career development opportunities, and political instability are among the main drivers of migration. This issue is further compounded by an aging workforce and insufficient numbers of new healthcare professionals entering the system [19].

Iran's educational and training capacity for healthcare professionals is another area of concern. Despite efforts to expand medical and nursing schools, the current training infrastructure is inadequate to meet the growing demand for healthcare services [20]. Medical and nursing schools face constraints in capacity, curriculum modernization, and training facilities, which has resulted in a limited output of well-trained healthcare professionals. Additionally, there are insufficient residency programs for medical graduates, leading to a shortage of specialists in key medical fields [21].

For instance, regarding the shortage of human resources in certain sectors, we refer to statements made by health system officials in Iran. Currently, approximately 200,000 individuals are providing nursing services across various levels in hospitals and healthcare centers affiliated with the Ministry of Health, the Social Security Organization, military hospitals, and the private sector. Of these, around 140,000 nurses are employed by the Ministry of Health. In the country, 2.5 nurses are needed per hospital bed, but there is currently a shortage of 100,000 nurses nationwide. The dentist-to-population ratio in Iran is approximately 3.29 dentists per 10,000 people. However, the distribution of physicians is uneven across the country, with some regions having more physicians than others. For example, 34% of the country's total physicians and 45% of the specialists practice in Tehran, which has only 11% of the national population. Additionally, about 21,000 midwives are currently working in the healthcare sector, both in public and private hospitals, and approximately 22,000

midwives are engaged in the health sector under the family physician program and health network system. However, there is a need for about 12,000 more midwives in the healthcare sector and around 8,000 additional midwives in the health sector.

Moreover, the Iranian health system has been slow to adopt innovative workforce models such as task shifting or the introduction of new healthcare roles like nurse practitioners or physician assistants [22]. This has further limited the ability of the system to address gaps in service delivery. As a result, the burden on the existing workforce continues to increase, exacerbating challenges related to high workloads and limited career pathways [23].

Consequences of Human Resources (HR) Shortages

The shortage of healthcare professionals in Iran has had far-reaching consequences on the overall healthcare system. One of the most significant impacts is on the quality of care provided to patients [24]. The inadequate number of healthcare workers often leads to higher patient-to-staff ratios, which compromises the quality of care and increases the risk of medical errors. Overworked and understaffed healthcare facilities struggle to maintain the standards of patient safety and care that are crucial to achieving positive health outcomes [25].

Accessibility to healthcare services has also been severely impacted. The shortage of healthcare workers, combined with the geographic imbalances in their distribution, has resulted in longer waiting times and limited access to essential services, particularly in rural and underserved regions [26]. Patients in these areas often have to travel long distances to access specialized care, further widening disparities in healthcare access. Additionally, the lack of healthcare workers in primary care settings has weakened preventive and community health services, which are vital for managing chronic conditions and improving population health [27].

The shortage of human resources in the health sector has also affected patient outcomes. Delays in treatment, inadequate follow-up, and reduced access to specialized care contribute to higher morbidity and mortality rates, particularly for patients with chronic illnesses [28]. The limited availability of specialists has been particularly detrimental to the management of complex medical cases, impacting the quality of life and health outcomes of affected patients [29]. Furthermore, the ongoing shortage of healthcare professionals has led to increased levels of burnout and job dissatisfaction among the existing workforce. Healthcare workers in Iran often face heavy workloads, long hours, and limited opportunities for career development, which negatively affect their well-being and job satisfaction [30]. The Covid-19 pandemic has only exacerbated these issues, as healthcare professionals faced immense pressure and inadequate support during the health crisis. High levels of burnout among healthcare workers have contributed to increased turnover rates and the exodus of experienced staff, further worsening the shortage [31].

The combined impact of these issues poses a significant threat to the sustainability of Iran's health system. Without adequate measures to address the human resource shortage, the healthcare system will continue to face challenges in delivering accessible, equitable, and high-quality care to all segments of the population [32]. The current situation underscores the urgent need for comprehensive policy interventions to strengthen the healthcare workforce, improve workforce planning and distribution, enhance training and education, and develop innovative solutions to support and retain healthcare professionals [33]. The current shortage of human resources in the Iranian health system is a complex and multifaceted issue with serious consequences for healthcare quality, accessibility, patient outcomes, and staff well-being. Addressing these challenges is essential to building a resilient and equitable health system capable of meeting the needs of the population [34].

Key challenges: geographic maldistribution

One of the most pressing challenges facing the Iranian healthcare system is the unequal distribution of healthcare professionals between rural and urban areas. Large cities like Tehran, Isfahan, and Shiraz enjoy a concentration of healthcare resources and personnel due to better facilities, infrastructure, and career opportunities [4]. However, rural and underserved regions face an acute shortage of doctors, nurses, and specialists. This geographic maldistribution creates disparities in access to essential healthcare services, with rural populations often lacking basic healthcare infrastructure and skilled professionals [8]. The rural-urban divide stems from various factors, including inadequate working conditions in rural areas, limited access to professional development, and social amenities that are scarce compared to urban centers. Moreover, the healthcare system does not have effective policies or incentive structures in place to attract healthcare workers to remote and underserved regions. Consequently, this imbalance in distribution leaves rural populations vulnerable, creating gaps in service delivery, healthcare quality, and patient outcomes [11].

Health Professional Migration

The migration of healthcare professionals, often referred to as "brain drain," is a critical issue impacting Iran's health system. Over recent years, Iran has experienced an increasing outflow of doctors, nurses, and medical specialists seeking better job prospects and working conditions abroad. This trend is driven by factors such as low salaries, lack of job satisfaction, limited career growth, political instability, and the desire for better financial rewards [19].

Healthcare professionals in Iran often encounter systemic challenges, such as limited opportunities for advancement and poor working environments. These factors push many skilled workers to seek opportunities

in countries that offer higher wages, improved work environments, and more stable political climates [26]. The loss of experienced healthcare workers to other countries weakens the domestic healthcare system, further exacerbating the existing shortages. The impact of migration extends beyond numbers; it also results in a loss of expertise and mentorship, affecting the training and development of new healthcare professionals in Iran.

Lack of Training and Skill Development

The Iranian healthcare system faces significant challenges related to training and skill development. The capacity of medical schools, nursing programs, and specialized training institutions is insufficient to meet the growing demands of the population [18]. This is compounded by outdated curricula and a lack of resources for hands-on training. Medical and nursing schools are often underfunded, leading to an inadequate number of graduates entering the workforce each year. The lack of well-structured training programs, particularly in specialized fields, limits the availability of skilled professionals such as surgeons, oncologists, and other specialists [22].

There is also a noticeable gap in continuous professional development for practicing healthcare workers. Inadequate opportunities for ongoing training and upskilling prevent healthcare professionals from staying updated with the latest medical advancements and best practices. This not only impacts the quality of care but also limits the potential for healthcare workers to specialize in fields that are crucial for addressing emerging healthcare challenges [31].

Limited Incentives and Support Systems

Low salaries, poor working conditions, and limited career advancement opportunities are major barriers to retaining healthcare workers in Iran. Many healthcare professionals face heavy workloads, long hours, and inadequate support systems, contributing to high levels of job dissatisfaction and burnout. The lack of financial incentives, combined with insufficient recognition and professional growth opportunities, creates a demotivating environment for healthcare workers [3, 6]. Iran's healthcare sector has not prioritized the development of robust incentive structures that reward healthcare workers for their dedication and service. In countries with stronger healthcare systems, financial incentives, performance-based pay, and well-defined career ladders play a crucial role in motivating staff and enhancing retention [19]. However, in Iran, healthcare workers often face stagnant salaries that do not reflect their workload or qualifications, resulting in a continuous outflow of skilled professionals to private sectors or other countries [14].

Moreover, the lack of support systems such as health and wellness programs, mental health services, and flexible work arrangements adds to the burden on healthcare workers [17]. The challenges faced by the healthcare workforce were further exposed during the COVID-19 pandemic, which placed additional strain on already overworked and under-resourced professionals. Many workers reported feeling unsupported and overwhelmed, with inadequate protective measures and limited mental health support [22]. Addressing these challenges requires a multi-pronged approach focusing on improving workforce distribution, creating supportive working environments, enhancing training and skill development, and providing financial and non-financial incentives [28]. Policies should be designed to bridge the urban-rural divide, reduce the outflow of skilled workers, and build a well-trained, motivated, and adequately compensated healthcare workforce. Developing a resilient healthcare system that effectively meets the needs of the population hinges on addressing these key challenges and strengthening the country's human resources for health [30].

Policy options and recommendations

1. Enhance Workforce Planning and Distribution

To address the geographic imbalances in the distribution of healthcare professionals, effective workforce planning is crucial. One key strategy is to incentivize the placement of healthcare workers in underserved areas. Rural placement programs can be implemented where newly trained doctors and nurses are required to serve in rural areas for a set period. These programs could be complemented with financial bonuses and additional benefits such as housing, educational support for children, and loan forgiveness, making rural placements more attractive [35].

Moreover, establishing centralized data systems for workforce planning and distribution is essential. A robust data system can help track and predict workforce needs and imbalances, ensuring that policy decisions are based on accurate and up-to-date information. By monitoring and forecasting trends in health service demands and healthcare workforce supply, policymakers can proactively implement measures to fill gaps and redistribute resources efficiently [36].

2. Strengthen Retention Strategies

One of the critical reasons behind the outmigration of healthcare workers from Iran is inadequate salary structures and poor working conditions. To counter this, it is vital to improve salary structures to make them more competitive and reflective of the workload and qualifications of healthcare professionals. Additionally, enhancing working conditions by providing necessary infrastructure, support systems, and job security would encourage retention and reduce outmigration [37].

Offering career development opportunities and continuous professional development programs can help healthcare workers advance in their careers while staying updated with the latest medical practices. Providing a clear career path, training opportunities, and recognition can boost morale and job satisfaction. Furthermore, developing policies that promote work-life balance and address burnout is crucial. This could

involve implementing flexible work schedules, mental health support programs, and stress management training, ensuring that healthcare workers are supported and motivated [38].

3. Invest in Education and Training Programs

The shortage of skilled healthcare professionals in Iran is partly due to inadequate investment in education and training. It is necessary to increase investment in medical and nursing schools, particularly in underserved regions, to boost local capacity. Establishing medical schools in rural areas can encourage students from those areas to pursue careers in healthcare and return to serve their communities [39]. Expanding specialized training programs and residency opportunities can address shortages in key specialties, ensuring that there are enough specialists to meet the growing needs of the population. Additionally, establishing continuing education frameworks can help healthcare professionals update their skills and adapt to advancements in medical knowledge and technology, improving the quality of care provided to patients [40].

4. Promote Task Shifting and New Workforce Models

To optimize the use of existing human resources, task shifting models should be explored. By enabling nurses and community health workers to perform certain tasks traditionally done by doctors, healthcare services can be delivered more efficiently, especially in underserved regions. For instance, trained nurses can handle routine follow-up care, immunization, and health education [41]. Introducing new roles like nurse practitioners, physician assistants, and community health workers can also fill gaps in the workforce. These roles can complement existing services and extend healthcare coverage, particularly in rural and remote areas. Task-shifting and new roles should be supported by appropriate training, certification, and regulation to ensure that these professionals are competent and their scope of practice is clearly defined [42].

5. Enhance Public-Private Partnerships

The private sector has a crucial role to play in addressing healthcare workforce shortages. Encouraging private sector involvement in training and education can expand the capacity of medical and nursing schools, reducing the pressure on public institutions. For example, private hospitals and clinics can be incentivized to provide training slots for medical and nursing students, enhancing their practical skills and exposure [43].
Collaborating with non-governmental organizations (NGOs) can also help bridge gaps in healthcare delivery, particularly in underserved regions. NGOs can provide healthcare services, training, and support in areas where public resources are limited. Public-private partnerships can therefore help expand capacity and improve service delivery, ensuring that healthcare services reach all segments of the population [44].

6. Utilize Digital Health and Telemedicine

Digital health tools and telemedicine offer immense potential to extend healthcare access to remote areas with limited human resources. Promoting digital health tools such as electronic health records, mobile health applications, and health information systems can improve the efficiency of healthcare delivery and workforce management [45].
Telemedicine should be further developed and integrated into the healthcare system to enable healthcare professionals to provide remote consultations, diagnostics, and follow-up care to patients in underserved regions. This would reduce the need for patients to travel long distances for basic healthcare services. To ensure the effectiveness of telemedicine, it is essential to develop policies that regulate and support the adoption of telehealth services, ensuring patient safety, privacy, and quality standards [46]. These policy options offer a comprehensive approach to addressing the shortage of human resources in the Iranian healthcare system. By focusing on equitable workforce distribution, retention, education, innovative workforce models, partnerships, and digital health, Iran can build a resilient and well-equipped health system capable of meeting the needs of its population [47].

Implementation strategy

To effectively address the shortage of healthcare professionals in Iran, a structured implementation strategy is essential. This strategy should encompass both short-term and long-term actions that are phased to ensure sustainable improvements in the healthcare workforce. By focusing on pilot projects, capacity-building initiatives, and comprehensive structural reforms, this approach aims to create a more robust and equitable healthcare system.

Short-Term Actions

1. Pilot Projects

Initiating pilot projects in selected underserved regions can provide valuable insights into effective strategies for addressing healthcare workforce shortages. These projects may include:

- **Rural Placement Programs:** Launch pilot programs that incentivize newly graduated healthcare professionals to work in rural areas for a defined period. This could involve offering financial bonuses, housing assistance, and professional development opportunities. Success stories from these pilot projects can be used to advocate for broader implementation and attract more participants;
- **Task-Shifting Initiatives:** Implement pilot programs that explore task-shifting models, allowing trained nurses and community health workers to perform specific tasks traditionally handled by doctors. For instance, community health workers could conduct routine check-ups and health education, freeing up doctors to focus on more complex cases. Monitoring

and evaluating these pilots will provide critical data to inform future scaling.

2. Capacity-Building Initiatives

Short-term capacity-building initiatives are vital to ensuring that healthcare professionals are well-prepared to meet the needs of the population. These initiatives may include:

- **Training Workshops:** Conduct workshops for healthcare professionals in underserved regions to enhance their skills and knowledge. These workshops can focus on essential areas such as chronic disease management, primary care practices, and digital health tools;
- **Mentorship Programs:** Establish mentorship programs that pair experienced healthcare professionals with recent graduates, especially in rural areas. Mentors can provide guidance, support, and encouragement, helping new professionals adapt to their roles and the challenges of working in underserved settings.

3. Incentives for Rural Workforce Placement

Developing targeted incentives for healthcare workers to serve in rural areas is crucial for addressing geographic maldistribution. These incentives may include:

- **Financial Bonuses:** Introduce financial bonuses for healthcare workers who commit to a certain period of service in rural areas. This can serve as a significant motivator for recent graduates and existing professionals looking to transition to different roles;
- **Housing and Relocation Assistance:** Provide support for relocation and housing costs to ease the transition for healthcare workers moving to rural areas. Offering assistance with housing can make rural positions more attractive and help to mitigate the initial challenges of relocating.

Long-term actions

1. Structural Reforms

Long-term structural reforms are essential to create a sustainable and effective healthcare workforce. Key reforms may include:

- **Revising Health Workforce Policies:** Develop comprehensive policies that focus on equitable distribution, retention, and ongoing professional development. This should involve stakeholder engagement to ensure that policies are responsive to the needs of healthcare workers and the communities they serve;
- **Establishing a Centralized Workforce Planning Body:** Create a centralized body responsible for workforce planning and distribution. This body should monitor healthcare workforce needs, collect and analyze data, and develop strategies to address imbalances.

2. Continuous Workforce Monitoring

Implementing a robust system for continuous workforce monitoring is crucial for adapting to changing healthcare needs. This system may involve:

- **Regular Workforce Assessments:** Conduct regular assessments to evaluate the supply and demand of healthcare professionals across regions. This data will be invaluable for informing policy decisions and identifying areas that require intervention;
- **Feedback Mechanisms:** Establish mechanisms for healthcare workers to provide feedback on their experiences, working conditions, and challenges. This feedback will help policymakers understand the effectiveness of current strategies and make necessary adjustments.

3. Expansion of Education Programs

To ensure a steady pipeline of healthcare professionals, expanding education programs is vital. Long-term actions should include:

- **Investing in Medical and Nursing Schools:** Increase funding for medical and nursing schools, especially in rural areas, to boost the capacity of these institutions. This investment should prioritize creating new programs and expanding existing ones to accommodate more students;
- **Enhancing Specialized Training Opportunities:** Develop specialized training programs and residency opportunities in high-demand fields. Collaborating with private institutions and international partners can help improve the quality of training and broaden the range of specialties available to new healthcare professionals.

A phased implementation strategy that includes both short-term actions and long-term reforms is essential to addressing the human resource shortages in Iran's healthcare system. By prioritizing pilot projects, capacity-building initiatives, and targeted incentives, policymakers can create immediate improvements. At the same time, structural reforms, continuous monitoring, and investment in education programs will lay the groundwork for a sustainable and effective healthcare workforce capable of meeting the needs of the Iranian population.

Conclusions

Addressing the shortage of human resources in Iran's healthcare system is a critical public health priority that directly affects healthcare access, quality, and outcomes. Geographic maldistribution, inadequate numbers of trained professionals, and workforce burnout exacerbate health inequities, particularly in rural areas, while straining the system's effectiveness. Implementing strategies to improve workforce planning, retention, education, and innovative models is essential for creating a more equitable and sustainable healthcare environment. Policymakers must act urgently to enhance healthcare access and outcomes, ensuring a resilient system that meets the needs of both patients and professionals.

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Authors' contributions

Designed the study: MS, MB, and MM. Conceived the manuscript: FE, FS, and BDT. Drafted the manuscript: MS, MB, and FE. Revised the manuscript: MB, and MM. Performed a search of the literature: FE, BDT, and FS. Critically revised the manuscript: MS, and MB. Conceptualization, and methodology: MB. Investigation and data curation: MB, and MM. Original draft preparation: MB, MM, and FS. Final editing. All authors have read and approved the latest version of the paper for publication.

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