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REVIEWS

Cost-Effectiveness of Hepatitis A Vaccination in Patients with Hepatitis C: A Systematic Review

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Keywords

Hepatitis A • Hepatitis C • vaccination • Cost-effectiveness • Economic evaluation • Systematic review

Summary

Background. In patients who have chronic Hepatitis C virus (HCV), hepatitis A virus (HAV) infection may cause such debilitating complications as fulminant hepatitis and liver failure. This population is considered a priority group for HAV vaccination against HAV although its cost-effectiveness is still questioned. This is a systematic review to assess the cost-effectiveness of HAV vaccination against chronic HCV to guide clinical practice and the policy of the general population.

Methods. A comprehensive literature search was performed in the databases of PubMed, Scopus, Web of Science, and Embase between January 1990 and August 2024. The studies that were taken were those that determined the cost-effectiveness, cost-utility, or cost-benefit of HAV vaccination in HCV patients and reported economic consequences including incremental cost-effectiveness ratios (ICERs), quality-adjusted life years (QALYs) or life-years saved. After surveying through the records to narrow down the potential studies to 216, the number of potential research papers had to be filtered out to the four studies which satisfied the inclusion criteria, but which did not contain any duplicates, irrelevant studies or lacked any economic assessment. Data were extracted and synthesized narratively.

Results. The included studies were conducted in the USA and Canada and used decision-analysis or Markov models to compare no vaccination, selective/screen-and-vaccinate strategies, and universal vaccination. Selective vaccination was consistently the most cost-effective strategy, with an ICER of approximately \$51,000 per QALY gained in one study and cost per life-year saved ranging from \$22,256 to \$102,064 depending on age in another. Selective vaccination also prevented 128 symptomatic HAV cases per million population over 5 years. Universal vaccination was cost-effective only when HAV infection rates were high (>0.56% per year) or under specific cost structures, such as those of the Department of Veterans Affairs. These findings remained robust in sensitivity analyses.

Conclusion. This is because selective HAV vaccination is the most cost-effective solution in patients with chronic HCV, which happens to be more affordable in areas with low HAV prevalence. Universal immunization can be reasonably justified when the rates are high enough but care should be taken to maximize resource use. The evidence-based vaccination strategies can help to decrease the burden of HAV in this vulnerable population with the help of these findings.

Introduction

Hepatitis A and Hepatitis C are important health issues in the world with their own epidemiological and clinical peculiarities [1, 2]. Hepatitis A virus (HAV) is most commonly transmitted fecal-orally whereby acute self-limiting liver disease is commonly experienced. On the contrary, Hepatitis C virus (HCV) is a blood pathogen, which results in chronic liver disease, and millions of individuals worldwide are infected, and the virus causes serious patients as liver cirrhosis and hepatocellular carcinoma [3, 4]. There is an increased risk of adverse events in patients with chronic liver diseases (especially those with HCV infection) in case of co-infection with HAV; fulminant hepatitis and liver failure, which is why preventive interventions need to be taken into account [5].

HAV vaccination has proven both a safe and efficient method of preventing Hepatitis A and strong immune responses have been observed even in patients with underlying liver conditions [6]. The world health organizations such as the World Health Organization (WHO) and Centers of Disease Control and Prevention (CDC) recommend HAV vaccination in people with chronic liver disease including those who are infected with the HCV [7].

Vaccination, by preventing cases of HAV infection superimposition, can play an important role in reducing the clinical and economic burden of dealing with co-infections in this at-risk group. In spite of these suggestions the cost-effectiveness of routine HAV vaccination in HCV patients is a matter of ongoing debate [8].

Cost-effectiveness studies are important in informing healthcare policies, especially in health care environments where healthcare services are scarce [9]. The economic analysis of the state of vaccination programs is based on the costs of their implementation compared against healthcare savings due to prevented complications and enhanced health results. The case of HAV vaccination against HCV-infected people might have the advantage of informing the public health policy, allocating resources more effectively and eventually enhance a patient outcome. Nevertheless, the research is not covered with thorough reviews synthesizing the evidence on the same topic, which forms the gap in the literature [10].

This systematic review has a chance to fill this gap because it will evaluate the available evidence on the cost-effectiveness of HAV vaccination in the HCV patients. The objective of this review is to offer a detailed insight into the economic and clinical consequences of HAV vaccination among this high-risk group by synthesizing the research results of the various healthcare settings and groups of people. It is hoped that the results can be used by policymakers, healthcare providers and researchers to influence the adoption of evidence-based interventions to vaccinate people with chronic HCV infection.

Methods

SEARCH STRATEGY

A comprehensive literature search was conducted to locate the studies that measure the cost-effectiveness of the Hepatitis A vaccination among Hepatitis C patients. The search of electronic databases including PubMed, Scopus, Web of Science, and Embase was conducted between January 1, 1990, and August 30, 2024. The search strategy included Medical Subject Headings (MeSH) and free-text terms (*e.g.* Hepatitis A, Hepatitis C, vaccination, cost-effectiveness, economic evaluation and so forth) and additional synonyms. Further search of the reference lists of the relevant articles and gray literature such as reports by health organizations was conducted. No language limitations were imposed so as to make the search as extensive as possible.

INCLUSION CRITERIA

Studies that satisfied the following requirements were included:

1. Concentrated on the Hepatitis A vaccination's cost-effectiveness, cost-utility, or cost-benefit.
2. Patients with persistent Hepatitis C infection were the target.
3. Economic results that are reported, such as cost savings, quality-adjusted life years (QALYs) or life-years saved, or incremental cost-effectiveness ratios (ICERs).
4. Made use of well-known frameworks for economic evaluation, such as decision tree analysis and Markov models.

5. Published in reputable health economic evaluation sources or peer-reviewed journals.

EXCLUSION CRITERIA

Research was disqualified if it

1. Ignored economic analysis and concentrated only on the clinical effectiveness or safety of the Hepatitis A vaccine.
2. Targeted groups or general populations that weren't Hepatitis C patients.
3. Were case reports, editorials, commentary, or narrative reviews.
4. Insufficient information to extract important economic indicators.

RISK OF BIAS ASSESSMENT

At the individual study level, the risk of bias was assessed with a modified Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. The tool is used to measure the quality of methodology of economic assessment, results reporting, modelling practices, and input transparency. The two independent reviewers assessed each study and possibly agreed or came to a consensus with a third reviewer to overcome the differences [11]. Based on predetermined criteria, studies were categorized as having a low, moderate, or high risk of bias.

DATA EXTRACTION AND ANALYSIS

Two reviewers analyzed the data using a standardized form and independently extracted it. Data extracted were characteristics of the study (*e.g.*, author, year, and country), population (*e.g.*, age, level of disease, *etc.*), strategy of vaccination, methods of economic evaluation, and outcomes (*e.g.*, ICERs, QALYs). The major result was that Hepatitis A immunization was cost effective in comparison to none, or other interventions.

Results

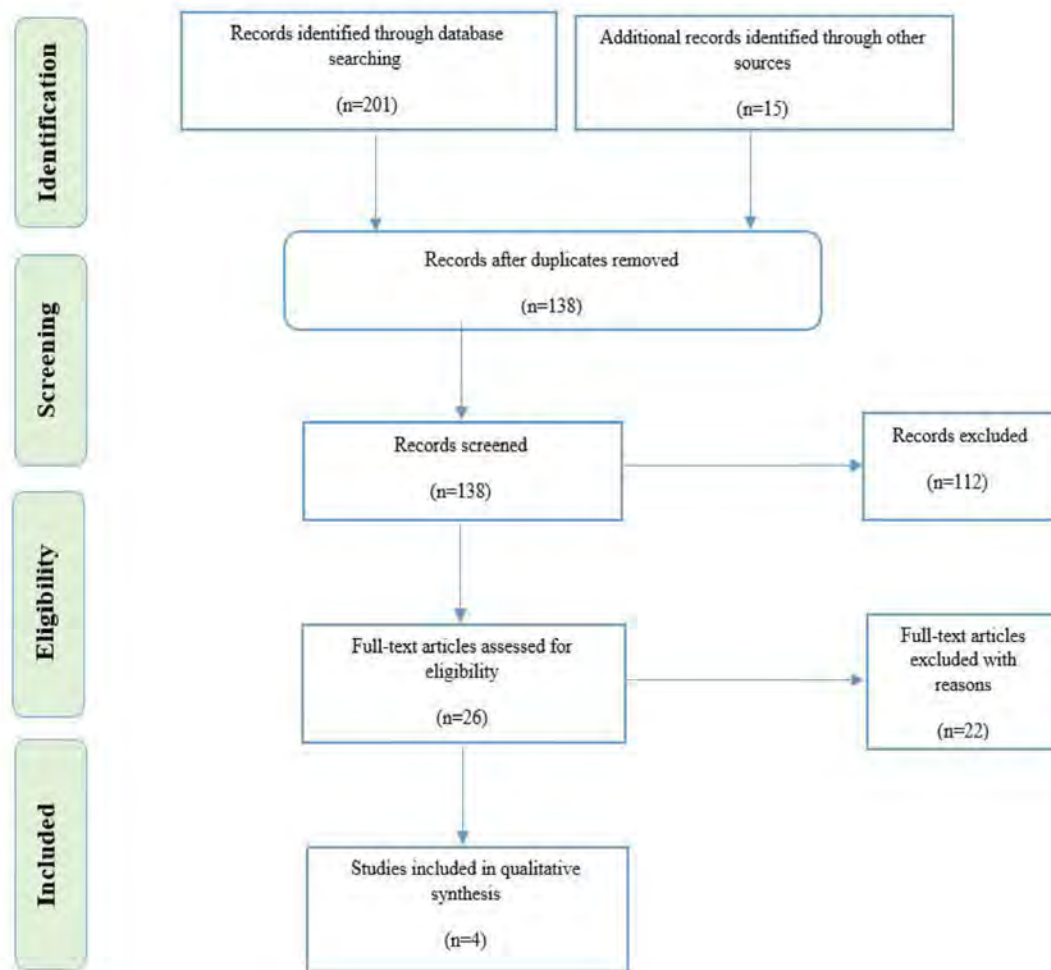
The initial literature search located a number of 216 studies. Having eliminated 78 duplicates, 138 unique studies were left to screen. Screening of these studies was done using their titles and abstracts to determine how relevant they are to the research question. In this step, 112 studies were eliminated as they failed to meet the inclusion criteria such as they either did not deal with general populations, or lacked economic appraisals and dealt with unrelated issues.

The remaining 26 studies underwent full-text eligibility assessments. Following such stringent screening process there were 4 studies, which had all the inclusion criteria and were chosen to undergo the final analysis. Figure 1 presents a flowchart that gives an overview of the selection procedure of the study.

In this study, Table I provides an overview of the characteristics, methodologies, and key findings of the included studies. The quality and transparency of the included studies were assessed with the help

Tab. I. Characteristics and Key Findings of Included Studies.

Study	First Author	Country	Year	Number of Patients	Follow-Up Duration	Hepatitis A Vaccine Dose	Study Methodology	Key Findings
Cost-Effectiveness of Hepatitis A Vaccination for Individuals with Chronic Hepatitis C	Michael K. Chapko	USA	2010	Not specified	Not specified	Not specified	Decision analysis model using Markov models to simulate different vaccination strategies (no vaccination, targeted, and universal) with costs evaluated from VA and private sector perspectives.	Vaccination is cost-effective only for individuals who cleared HCV when using VA costs; otherwise, it is not cost-effective.
Cost-Effectiveness of Hepatitis A Vaccination in Patients with Chronic Hepatitis C Viral Infection in the United States	Miguel R. Arguedas	USA	2002	Hypothetical population	Until death (long-term)	Primary + booster doses (assumed)	Markov state-transition model comparing no vaccination, targeted vaccination, and universal vaccination. Probabilities of HCV progression and quality-of-life weights were used, with societal costs (Medicare) factored in.	Targeted vaccination is cost-effective at \$51,000 per QALY gained; universal vaccination is not cost-effective due to extremely high incremental cost per QALY.
The Cost-Effectiveness of Hepatitis A Vaccination in Patients with Chronic Hepatitis C	Robert P. Myers	Canada	2000	Hypothetical cohort	5 years	Havrix, primary + booster	Decision analysis with three strategies: compared no vaccination, selective vaccination, and universal vaccination. Hospital data and literature were used for cost and outcome estimates. Sensitivity and threshold analyses were conducted for optimal strategies under different scenarios.	Selective vaccination prevents 128 HAV cases per 1 million patients. Universal vaccination is cost-effective only if HAV infection rate exceeds 0.56%.
Study The Cost-Effectiveness of Vaccinating Chronic Hepatitis C Patients Against Hepatitis A	R. Jake Jacobs	USA	2002	Hypothetical cohorts of 100,000 chronic HCV patients	Lifetime (Markov model; life-years saved)	+ booster (two-dose series; 45,000 initiate, 35,550 receive second dose)	Markov model comparing screen-and-vaccinate strategy (anti-HAV screening followed by vaccination of susceptible patients) with no vaccination; health system and societal perspectives; sensitivity analyses.	Vaccination reduced symptomatic HAV cases by 63-72% depending on age. Screening and vaccination costs \$5.2 million per cohort, partially offset by \$1.5-\$2.8 million reductions in HAV treatment costs and \$0.2-\$1.0 million reductions in work-loss costs. Health system cost per life-year saved: \$22,256 (age 30), \$50,391 (age 45), \$102,064 (age 60); societal ratios: \$13,222, \$41,656, \$97,651. Cost-effectiveness most favorable for younger patients; most sensitive to HAV infection and hospitalization rates and discount rate.

Fig. 1. PRISMA Flowchart of Study Selection Process.

of the CHEERS checklist. This evaluation covered several important areas of the respective studies, such as their report clarity, methodological rigor, and study results transparency. The results of this analysis are presented in Table II that gives an in-depth description of the compliance of each study with the CHEERS criteria [11].

Decision analysis models were used to assess the cost-effectiveness of hepatitis A vaccination in hepatitis C patients with chronic hepatitis. These studies used decision-analysis or Markov models to compare no vaccination with selective and vaccinate strategies and in some cases, universal vaccination [10, 12-14]. The key findings are as follows:

- **Chapko et al. (2010)** concluded that vaccination was cost-effective only to patients who had overcome hepatitis C when the healthcare costs of the Department of Veterans Affairs (VA) were considered. Quite to the contrary, it was not cost-effective in private sector or low HAV infection rates [13].
- **Arguedas et al. (2002)** established a numerically significant incremental cost-effectiveness ratio (ICER) of targeted vaccination with no vaccination of 51,000 per quality-adjusted life year (QALY). Targeted vaccination was better than universal vaccination by a wide margin, as the ICER of universal vaccination was 3.9 million dollars per QALY [12].
- **Myers et al. (2000)** demonstrated the preventive cases of 128 symptomatic HAV per 1 million patients in five years with selective vaccination. Nevertheless, the cost-effectiveness of universal vaccination became effective in the case when HAV infection rate annually was more than 0.56 per year. The cost effective type below this threshold was selective vaccination and the cost of universal vaccination was huge [14].
- **Jacobs et al. (2002)** evaluated a screen-and-vaccinate strategy in hypothetical cohorts of 100,000 chronic HCV patients at ages 30, 45, and

Tab. II. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) for Evaluating Included Studies.

CHEERS Item	Chapko et al. (2010)	Arguedas et al. (2002)	Myers et al. (2000)	Jacobs et al. (2002)
1. Title	Yes	Yes	Yes	Yes
2. Abstract	Yes	Yes	Yes	Yes
3. Introduction: Background and objectives	Yes	Yes	Yes	Yes
4. Methods: Target population and subgroups	Partially	Yes	Yes	Yes
5. Methods: Setting and location	Yes	Yes	Yes	Yes
6. Methods: Study perspective	Yes	Yes	Yes	Yes
7. Methods: Comparators	Yes	Yes	Yes	Yes
8. Methods: Time horizon	Yes	Yes	Yes	Yes
9. Methods: Discount rate	Yes	Yes	Yes	Yes
10. Methods: Choice of health outcomes	Yes	Yes	Yes	Yes
11. Methods: Measurement of effectiveness	Yes	Yes	Yes	Yes
12. Methods: Measurement and valuation of preference-based outcomes	Yes	Yes	Yes	No
13. Methods: Estimating resources and costs	Yes	Yes	Yes	Yes
14. Methods: Currency, price date, and conversion	Yes	Yes	Yes	Yes
15. Methods: Model assumptions	Yes	Yes	Yes	Yes
16. Methods: Analytic methods	Yes	Yes	Yes	Yes
17. Methods: Study parameters	Yes	Yes	Yes	Yes
18. Methods: Incremental costs and outcomes	Yes	Yes	Yes	Yes
19. Methods: Characterizing uncertainty	Yes	Yes	Yes	Yes
20. Methods: Characterizing heterogeneity	Partially	Partially	Partially	Partially
21. Results: Study findings	Yes	Yes	Yes	Yes
22. Results: Summary of main results	Yes	Yes	Yes	Yes
23. Results: Subgroup analyses	No	No	No	Yes
24. Results: Sensitivity analyses	Yes	Yes	Yes	Yes
25. Results: Limitations	Yes	Yes	Yes	Yes
26. Discussion: Generalizability	Partially	Partially	Partially	Partially
27. Discussion: Current knowledge	Yes	Yes	Yes	Yes
28. Other: Funding source	Unclear	Unclear	Unclear	Yes
29. Other: Conflicts of interest	No	No	No	No

60 years. Vaccination reduced symptomatic HAV cases by 63-72% depending on age. Screening and vaccination costs (\$5.2 million per cohort) were partially offset by reductions in HAV treatment costs (\$1.5-\$2.8 million) and work-loss costs (\$0.2-\$1.0 million). From the health system perspective, the cost per life-year saved was \$22,256 at age 30, \$50,391 at age 45, and \$102,064 at age 60; societal ratios were \$13,222, \$41,656, and \$97,651, respectively. Cost-effectiveness was most favorable for younger patients and was most sensitive to HAV infection and hospitalization rates and the discount rate [10].

These findings imply that selective vaccination of HAV in patients with chronic hepatitis C is cost-effective, particularly in younger patients and in areas with low HAV infection rates [10]. Universal vaccination can only be justified in those populations, which have a higher rate of infection, and the incremental ratio of cost-effectiveness is better [12, 14].

Discussion

This systematic review suggests that Hepatitis A vaccination is cost effective on chronic Hepatitis C patients particularly when they are subjected to particular or selective vaccination procedures. The research articles involved in the study continually established that selective vaccination, i.e. vaccinating individuals who have never received a HAV vaccination previously, is economically the most efficient means to apply especially in regions with low incidences of HAV infection [12]. On the other hand, the price of the universal vaccination became cost-effective only in a setting with higher infection rates of HAV (>0.56%) or on specific cost-structure, such as in the Department of Veterans Affairs (VA) setting [14]. The implications of these results to clinical practice, the policy of health care of the people and future research are important.

The reviewed studies have also presented consistent results in that target vaccination measures are more

cost-effective compared to universal vaccination [12-15]. For example, Arguedas et al. (2002) reported an ICER of approximately \$51,000 per QALY gained for targeted vaccination, whereas universal vaccination had an ICER of about \$3.9 million per QALY and was not economically viable in most situations [13]. Similarly, Jacobs et al. (2002) found that screen-and-vaccinate strategies cost \$22,256-\$102,064 per life-year saved depending on age, with the most favorable ratios in younger patients [10]. Equally, Chapko et al. (2010) reported that in the VA cost analysis, vaccination only proved to be cost-effective among patients who had passed the Hepatitis C infection, but not in the market [13]. Such results highlight the necessity of micro-adapting the approaches to vaccination in relation to special types of patients and healthcare facilities.

Myers et al. (2000) emphasized that selective vaccination could prevent 128 symptomatic HAV cases per million patients and remained cost-effective unless annual HAV infection rates exceeded 0.56% [16]. Jacobs et al. (2002) further demonstrated that cost-effectiveness improves substantially when vaccination is provided at younger ages [10].

These findings are consistent with the broader literature regarding cost-effectiveness of vaccination among high-risk groups [16-19]. As an example, the research of influenza and pneumococcal vaccines has also shown that directed vaccination has low costs compared to general ones on certain subsets of people, like the elderly, or people with weakened immunity [16]. Nevertheless, HAV vaccination is cost-effective among Hepatitis C patients and these factors which include the prevalence of the HAV immunity, the cost of vaccination and the progression of Hepatitis C are unique determinants of the cost-effectiveness of the vaccination [12, 14]. All these draw our attention to the fact that the analysis of the strategies of vaccination requires specific backgrounds when considered.

IMPLICATIONS FOR PRACTICE AND POLICY

These findings of this review have a number of significant implications on the clinical practice and the policy of public health. To begin with, selective vaccination must be fundamental among patients with chronic Hepatitis C, especially those that lack previous immunity against HAV. This is a solution that will maximize health benefits and minimize costs. Second, vaccination programs should be made according to the regional HAV infection rates, which should be considered by policy-makers. Universal vaccination might not be necessary in a region with a low prevalence of HAV but one where the HAV is prevalent, it may be an affordable solution. Lastly, the issue of low access and affordability of vaccines should be considered by healthcare systems as they have a profound impact on the cost-effectiveness of the procedure. In addition, vaccination strategies should prioritize younger patients with chronic HCV, in whom cost-effectiveness is most favorable.

STRENGTHS AND LIMITATIONS

The strengths of this review are that it has a good search strategy, has study selection, and has used good economic evaluation frameworks to synthesize the findings. Nevertheless, there exist some restrictions as well. First, the studies obtained included those which were carried out in high-income states (USA and Canada), thus restricting the extrapolation of the results to the low- and middle-income countries where the prevalence of Hepatitis C and HAV might vary. Second, other studies utilized hypothetical cohorts or presumptions regarding the query of HAV infection rates that would not reflect the reality. Lastly, only the studies published in English were reviewed which may exclude some of the relevant data in the non-English speaking regions. One included study (Jacobs et al., 2002) reported outcomes as life-years saved rather than QALYs, which limits direct comparability with other economic evaluations.

Conclusion

To sum up, this systematic review has shown that selective Hepatitis A immunization is the most cost-effective strategy for patients with chronic Hepatitis C, especially in younger patients and in areas with low levels of HAV infection. Universal vaccination can be based on high-prevalence regions or following certain cost design, but the targeted interventions should be in the first place to maximize resources expenditure. These results can inform clinicians, policymakers, and researchers, as it is possible to use evidence-based vaccination strategies to enhance the results in this group of high risk.

Key Point

This systematic review suggests that selective vaccination against Hepatitis A is usually the most cost-efficient strategy to use with chronic Hepatitis C patients and has benefits over universal vaccination or no vaccination in the majority of epidemiological settings. Universal vaccination seems to be cost-effective in the environment with high incidence of HAV or in healthcare systems with particular cost models, including the U.S. Veterans Affairs. The results indicate the significance of integrating the vaccination plans with epidemiological characteristics of the region and the resources available to maximize the health outcomes. Specific vaccination activities can have a significant impact on the clinical and economic cost of HAV-HCV coinfection and the distribution of resources in a more effective way. However, the relevance of the existing evidence is limited due to the prevalence of model-based studies in high-income nations, which highlights the necessity of real-life research in various healthcare settings.

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Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Center for Health Management and Economics Research, Health Management Research Institute, Iran University of Medical Sciences (Project Code. 28260).

Consent for publication

Not applicable.

Availability of data and materials

This review is based entirely on previously published studies. No new datasets were generated or analysed. All data supporting the findings of this review are included in the published article, and are available from the corresponding author on reasonable request.

Conflict of interest statement

The authors declare that they have no competing interests.

Authors' contributions

BDT, MB, and SA contributed to the conception and design of the study. BDT, SA conducted the search, and MGh was co-moderator. BDT, SA, MB, MM, PH, and MGh conducted screening and selecting the final studies, which AR discussed regularly. BDT, AR, SA, MM, MB, MGh, and PH wrote the initial draft and contributed to manuscript revisions. BDT, PH, MB: performed a search of the literature. BDT, MB: editing All authors read and confirmed the final manuscript.

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REVIEWS

Strategic Pharmaceutical Procurement for Surgical Care in Public Hospitals: A Scoping Review of Health System Architecture and Payment Reforms

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Keywords

Strategic Purchasing • Pharmaceutical Procurement • Procurement Models • Hospital Purchasing • Payment Reforms • Bundled Payments • Health Financing • Public Hospitals

Summary

Background. Rising surgical expenditures challenge the financial sustainability of public health systems. Pharmaceutical procurement is an important component of surgical care, but procurement choices are shaped by financing, governance, pricing policy, and provider-payment incentives. This scoping review mapped pharmaceutical procurement strategies used in public hospital surgical care and examined how health system architecture and payment reforms influence their design and implementation.

Methods. We conducted a scoping review following PRISMA-ScR and a prospectively registered protocol. PubMed, Scopus, and Web of Science were searched for English-language literature published from 1 January 2018 through 31 December 2025 using a Population-Concept-Context framework. Forty-three sources were included after duplicate removal, title/abstract screening, and full-text assessment. Procurement mechanisms, pricing and reimbursement levers, provider-payment arrangements, health system context, and reported outcomes were charted and synthesized narratively.

Results. Two broad and overlapping patterns were identified. Centralized and pooled procurement approaches, including

national or regional tendering and group purchasing, remain the dominant mechanisms for obtaining price and volume advantages. Value-oriented procurement is less mature and is typically enabled by broader payment reforms rather than functioning as a payment model itself. In particular, bundled and episode-based payments can shift hospital incentives from minimizing pharmaceutical acquisition prices toward managing total episode cost and outcomes. The evidence base is concentrated in high-income settings, and direct evidence linking bundled payment to selection of surgical pharmaceuticals remains limited.

Conclusion. Strategic pharmaceutical procurement is context-dependent and should be aligned with health system governance, pharmaceutical pricing policy, and provider-payment incentives. The evidence supports an adaptive approach in which high-volume, substitutable products are suited to competitive or pooled procurement, whereas higher-cost or outcome-sensitive products may require value assessment, negotiated agreements, and stronger clinical-data infrastructure. These conclusions should be interpreted cautiously because the evidence is heterogeneous and predominantly descriptive.

Introduction

Globally, healthcare expenditures are increasing at an unsustainable rate, placing substantial pressure on public finances [1]. The hospital sector accounts for the largest share of these expenditures and represents approximately 31% of national health spending in a high-cost country such as the United States [2]. Within the hospital setting, costs associated with surgical care are a major contributor to resource utilization. Common inpatient surgical procedures such as knee and hip arthroplasty, cesarean section, cholecystectomy, and coronary artery bypass grafting are performed at high volumes and are inherently resource-intensive [3]. One important yet often underestimated component of these costs is pharmaceutical expenditure, which encompasses a wide range of medications essential to the preoperative phase of care, including anesthetic agents, prophylactic antibiotics, anticoagulants, analgesics, and other specialty pharmaceuticals [4].

Public hospitals, which constitute the backbone of service delivery in many national health systems, are at the forefront of efforts to manage these rising costs while maintaining or improving the quality of care [5]. In this context, the methods used to purchase or procure pharmaceuticals are not merely administrative functions; rather, they represent critical strategic levers for achieving efficiency and value [6]. However, the procurement strategies available to a public hospital are not determined in isolation. They are path-dependent and heavily influenced by the institutional architecture of the national health system [7]. The financing mechanisms (*e.g.*, general taxation versus social health insurance), provider payment models (*e.g.*, FSS versus bundled payments), and governance structures (*e.g.*, centralized versus decentralized) of a health system create a unique set of incentives and constraints that determine which procurement models are feasible and effective [8]. For example, the procurement approach adopted in a centrally funded single-payer system such as the

United Kingdom's National Health Service is inherently different from that of a fragmented, multi-payer social health insurance system such as Germany's [9].

An important observation from the outset is the profound interdependence between the methods used to reimburse healthcare providers for surgical services and the approaches employed to procure essential inputs, such as pharmaceuticals. In traditional FFS systems, where hospitals are reimbursed separately for each service and episode of care, the prevailing financial incentive is to minimize the unit cost of each input. Such an environment naturally favors procurement strategies such as competitive tendering, in which the primary objective is to secure the lowest possible price for each vial, tablet, or pharmaceutical product [7].

However, the global transition toward value-based healthcare has introduced Alternative Payment Models (APMs) such as bundled and episode-based payments, which provide a single comprehensive payment for an entire episode of care. Under these arrangements, hospitals assume financial responsibility for the total cost of the care episode [10]. This fundamentally alters the procurement calculus. The incentive shifts from minimizing the cost of individual inputs to minimizing the total cost of the entire episode of care. Consequently, a medication with a higher acquisition cost that results in fewer complications, shorter lengths of stay, or lower readmission rates may become the most economically rational choice, even though it would appear less attractive under a conventional FFS framework [11].

Although extensive literature evaluates the clinical and financial effects of alternative payment models, their implications for pharmaceutical procurement have not been synthesized consistently. The present review therefore treats procurement mechanisms, pharmaceutical pricing/reimbursement levers, and provider-payment models as analytically distinct but interacting domains. This distinction is important because a bundled payment does not itself purchase a medicine; instead, it changes the financial incentives under which hospitals make procurement and formulary decisions. The review maps the available evidence, identifies dominant procurement patterns, and examines where payment reform may create conditions for more value-oriented purchasing.

The primary objective of this review is to identify, map, and synthesize the literature on pharmaceutical procurement strategies relevant to common surgical procedures in public hospitals. The secondary objectives are to:

- Categorize the identified procurement strategies into a coherent typology (e.g., volume-based models emphasizing economies of scale versus value-based models focusing on clinical outcomes).
- Analyze the relationship between a country's overarching health system architecture (classified by financing and delivery structures) and the specific pharmaceutical purchasing strategies employed.
- Identify critical knowledge gaps within the current literature to inform future research agendas for

policymakers, hospital administrators, and health services researchers.

- Propose the core components of an evidence-based strategic purchasing model that is adaptable across diverse health system contexts.

Conceptual Framework for Analyzing Pharmaceutical Procurement

DEFINING STRATEGIC PURCHASING IN SURGICAL CARE

In health economics, strategic purchasing extends beyond the administrative act of procurement. It is a proactive, evidence-informed process through which purchasers seek to maximize health-system value for available resources [12]. For surgical pharmaceuticals, this requires attention to acquisition price, quality, supply continuity, downstream clinical outcomes, and total episode cost. To avoid conceptual overlap, this review distinguishes three interacting layers: (1) direct procurement mechanisms used to acquire medicines; (2) pricing and reimbursement levers that influence the net price or coverage conditions of medicines; and (3) provider-payment mechanisms that alter hospital incentives but are not procurement mechanisms themselves.

Direct volume-based procurement mechanisms: These strategies aggregate demand or competition to reduce unit prices and improve purchasing leverage. Key examples include:

- Tendering: A formal procedure where suppliers are invited to bid for a contract to supply specific goods. This can be open (accessible to all qualified suppliers) or restricted (invitation-only) [13].
- GPOs: Entities that aggregate the purchasing volume of multiple member institutions (e.g., a network of hospitals) to negotiate discounts from manufacturers and distributors that individual members could not secure independently [14].
- Direct value-oriented procurement mechanisms: These approaches link purchasing or contractual terms more explicitly to expected value, uncertainty, or observed performance. A key example is:
 - Outcome- or performance-linked purchasing: Contracts may condition price, rebate, reimbursement, or continued coverage on predefined clinical, utilization, or economic outcomes. Such arrangements are most relevant for high-cost products when uncertainty about real-world value is substantial [16].
- Risk-sharing and managed-entry agreements: These are negotiated arrangements between purchasers/payers and manufacturers that may include financial rebates, expenditure caps, price-volume terms, or performance-based conditions. Financial agreements should be distinguished from true outcome-based agreements because the former can lower net prices without requiring outcome measurement [56–58].
- Provider-payment mechanisms (enabling

environment): Bundled and episode-based payments are not pharmaceutical procurement models. They are provider-payment arrangements that make hospitals or provider organizations financially accountable for a defined episode of care. By exposing providers to total episode cost, these models can change formulary and procurement incentives, including the willingness to select a higher-acquisition-cost medicine when it plausibly reduces complications, length of stay, or readmissions. CMS BPCI Advanced, launched in 2018, is a prominent example of this incentive structure; however, direct evidence on medication-level selection effects remains limited [59, 60].

- **Pricing, reimbursement, and regulatory levers:** These system-level mechanisms shape the prices and conditions under which procurement occurs. They include external and internal reference pricing, health technology assessment and value-based pricing, formulary management, direct price negotiation, tendering, pooled procurement, and confidential discounts or rebates. WHO guidance emphasizes that external reference pricing is commonly combined with negotiation and depends on reliable price information, while OECD analyses note that confidential rebates can create a gap between list and net prices and complicate international price comparisons [56–58]. These levers should therefore be interpreted as part of the policy environment surrounding procurement rather than as interchangeable procurement models.

HEALTH SYSTEM TYPOLOGY AND PATH DEPENDENCY

The procurement strategies available to a hospital or purchasing agency are not formulated in a vacuum; they are heavily influenced by the overarching architecture of the national health system. Based on established health

policy frameworks [7], these systems can be broadly categorized according to their primary financing and service delivery arrangements (Tab. I).

A country's health system classification is not merely a descriptive label. It reflects a deep institutional architecture that has evolved over decades. This structure creates a "path dependency", making certain policy choices including those related to procurement more natural or feasible than others. For instance, a system funded by a single government entity through general taxation possesses an inherent capacity for centralized, single-payer purchasing. Conversely, a system funded by hundreds of quasi-private sickness funds lacks this centralized capability but may offer a more fertile, competitive environment for innovative, value-based contracting between payers and providers. Recognizing this institutional path dependency is critical for understanding why specific procurement models succeed or fail in different global contexts.

METHODS

This scoping review followed a predefined protocol and was reported in accordance with PRISMA-ScR. The protocol was prospectively registered on the Open Science Framework (OSF) to support transparency and reproducibility [20, 23]. The review question and eligibility criteria were structured using the Population-Concept-Context (PCC) framework in line with Joanna Briggs Institute guidance. The three PCC components were:

- **Population:** The review included studies focusing on public or publicly funded hospitals. Studies exclusively examining pharmaceutical procurement in private, for-profit hospital systems were excluded to maintain a strict focus on the public sector context.
- **Concept:** The core concept was pharmaceutical

Tab. I. Characteristics of National Health System Models.

Health System Domain	Beveridge Model (e.g., UK, Spain)	Bismarck Model (e.g., Germany, France)	National Health Insurance (e.g., Canada, South Korea)	Out-of-Pocket Model (e.g., Many low- and middle-income countries (LMICs))
Financing	General taxation. Government acts as the single payer [9, 18].	Mandatory payroll contributions to non-profit "sickness funds" [18, 19].	Government-run insurance program with universal premiums. Single payer [18, 19].	Direct patient payments at the point of care. Minimal risk pooling [18, 19].
Service Delivery	Predominantly public institutions. Many physicians are government employees [9, 19].	Mix of public and private (often non-profit) providers [18, 19].	Predominantly private sector providers funded by public insurance [19].	Mix of public, private, and informal providers [18].
Access Level	Universal access as a right of citizenship [19].	Universal access guaranteed, but tied to employment or fund membership [19].	Universal access guaranteed for contributing citizens [19].	Access strictly dependent on individual ability to pay [19].
Key Implication for Purchasing	High potential for centralized monopsony power and national tendering [7].	Decentralized purchasing creating a fragmented market. Fosters GPO development [7].	Single-payer insurer holds strong price negotiation leverage, but provider purchasing remains fragmented [19].	Highly fragmented, price-sensitive purchasing at the provider or patient level [7].

Note: The "Key Implication for Purchasing" row represents the authors' synthesis of how financing and governance arrangements may shape purchasing options; it is not a direct quotation from the cited sources.

procurement or purchasing in relation to strategic, financial, or policy mechanisms. Eligible concepts included competitive tendering, pooled procurement and GPOs, outcome- or performance-linked purchasing, risk-sharing/managed-entry agreements, reference-pricing and negotiation policies, formulary management, and the influence of provider-payment reforms on procurement decisions. Studies concerned only with physical logistics (*e.g.*, warehousing or distribution) without a purchasing, pricing, financing, or formulary component were excluded.

- **Context:** The context was common inpatient surgical care in public or publicly funded hospitals, including orthopedic, cardiovascular, general surgical, and obstetric/gynecologic procedures. Outpatient-only, primary-care, and long-term-care settings were excluded unless the evidence directly informed an inpatient surgical episode or public-hospital procurement decision.

Publications from 1 January 2018 through 31 December 2025 were eligible. The start date was selected deliberately because 2018 marks an important period in the expansion of contemporary episode-based payment reform, including the launch of CMS BPCI Advanced, while subsequent years saw renewed international guidance on pharmaceutical pricing and procurement, including the 2020 WHO guideline on country pharmaceutical pricing policies [56, 59]. Restricting the review to this period was intended to capture current procurement and payment architectures rather than provide a historical review. Only English-language literature was included. Eligible peer-reviewed quantitative, qualitative, mixed-methods, economic-modeling, and review designs were considered, together with predefined grey literature from WHO, OECD, and the World Bank. Commentaries, editorials, and letters were excluded.

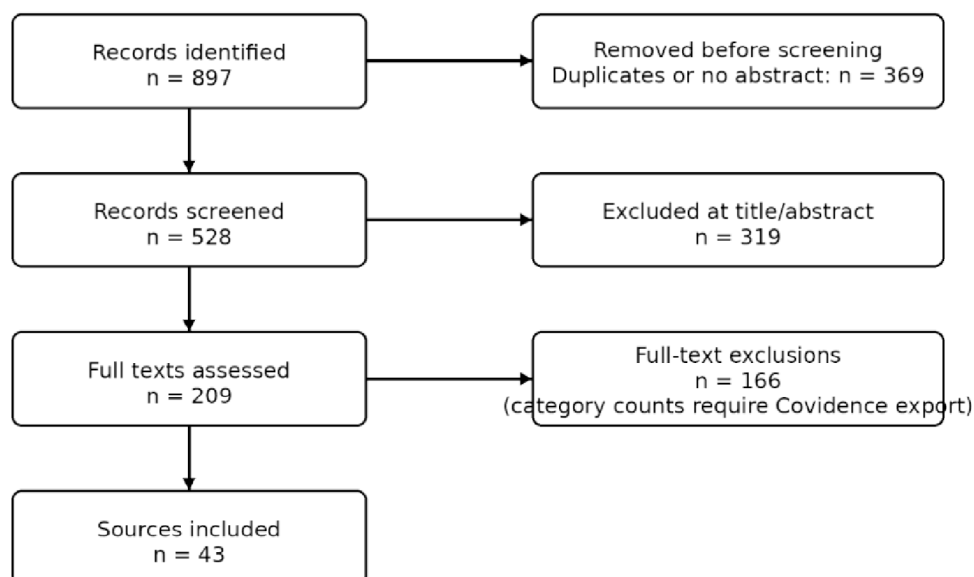
To address PRISMA-ScR Item 8, the search was developed iteratively around three domains: pharmaceutical procurement/purchasing, surgical or perioperative care, and health-system/payment architecture. Controlled vocabulary and free-text terms were adapted to the syntax of PubMed, Scopus, and Web of Science. Backward and forward citation tracking was also performed for included full-text sources. The complete database-specific search syntax, field tags, and restrictions is provided in Supplementary Appendix, Table S1. Because database interfaces use different field conventions, equivalent concepts were translated rather than copied verbatim across platforms.

All identified citations were imported into Covidence. The study flow comprised 897 records identified; 369 records were removed before title/abstract screening because of duplication or absence of an abstract, leaving 528 records for title/abstract screening. Of these, 319 were excluded at the first screening stage and 209 full texts were assessed for eligibility. A further 166 full-text records were excluded, leaving 43 sources in the final synthesis (Fig. 1). Detailed full-text exclusion categories should be reported from the Covidence audit trail in the final submission package.

Phase 1 (Title and Abstract Screening): Two reviewers independently screened each unique record against the predefined eligibility criteria. Records judged potentially eligible by either reviewer progressed to full-text assessment.

Phase 2 (Full-Text Screening): The same two reviewers independently assessed retrieved full texts for final inclusion. Where prioritization or relevance-ranking functions were used within the review software, these were used only to order screening workflow and did not determine eligibility. Inclusion and exclusion decisions remained reviewer-based.

Fig. 1. PRISMA-ScR flow diagram of study selection.



Tab. II. Data Charting Framework.

Category	Extracted Variable	Description and Rationale
Publication Details	Author, Year, Country of Origin	Provides fundamental bibliographic data and enables the geographical mapping of the evidence base.
Health System Context	Primary Health System Typology	Classifies the country's health system based on financing models (e.g., Beveridge, Bismarck, National Health Insurance). Acts as the primary variable for comparative analysis.
Study Characteristics	Study Design, Aims/Objectives	Identifies the nature of the evidence (e.g., policy analysis, economic modeling, case study) to evaluate the methodological strength of the literature.
Population	Type of Hospital	Verifies that the study setting aligns with public/publicly funded hospitals (eligibility criterion).
Surgical Context	Surgical Procedure/Specialty	Identifies specific surgical procedures discussed (e.g., orthopedics, cardiology) to distinguish generic procurement models from procedure-specific ones.
Procurement Model	Primary Strategy Implemented	Conceptually categorizes the direct purchasing strategy (e.g., tendering, pooled/GPO procurement, outcome-linked contracting) and separately records payment mechanisms that influence procurement incentives.
Model Specifics	Key Mechanisms and Levers	Extracts implementation specifics such as negotiation processes, pricing/rebate conditions, performance metrics, risk-sharing provisions, and links to provider-payment arrangements.
Outcomes	Stated Objectives and Reported Results	Captures the intended goals of the procurement model (e.g., cost containment) and any reported impacts on cost, access, or quality

Disagreements at either stage were resolved through discussion and, when required, adjudication by a third reviewer. A formal inter-rater agreement statistic (e.g., Cohen's kappa) was not reported in the available review records; accordingly, no agreement coefficient is claimed here. Reasons for full-text exclusion were documented in the review-management workflow and should be exported by category for the final PRISMA-ScR reporting package (Tab. S2).

A standardized data charting form was collaboratively developed by the research team to guide the extraction of relevant information (Tab. S3). To ensure clarity, consistency, and comprehensiveness, the form was pilot-tested on a purposive sample of five included articles and subsequently refined prior to full data extraction [22]. This structured approach ensured that the unstructured information within the selected articles was transformed into a cohesive, synthesized dataset directly aligned with the review's objectives [23]. Table II outlines the data charting framework utilized.

Methodological quality and confidence: No formal risk-of-bias tool was prespecified because the purpose was evidence mapping rather than pooled effect estimation. During synthesis, however, the research team considered study design, directness to surgical pharmaceutical procurement, and whether findings were empirical, modeled, or policy-descriptive when interpreting confidence in conclusions.

Results

Forty-three sources were included in the final synthesis. The evidence base was heterogeneous and was concentrated in high-income settings, especially North America and Europe, with a smaller cluster

from the Asia-Pacific region and limited representation from LMICs. Study designs were predominantly policy analyses, descriptive case studies, economic or simulation models, and observational evaluations, with fewer systematic or scoping reviews. Orthopedic and cardiovascular surgical pathways were among the most frequently discussed procedure areas. Because the available manuscript dataset did not retain a complete study-level extraction table, exact country-, design-, procedure-, and procurement-model counts should be populated from the original charting/Covidence export in Supplementary Table S3 before resubmission.

SYNTHESIS OF PROCUREMENT MODELS

The synthesis was organized using the revised conceptual framework: direct procurement mechanisms (volume-based and value-oriented), pricing/reimbursement levers, and provider-payment mechanisms that create incentives for procurement behavior. Table III maps these domains across major health-system archetypes. This structure also operationalizes path dependency by asking which purchasing mechanisms are institutionally feasible given the concentration of purchasing authority, payer fragmentation, and provider financial risk.

The synthesis of the charted data was organized thematically around a typology of procurement models, as presented in Table I, followed by a comparative cross-system analysis based on the major health system archetypes.

1. The Dominance of Volume-Based Procurement: Tendering and Group Purchasing
2. The Emergence of Value-Oriented Procurement and Payment-Enabled Incentives

A growing segment of the literature, particularly from the United States and Europe, describes movement toward value-oriented contracting and more explicit

Tab. III. Matrix of Procurement and Payment-Incentive Domains Across Health System Archetypes.

Mechanism / Incentive Domain	Beveridge Systems	Bismarck Systems	NHI / Hybrid Systems
National/Centralized Tendering	Dominant procurement mechanism enabled by centralized purchasing authority and monopsony power.	Less common due to fragmented payer structures; limited regional initiatives exist.	Used by national insurers to establish reimbursement prices and negotiate with manufacturers.
GPOs	Limited use because centralized procurement often fulfills this function.	Widely used by hospitals to aggregate demand and strengthen bargaining power.	Predominant in private provider markets, particularly in the United States.
Value-oriented / performance-linked purchasing	Emerging through centrally driven pilot initiatives.	Limited implementation; being explored by individual sickness funds.	Major area of innovation led by public payers such as Medicare.
Bundled or episode-based payment (provider-payment incentive; not a procurement mechanism)	Selective use within broader payment-reform initiatives; potential to create incentives for total-cost-of-care procurement.	Piloted by selected insurers/provider networks; effect on pharmaceutical procurement depends on how financial accountability is delegated.	Prominent in U.S. public-payment innovation (e.g., BPCI Advanced); direct medication-level procurement effects remain incompletely documented.

consideration of total care costs and outcomes. This should not be interpreted as a wholesale “paradigm shift”: volume-based approaches remain dominant in many settings, while value-oriented approaches are heterogeneous, selective, and often experimental.

Provider value-based payment programs can alter the economic environment in which procurement decisions are made by linking hospital revenue to quality and efficiency. Direct pharmaceutical value-oriented mechanisms, by contrast, include performance-linked rebates, risk-sharing agreements, and negotiated managed-entry arrangements. Maintaining this distinction prevents provider payment from being misclassified as procurement.

Bundled and episode-based payments illustrate the interaction between provider payment and procurement. Under CMS BPCI Advanced, participants were accountable for total Medicare expenditures and quality over defined clinical episodes, including many surgical episodes and Part B drugs [59]. Evaluations have reported Medicare savings for surgical episode groups while generally maintaining measured quality, although the savings have largely been attributed to broader care redesign and post-acute utilization rather than demonstrated medication-specific substitution [60]. Thus, bundled payment provides a plausible incentive for value-conscious pharmaceutical selection, but direct empirical evidence linking the model to specific perioperative medicine choices remains an important gap.

HOW HEALTH SYSTEM ARCHITECTURE SHAPES PHARMACEUTICAL PROCUREMENT

When the synthesized evidence is mapped onto major health system archetypes, distinct patterns emerge that underscore the powerful influence of health system architecture on PPSs. These findings are summarized in Table III.

BEVERIDGE MODEL

The literature relating to Beveridge-type health systems, such as that of the United Kingdom, highlights the advantages of centralized procurement. The single-payer structure facilitates national-level negotiations and tendering processes, generating substantial monopsony purchasing power that can be leveraged to reduce pharmaceutical prices [13]. Evidence suggests that centralized tendering constitutes the dominant procurement mechanism in these systems, reflecting the institutional capacity of a unified purchaser to coordinate procurement activities across the healthcare sector [26]. The implementation of value-based procurement approaches appears to remain at a relatively early and experimental stage, often driven by centrally coordinated policy initiatives designed to align resource allocation with quality and outcome objectives [29].

BISMARCK MODEL

In countries operating under Bismarck-style social health insurance systems, such as Germany and France, the procurement landscape is considerably more fragmented. The evidence points to a hybrid model in which statutory health insurance funds play a central role in price negotiations and reimbursement decisions, while hospitals frequently rely on GPOs to strengthen their purchasing power for products that fall outside centralized reimbursement arrangements [32]. Consequently, procurement strategies in these systems tend to combine elements of centralized negotiation with decentralized purchasing mechanisms, reflecting the pluralistic nature of their financing and governance structures.

NATIONAL HEALTH INSURANCE AND HYBRID SYSTEMS

The United States, as the most prominent example of a hybrid health system, demonstrates the broadest spectrum of pharmaceutical procurement models. Public

Tab. IV. Key Themes and Supporting Evidence Identified Across the Included Studies.

Key Theme	Supporting Evidence from Included Studies	Representative References
Centralized procurement reduces pharmaceutical prices and improves affordability	Multiple large-scale procurement programs reported sustained reductions in pharmaceutical expenditures and improved access to medicines.	[33-38]
Data-driven supply chain management improves efficiency and inventory performance	Studies employing AI, machine learning, and optimization approaches consistently reported improvements in forecasting, inventory control, and cost reduction.	[39-45]
Strong governance and regulatory coordination are critical success factors	Comparative and case studies identified governance quality as a key determinant of procurement effectiveness.	[38, 46-52]
Procurement models require adaptation to local institutional and market conditions	Systematic reviews and comparative analyses reported variable outcomes depending on legal, technical, and market environments.	[38, 47]
Implementation challenges may undermine procurement reforms	Empirical studies documented risks related to supply shortages, stakeholder resistance, and system integration barriers.	[48, 49, 53-55]
Performance-based financing and public-private collaboration may strengthen procurement outcomes	Evidence from several settings suggested positive effects when procurement reforms were linked to performance incentives and collaborative governance arrangements.	[51, 52]
Centralized purchasing: quantitative example	Brazilian centralized rituximab purchasing achieved discounts close to 70% of the reference price and was estimated to save BRL 81.6 million (13.8%) versus a modeled hospital-purchasing scenario; the example is not surgery-specific and is presented to illustrate scale effects rather than provide a pooled estimate.	[26]
Bundled payment: episode-level evidence	CMS BPCI Advanced evaluations reported savings for surgical clinical episodes with quality generally maintained; published evaluation summaries attribute much of the savings to care redesign and post-acute utilization, while direct medication-selection effects remain insufficiently reported.	[59, 60]
Pricing opacity / reference pricing	WHO and OECD sources indicate that external reference pricing is often combined with negotiation and that confidential discounts/rebates can cause public list prices to differ materially from net transaction prices, complicating cross-country comparisons.	[56-58]

payers, particularly Medicare, serve as major drivers of value-based healthcare innovation and have pioneered bundled payment initiatives and VBP programs that are extensively documented in the literature [29]. At the same time, the country's large and highly fragmented hospital sector relies heavily on powerful GPOs to achieve economies of scale and manage pharmaceutical expenditures [27]. This dual dynamic makes the United States a particularly rich source of evidence regarding the coexistence of multiple procurement strategies operating simultaneously within a single health system. The findings suggest that hybrid systems may provide fertile ground for procurement innovation by enabling the coexistence of both market-based and policy-driven approaches to pharmaceutical purchasing (Tab. IV).

Discussion

INTERPRETATION OF THE MAIN FINDINGS

The findings of this scoping review suggest that PPSs for common surgical procedures in public hospitals cannot be understood as isolated managerial decisions;

rather, they are deeply embedded within the broader institutional, financing, and governance arrangements of health systems. Across the reviewed evidence, two parallel procurement paradigms emerged. The first is a volume-based paradigm, in which centralized tendering and GPOs remain the dominant and most widely documented mechanisms for controlling pharmaceutical expenditures through economies of scale and enhanced bargaining power. The second is a value-based paradigm, driven largely by provider-payment reforms, where procurement decisions increasingly consider the contribution of pharmaceuticals to overall episode-of-care costs and patient outcomes rather than acquisition price alone.

The comparative analysis further demonstrated that the feasibility and effectiveness of procurement strategies are strongly conditioned by health system architecture. In Beveridge-type systems, centralized governance structures facilitate national procurement mechanisms and generate substantial monopsony purchasing power that can be leveraged to reduce pharmaceutical prices. In Bismarck systems, fragmented financing arrangements encourage collective purchasing arrangements such as

GPOs to compensate for dispersed bargaining power. Hybrid and National Health Insurance systems exhibit the greatest diversity of procurement approaches, reflecting the coexistence of centralized payment reforms and decentralized purchasing mechanisms. These findings support the view that procurement strategies are path-dependent and cannot be transferred uncritically across health system contexts.

A particularly important finding is the interaction between provider-payment reform and procurement incentives. Provider-payment mechanisms such as bundled payments should not be treated as procurement models; rather, they determine who bears financial risk and therefore alter the objective function facing hospitals. Under FFS, procurement may remain focused on acquisition price when downstream costs are separately reimbursed. Under episode-based accountability, hospitals have stronger incentives to consider whether a medicine affects complications, length of stay, readmissions, and other episode costs. The evidence supports this incentive pathway conceptually and at the episode level, but medication-specific causal evidence remains limited.

CROSS-CUTTING THEMES EMERGING FROM THE EVIDENCE

Several recurring themes were consistently identified across the reviewed literature.

First, centralized and aggregated procurement mechanisms were commonly associated with lower pharmaceutical prices or expenditures, although effect size varied by market structure, product competition, and governance. A concrete example outside a narrowly surgical setting is Brazil's centralized rituximab purchasing program, which reported discounts close to 70% of the reference price and estimated savings of BRL 81.6 million compared with a hypothetical hospital-purchasing scenario [26]. Such estimates illustrate potential scale effects but should not be generalized directly to perioperative medicines or other health systems.

Second, data-driven supply chain management approaches including advanced forecasting systems, optimization algorithms, and digital inventory management tools were repeatedly linked to improvements in operational efficiency and reductions in stockouts and supply disruptions. These findings highlight the growing importance of analytics and digital infrastructure as enabling components of strategic procurement.

Third, pricing and reimbursement mechanisms interact with procurement and can materially alter the net price paid. External reference pricing may anchor negotiations, but confidential rebates and discounts can make public list prices poor proxies for transaction prices. This opacity is particularly important for cross-country comparisons and may limit the transferability of apparent price advantages [56-58].

Fourth, governance quality emerged as a critical determinant of procurement performance. Successful procurement initiatives were generally characterized by

strong regulatory oversight, transparent accountability mechanisms, effective stakeholder coordination, and clear implementation frameworks. Conversely, weak governance structures were frequently associated with implementation challenges and reduced effectiveness.

Fifth, the evidence emphasized the importance of continuous monitoring, stakeholder engagement, and performance-based incentives in sustaining procurement improvements over time. Procurement reforms should therefore be viewed as ongoing organizational processes rather than one-time policy interventions.

Despite these positive findings, implementation challenges remain substantial. Several studies reported persistent risks of supply shortages, stakeholder resistance, market concentration, and operational difficulties associated with large-scale procurement reforms. These findings suggest that procurement strategies must be adapted to local institutional, regulatory, and market conditions rather than being adopted as universal solutions.

KNOWLEDGE GAPS AND FUTURE RESEARCH PRIORITIES

This scoping review identified several important gaps in existing literature.

First, there is a notable absence of comparative effectiveness research directly evaluating alternative procurement models for the same pharmaceutical products and surgical procedures within comparable health system contexts. Most studies focus on a single procurement strategy in isolation, limiting the ability to determine which approaches perform best under specific circumstances.

Second, the geographical distribution of evidence remains heavily concentrated in high-income countries, particularly those in North America and Europe. Evidence from LMICs remains limited, despite the fact that these settings often face the most significant challenges related to affordability, supply security, and procurement capacity.

Third, while value-oriented procurement and provider-payment reforms are frequently discussed together, empirical evidence on their distinct and joint effects remains scarce. In particular, direct evidence connecting bundled payment exposure to medication selection, utilization, or pharmaceutical spending within surgical episodes is limited. Longitudinal evaluations should distinguish changes in drug acquisition, formulary choice, downstream utilization, patient outcomes, and total episode cost.

Fourth, a substantial implementation gap exists between high-level policy discussions surrounding payment reforms and the operational realities of hospital pharmacy and procurement departments. More research is needed to understand how procurement practices evolve in response to changing reimbursement structures and organizational incentives.

Finally, a particularly important gap concerns the limited integration of procurement and provider-payment research. Most studies examine procurement

mechanisms and payment reforms as separate policy domains, despite growing evidence that their interaction may substantially influence pharmaceutical utilization, hospital decision-making, and episode-level costs. Future research should explicitly investigate these interdependencies and their implications for strategic purchasing.

TOWARDS A HYBRID STRATEGIC PHARMACEUTICAL PROCUREMENT FRAMEWORK

The synthesized evidence suggests that no single procurement model is capable of simultaneously achieving all policy objectives related to cost containment, quality improvement, supply security, and value creation. Consequently, a truly strategic approach to pharmaceutical procurement should be adaptive, context-sensitive, and capable of integrating multiple procurement mechanisms.

Based on the evidence reviewed, this study proposes an evidence-informed framework consisting of four interrelated components: (1) procurement stratification, (2) data and analytical infrastructure, (3) integrated governance and clinical engagement, and (4) contextual adaptation to health system architecture.

1. Procurement Stratification Rather Than Uniform Purchasing

The proposed framework rejects a one-size-fits-all approach to pharmaceutical procurement and instead advocates for the classification of pharmaceuticals according to their economic and clinical characteristics. For generic and high-volume products, such as standard anesthetic agents, generic antibiotics, and intravenous solutions, the primary objective should be cost minimization. In these cases, volume-based procurement mechanisms - including transparent national or regional tenders in centralized systems and participation in large, efficient GPOs in fragmented systems - represent the most effective strategies for maximizing economies of scale and reducing acquisition costs. In contrast, for high-cost, high-impact pharmaceuticals, such as advanced anticoagulants that reduce hospital length of stay or innovative hemostatic agents that prevent serious bleeding complications, the primary objective should be value optimization. In such circumstances, value-based procurement mechanisms are more appropriate. These may include risk-sharing agreements with manufacturers or, more effectively, the integration of pharmaceutical decision-making within bundled payment arrangements for the entire surgical episode, where higher acquisition costs may be justified by reductions in total episode-of-care expenditures.

Minimum requirements for resource-constrained settings

For LMIC and resource-constrained settings, implementation should begin with a minimum viable procurement architecture rather than assuming high-income data capacity. The minimum institutional requirements are a legally authorized purchasing

entity or pooled mechanism; transparent tender and conflict-of-interest rules; a basic formulary with clinical stewardship; routine capture of purchase price, volume, supplier, stockout, expiry, and lead-time data; and a governance forum linking procurement, pharmacy, finance, and clinical leadership. Outcome-linked contracts should be introduced only where patient-level utilization and outcome data can be linked reliably to costs. Where such infrastructure is absent, transparent competitive procurement, pooled purchasing, framework agreements, supplier diversification, and simple performance dashboards may offer greater value than complex risk-sharing contracts.

2. Data and Analytical Infrastructure

Strategic pharmaceutical procurement is not feasible without robust data systems. Public hospitals and health systems should invest in information infrastructures capable of tracking not only pharmaceutical acquisition costs but also the relationships between pharmaceutical utilization, patient outcomes, episode-level expenditures, readmission rates, and supply chain performance. Such data are essential for evaluating value and constitute a prerequisite for meaningful participation in value-based procurement arrangements.

3. Integrated Governance and Clinical Engagement

Strategic procurement cannot function as an isolated responsibility of pharmacy or procurement departments. Instead, it requires an integrated governance structure that brings together hospital administrators, financial managers, pharmacists, surgeons, anesthesiologists, and other relevant stakeholders. This collaborative body should be responsible for evidence-informed decision-making, including the evaluation of the overall cost-benefit profile of new pharmaceutical products and their contribution to clinical and economic outcomes.

4. Adaptation to Health System Context

The proposed framework should be regarded as adaptive rather than prescriptive. Consistent with the principle of path dependency, procurement strategies must be aligned with the institutional characteristics of the surrounding health system.

In Beveridge-type systems, efforts should focus on strengthening the analytical capabilities of centralized procurement agencies to incorporate value-based criteria into purchasing decisions for high-impact pharmaceuticals.

In Bismarck-type systems, emphasis should be placed on strengthening the governance capacity of GPOs and enabling collaboration between hospitals and sickness funds to pilot bundled payment and value-based procurement initiatives.

In hybrid and National Health Insurance systems, procurement strategies should be closely aligned with the incentives generated by public payer programs, particularly bundled payment and VBP initiatives, to ensure consistency between reimbursement mechanisms and procurement objectives.

LIMITATIONS

This review should be interpreted in light of several methodological limitations. First, as a scoping review, it was designed to map concepts and evidence rather than estimate pooled effectiveness; no formal risk-of-bias appraisal was prespecified. Confidence in the findings is therefore constrained by the predominance of descriptive policy analyses, case studies, economic models, and heterogeneous observational evidence. Second, the search was limited to three bibliographic databases, English-language sources, and a 2018-2025 publication window, which may have omitted relevant earlier or non-English evidence. Third, the evidence base is geographically concentrated in high-income settings, so the proposed framework should not be assumed to transfer directly to LMICs without adaptation. Fourth, several cited procurement studies address pharmaceuticals broadly rather than perioperative medicines specifically, limiting directness. Finally, policy and payment arrangements evolve rapidly; findings represent the evidence available through the stated search period.

POLICY, PRACTICE, AND RESEARCH IMPLICATIONS

The findings of this review have direct implications for key stakeholders.

IMPLICATIONS FOR POLICYMAKERS

Payment reforms and procurement policies should be developed in parallel. Policymakers should establish interoperable purchasing and claims data, common definitions for episode cost, transparent tender and rebate governance, and explicit rules for when value-based or risk-sharing agreements are justified. A practical minimum dashboard should include acquisition price and net price where available, supplier concentration, contract compliance, stockout days, emergency purchases, wastage/expiry, medicine utilization per procedure, length of stay, readmissions, complications, and total episode cost. Policy pilots should specify a comparator and evaluation period before scale-up.

IMPLICATIONS FOR HOSPITAL MANAGERS

Hospital managers should move from unit-price-only purchasing toward segmented category management. High-volume substitutable products can be managed through competitive tendering, pooled purchasing, and supplier-performance monitoring; high-cost or outcome-sensitive medicines require multidisciplinary review

of total-cost and clinical evidence. Hospitals should invest first in spend analytics, formulary analytics, procedure-level utilization data, supplier performance metrics, and linkage of pharmacy data with length-of-stay, complication, and readmission outcomes. A standing procurement governance committee should include procurement, pharmacy, finance, surgery, anesthesiology, quality, and – where relevant – payer representatives, with documented conflict-of-interest management and predefined escalation rules.

IMPLICATIONS FOR RESEARCHERS

The gaps identified in this review highlight several priorities for future research. There is a pressing need for:

Empirical comparative-effectiveness studies directly comparing the total costs and quality outcomes of volume-based versus value-based procurement strategies for specific surgical procedures. Also, In-depth case studies and implementation science research from LMICs to better understand the unique challenges and potential solutions associated with pharmaceutical procurement in resource-constrained settings. Longitudinal studies evaluating the long-term effects of different procurement models on patient outcomes, health equity, and pharmaceutical innovation.

In summary, although strategic pharmaceutical procurement models have demonstrated considerable benefits, continued research and context-specific adaptation remain essential to maximize their effectiveness and sustainability within public hospital settings.

FUTURE STUDIES

Future studies should focus on adapting strategic pharmaceutical procurement models to diverse health system contexts, integrating advanced analytical approaches, and evaluating their long-term impacts on health outcomes and system sustainability. Key research priorities identified in this review are summarized in Table V.

Conclusion

This scoping review mapped international evidence on strategic pharmaceutical procurement relevant to common surgical care in public hospitals through a comparative health-systems lens. The findings indicate

Tab. V. Key Research Questions for Advancing Strategic Pharmaceutical Procurement Models.

Research Question	Rationale
How can strategic pharmaceutical procurement models be adapted for LMICs?	Identifying context-specific barriers and enabling factors is essential to ensure effectiveness and sustainability.
What are the long-term effects of centralized procurement on surgical outcomes and health system resilience?	Longitudinal studies are needed to evaluate impacts beyond costs and availability, including patient outcomes.
How can advanced data analytics and artificial intelligence be integrated into pharmaceutical procurement models in public hospitals?	Technological innovations may further optimize efficiency, reduce shortages, and improve decision-making.

that procurement mechanisms are strongly conditioned by financing, governance, pricing policy, and the allocation of provider financial risk. Volume-based approaches remain the most established mechanisms for high-volume and substitutable medicines, while value-oriented purchasing is emerging selectively and requires stronger data and governance capacity. Provider-payment reforms such as bundled payments should be understood as incentive mechanisms that may support value-conscious procurement rather than as procurement models themselves. The most defensible path forward is therefore an adaptive hybrid framework that segments medicines by market and clinical characteristics, combines transparent procurement with appropriate pricing levers, and aligns hospital purchasing decisions with episode-level incentives where the necessary data infrastructure exists. Because the evidence is heterogeneous and concentrated in high-income settings, implementation should be piloted, measured, and adapted to local institutional capacity.

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Ethics approval and consent to participate

The Research Ethics Committee of the Iran University of Medical Sciences provided the ethical approval for this study (IR.IUMS.REC.1402.920) previously. All methods were performed in accordance with the relevant guidelines and regulations such as Declarations of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

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

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Competing interests Statement

The authors declare that they have no competing interests.

Authors' contributions

DC, IMA, and MM contributed to the conception and design of the study. HP, DC conducted the search, and IMA was co-moderator. DC, IMA, MM, and HP conducted screening and selecting the final studies, which SR discussed regularly. DC, IMA, and MM wrote the initial draft and contributed to manuscript revisions. DC, IMA, and MM performed a search of the literature. DC, IMA, HP, and MM editing All authors read and confirmed the final manuscript.

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Supplementary Materials

Tab. S1. Database-specific search strategies.

Important author verification note: The search syntax below has been reconstructed from the methods and conceptual domains stated in the manuscript. It must be checked against the original database search histories before being represented as the exact historical search used. The study-level table likewise requires completion from the original Covidence/data-charting export. Eligibility limits: English language; publication date 1 January 2018 through 31 December 2025. No study-design filter should be added unless it was used in the original search.
PubMed (reconstructed syntax for verification) ((("Drug Industry"[Mesh] OR "Pharmaceutical Preparations"[Mesh] OR pharmaceutical*[Title/Abstract] OR medicine*[Title/Abstract] OR drug*[Title/Abstract]) AND (procurement[Title/Abstract] OR purchasing[Title/Abstract] OR tender*[Title/Abstract] OR "group purchasing"[Title/Abstract] OR pooled procurement[Title/Abstract] OR "value-based purchasing"[Title/Abstract] OR "risk sharing"[Title/Abstract] OR "managed entry agreement*[Title/Abstract] OR "reference pricing"[Title/Abstract] OR rebate*[Title/Abstract] OR negotiation[Title/Abstract]) AND (surg*[Title/Abstract] OR perioperative[Title/Abstract] OR postoperative[Title/Abstract] OR arthroplast*[Title/Abstract] OR "joint replacement"[Title/Abstract] OR "coronary artery bypass"[Title/Abstract] OR cholecystectomy[Title/Abstract] OR cesarean[Title/Abstract]) AND (hospital*[Title/Abstract] OR "Hospitals, Public"[Mesh] OR "public hospital*[Title/Abstract] AND ("health system*[Title/Abstract] OR financing[Title/Abstract] OR reimbursement[Title/Abstract] OR "fee for service"[Title/Abstract] OR bundled payment*[Title/Abstract] OR "episode-based"[Title/Abstract] OR "global budget*[Title/Abstract] OR Beveridge[Title/Abstract] OR Bismarck[Title/Abstract] OR "national health insurance"[Title/Abstract])) AND ("2018/01/01"[Date - Publication] : "2025/12/31"[Date - Publication]) AND English[Language])
Scopus (reconstructed syntax for verification) TITLE-ABS-KEY ((pharmaceutical* OR medicine* OR drug*) AND (procurement OR purchasing OR tender* OR "group purchasing" OR "pooled procurement" OR "value-based purchasing" OR "risk sharing" OR "managed entry agreement*" OR "reference pricing" OR rebate* OR negotiation) AND (surg* OR perioperative OR postoperative OR arthroplast* OR "joint replacement" OR "coronary artery bypass" OR cholecystectomy OR cesarean) AND (hospital* OR "public hospital*") AND ("health system*" OR financing OR reimbursement OR "fee for service" OR "bundled payment*" OR "episode-based payment*" OR "global budget*" OR Beveridge OR Bismarck OR "national health insurance")) AND PUBYEAR > 2017 AND PUBYEAR < 2026 AND (LIMIT-TO (LANGUAGE, "English"))
Web of Science Core Collection (reconstructed syntax for verification) TS=((pharmaceutical* OR medicine* OR drug*) AND (procurement OR purchasing OR tender* OR "group purchasing" OR "pooled procurement" OR "value-based purchasing" OR "risk sharing" OR "managed entry agreement*" OR "reference pricing" OR rebate* OR negotiation) AND (surg* OR perioperative OR postoperative OR arthroplast* OR "joint replacement" OR "coronary artery bypass" OR cholecystectomy OR cesarean) AND (hospital* OR "public hospital*") AND ("health system*" OR financing OR reimbursement OR "fee for service" OR "bundled payment*" OR "episode-based payment*" OR "global budget*" OR Beveridge OR Bismarck OR "national health insurance")) Refined by: PUBLICATION YEARS=(2018-2025) AND LANGUAGES=(ENGLISH)
Search-process reporting fields to verify • Date each database was last searched • Exact platform/interface (e.g., PubMed, Scopus, Web of Science Core Collection) • Any database-specific filters not represented above • Citation-tracking dates and tools • OSF registration URL/DOI

Tab. S2. PRISMA-ScR counts reconciliation.

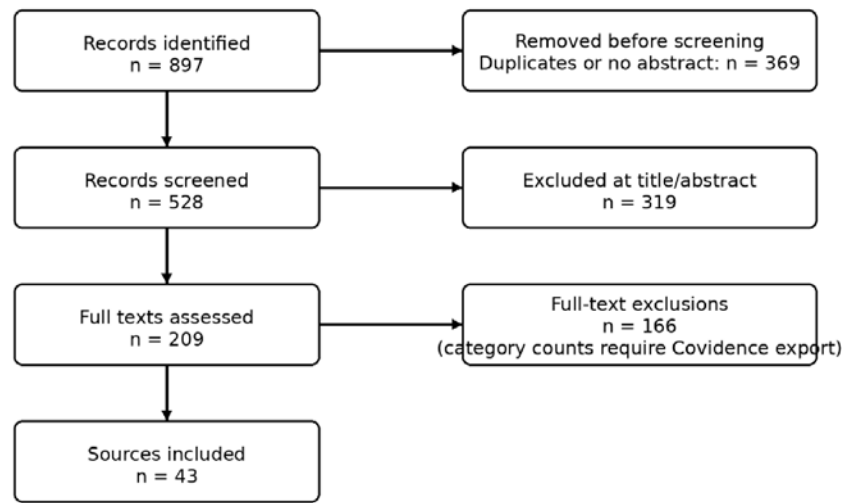
Stage	Count	Status / action
Records identified	897	Reported in manuscript figure
Removed before screening	369	Reported as duplicates or no abstract; separate category counts if available
Title/abstract screened	528	Reported
Excluded at title/abstract	319	Reported
Full texts assessed	209	Reported
Full texts excluded	166	Reported; add exclusion-reason categories from Covidence
Included in synthesis	43	Reported

Tab. S3. Characteristics of all included sources.

ID	Citation	Country/ region	Health- system type	Study design	Hospital setting	Surgical procedure/ specialty	Procurement mechanism	Pricing/ payment lever	Key outcome(s)	Directness to surgical pharma- ceuticals	Evidence- strength note
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Suggested evidence-strength note

Complete one row per included source using the original data-charting/Covidence export. Forty-three rows are provided to match the reported number of included sources. Do not infer or reconstruct missing fields from the manuscript reference list alone.
 For each source, use a descriptive rather than pseudo-quantitative label: empirical comparative/observational; single-site descriptive/QI; economic/modeling; policy analysis; systematic/scoping review; authoritative policy/guidance. Note whether the source directly evaluates surgical pharmaceuticals or is indirect/background evidence.

Fig. S1. Revised PRISMA-ScR flow diagram. Full-text exclusion categories remain to be verified from the Covidence audit trail.

Note: Full-text exclusion categories should be added from the original Covidence audit trail before submission.



REVIEWS

Renal Denervation vs. Pharmacotherapy for Resistant and Uncontrolled Hypertension: A Systematic Review of Cost-effectiveness Analyses

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Keywords

Renal Denervation • Cost-effectiveness • Hypertension • Pharmacotherapy

Summary

Introduction. Cardiovascular morbidity and mortality are associated with hypertension. Catheter-based renal denervation has been successfully used to treat resistant hypertension. The present study aimed to evaluate the cost-effectiveness of RDN compared with standard medical therapy in patients with resistant (RH) and uncontrolled hypertension (UH).

Methods. Literature searches were performed in PubMed, EMBASE, Web of science, Scopus and google scholar for full economic evaluations on RDN in patients with resistant and uncontrolled hypertension published between 1990 and 2026. Articles were screened for relevance based on preset inclusion and exclusion criteria. Final Studies in the review graded using the Quality of Health Economic Studies (QHES) instrument.

Results. A total of 43 articles were identified using our defined

criteria. Two types of studies were identified: cost-effectiveness studies and cost-utility studies, the majority of which were cost-utility studies (69%). The average quality score was 89.6 (range 65-95). Treatment with RDN resulted in a 30% reduction in cardiovascular mortality. The lowest and highest incremental cost per quality adjusted life years for patients with UH were observed in Canada (\$10,055.5) and Taiwan (\$63,802.35), respectively. These values for patients with RH were reported in the Netherlands (\$2,187.5) and Australia (\$39,613).

Conclusion. The results of this systematic review indicate that RDN is a cost-effective intervention in most cost-effectiveness models. In order to more accurately estimate the economic value of RDN, future research based on long-term clinical data and in diverse health system settings is necessary.

Introduction

Hypertension is one of the most significant causes of death and disease worldwide. Resistant hypertension (RH) occurs when blood pressure persists uncontrolled despite taking three antihypertensive medications (including a diuretic) [1]. In order to regulate blood pressure, several body systems are involved, including renin-angiotensin-aldosterone system, sympathetic nervous system, endothelin, natriuretic peptides, arterial system, and immune system. Any disruption in the functioning of these systems can lead to increased blood pressure [2]. Approximately one billion adults worldwide are affected by the disease, which accounts for nearly 9% of disability-adjusted life years (DALYs) and accounts for more than 9 million deaths each year [3]. The burden of high blood pressure on societies is considerable, and it is linked to cardiovascular and renal disease, as well as increased healthcare costs. Its prevalence is increasing in low- and middle-income countries, while it has decreased in some high-income countries, but remains high [4].

As antihypertensive drugs aimed at modulating sympathetic nervous system activity are often not

able to inhibit sympathetic stimulation completely, renal denervation (RDN) has been proposed as a complementary or alternative treatment for controlling uncontrolled blood pressure (UH) [5].

The RDN procedure reduces nerve messages passing to and from the kidneys by inactivating sympathetic nerves surrounding the renal arteries, lowering blood pressure [6]. As a result of its therapeutic benefits for patients with hypertension and chronic kidney disease, which are common causes of sympathetic nervous system activity, RDN is of particular importance to nephrologists [7]. In a recent systematic review and meta-analysis, RDN was associated with an average 8.5 mmHg reduction in systolic blood pressure and demonstrated sustained therapeutic benefits [6]. A number of controlled studies utilizing different catheter-based systems have demonstrated consistent reductions in both office and ambulatory blood pressure measurements [8]. According to a recent network meta-analysis, treatment with RDN (either monotherapy or adjunctive therapy) improved control of diastolic blood pressure (DBP) during waking hours. Also, RDN alone was found to significantly reduce systolic blood pressure (SBP) during the day [9]. In recent years, several studies have been conducted on

the cost-effectiveness of RDN. In the present study, we systematically reviewed recent literature on the cost-effectiveness of RDN compared with standard medical therapy in patients with resistant and uncontrolled hypertension.

Methods

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The protocol was registered on the PROSPERO register of systematic reviews (CRD420261321853).

Sources of information included PubMed, Web of Science, Scopus, EMBASE and google scholar. Among the search terms used were terms related to RDNs and economic evaluations. A search strategy was formulated using medical subject headings and free-text terms. Search terms were restricted from 1990 to 2026. A list of search syntax can be found in the online supplementary material.

SELECTION

In addition to searching databases, titles and abstracts of citations identified were manually screened for relevance. Eligibility criteria included published studies in English evaluating the cost-effectiveness of RDN in the treatment of patients with RH and UH. There was a full economic evaluation included in primary studies, which compared interventions in terms of cost-effectiveness, cost-utility, and cost-benefit.

DATA EXTRACTION AND SYNTHESIS

Detailed information about relevant aspects (first author, year of publication), general information (country, population, interventions, comparators), and methodology (type of economic evaluation, type of analysis, perspective, time horizon, costs, reported outcomes, discount rate, costing year, Willingness to Pay (WTP) threshold, and sensitivity analysis) was collected through a customized data extraction form. We extracted data with the help of two reviewers (A. S. and M. T), then cross-checked, discussed, and finally finalized our findings with the assistance of a third reviewer (H. O). A narrative synthesis was used to summarize findings due to the heterogeneity among studies. Cost data were converted to 2024 US\$, using the CCEMG-EPPI-Centre cost converter, to allow for easier comparison between studies [11]. When the specific price base year was not explicitly reported in the source study (*e.g.*, in conference abstracts), the publication year was assumed as the costing base year for inflation and conversion purposes.

QUALITY ASSESSMENT

A validated questionnaire for the assessment of the quality of health economic studies is known as the Quality of Health Economic Studies (QHEs). It consists of 16 criteria framed as yes/no questions. Each question is weighted, with a point value between 1 and 9. A QHEs

score ranges from 0 to 100 [12]. Various cut-off scores were determined to distinguish between study quality levels: very low quality=0-24, low quality=25-50, medium quality=51-75, and high quality=76-100. The quality of the studies was evaluated separately by two investigators (A.S. and M.T.) and, when needed, by a third investigator (H.O).

Results

The flow chart in Figure 1 shows the process of identifying studies. A database search identified 485 articles, 244 of which were excluded as duplicates. We identified 53 economic studies based on their titles and abstracts. The selection criteria were met by 43 articles [13-54].

STUDY CHARACTERISTICS

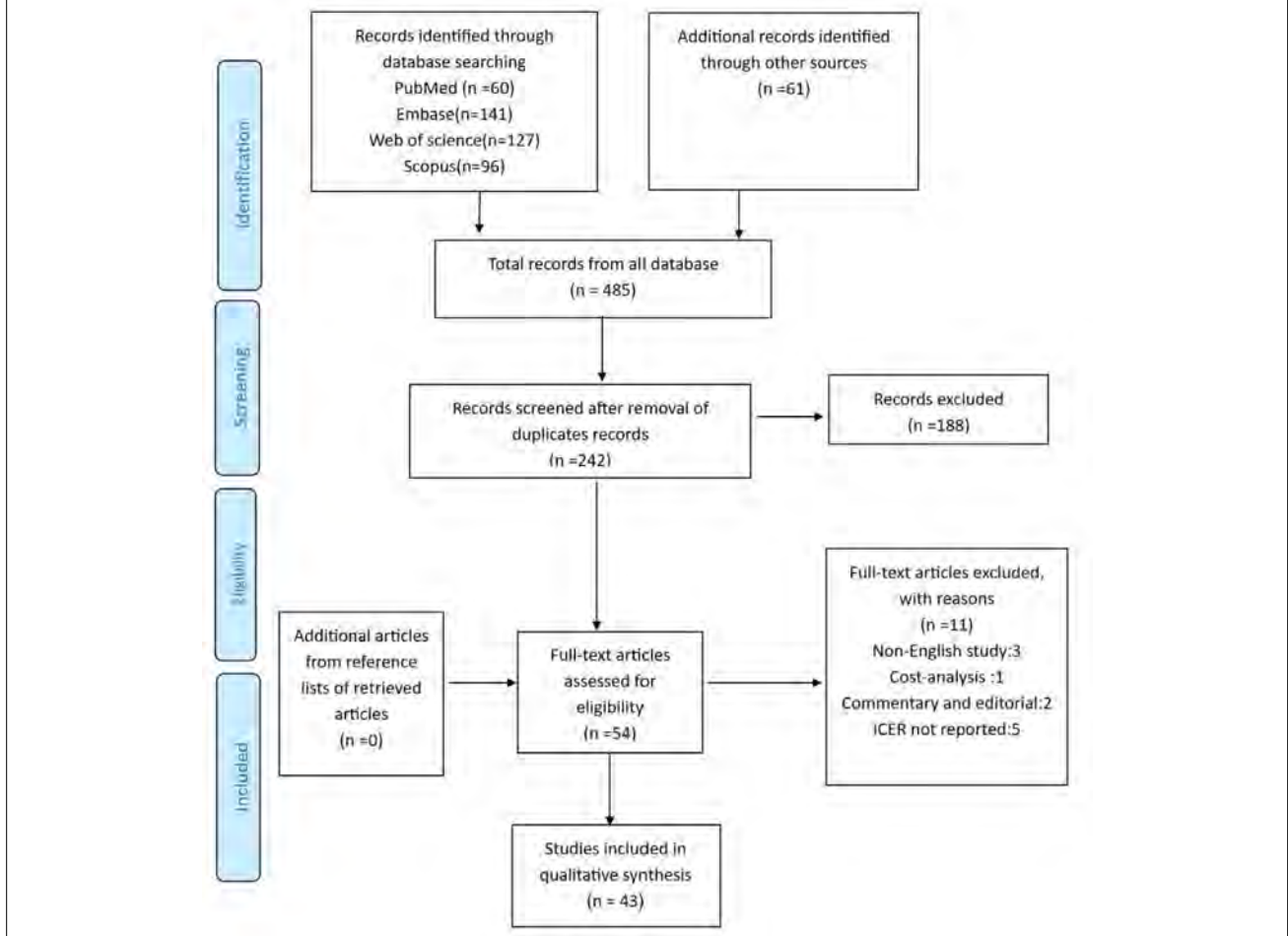
Most studies were conducted in the United Kingdom (n=8) [21, 22, 29, 32, 36, 39, 40, 53], the United States (n=6) [14, 25, 31, 43, 44, 54], and the Netherlands (n=6). This is followed by Canada [16, 38, 50], Sweden [18, 32, 37], and Germany [30, 42, 46], each with three studies; France [15, 27], Spain [23, 32], Colombia [33, 49], and Australia [26, 45], each with two studies; and finally, China [17], Japan [24], Thailand [17], Taiwan [19], Uzbekistan [13], South Korea [47], Italy [55] Mexico [52], the Czech Republic [32], and Israel [41], each with one study.

In total, 25 studies were conducted on patients with resistant hypertension [13-15, 21, 26-31, 33, 40, 41, 44-55] and 19 studies on patients with uncontrolled hypertension [16-20, 22-25, 32, 34-39, 42, 43, 55]. An empiric cost-effectiveness study was based on randomized controlled trials (RCTs). [27], while 42 studies used a modelling approach with multiple data sources [13-26, 28-55].

Also, cost-utility analysis was used in 30 studies [13-26, 28-43, 45-51, 53-55] and cost-effectiveness analysis in 11 studies [14, 15, 17, 21, 26-30, 44, 52]. Twenty-two studies used a payer perspective [16, 18, 21, 22, 24, 25, 27-30, 34, 36, 38, 39, 45, 47-49, 51-53, 55]; eight studies used a health system perspective [14, 15, 17, 23, 26, 33, 37, 50] and three studies used a societal perspective [19, 20, 31]. In eight studies, the perspective used was not specified [32, 35, 40, 42-44, 46, 54]. The study time horizon was reported to be at least 6 months and up to the end of the participants' lives. In two studies, the time horizon was not precisely specified [40, 48]. Other study characteristics (WTP threshold, discount rate) are reported in Tables I-II.

FINDINGS OF QUALITY ASSESSMENT

QHEs score was 89.6 points (SD=7.76 points). Table III describes the results of quality assessment in the literature based on the QHEs instrument. There were 17 studies with scores above 75, which are considered high-quality studies. The quality of two studies was rated as medium (51-74) [13, 27]. A majority of studies did not justify using the study perspective. There was no mention of the

Fig. 1. PRISMA flow chart for study selection.

funding source in one study [13]. In all the studies that were evaluated, full scores were achieved on each of the checklist items (Target, subgroup analysis, methods for extracting and valuing benefits, valid criteria and scales for outcomes, and conclusions (Fig. 2).

FINDINGS OF COST-EFFECTIVENESS OF RDN IN PATIENTS WITH UNCONTROLLED HYPERTENSION

Table IV presents the total costs, clinical outcomes, and ICERs for each comparator in the present study. According to Kandzari et al, catheter-based radiofrequency renal denervation (RF-RDN) was more cost-effective than standard care in the United States. SPYRALHTN-ON MED trial data were used to derive efficacy data. Applying the OSBP (office systolic blood pressure) reductions with RF-RDN observed in the SPYRAL HTN-ON MED trial, the relative risks of stroke, myocardial infarction, and cardiovascular death over a 10-year horizon were 0.80, 0.88, and 0.85, corresponding to a 20%, 12%, and 15% reduction in the probability of these events, respectively. At the incremental cost of \$11,275, RF-RDN increased quality-adjusted life years by 0.34 compared with standard care. In this study, the incremental cost-effectiveness ratio (ICER) was \$32,732 per QALY [25].

According to Lian et al., a study of netrodRDN's cost-effectiveness from a health system perspective in Japan showed a 30.61 reduction in cardiovascular, cerebrovascular, and renal events when compared with drug therapy. In this study, the ICER per QALY was \$3,451 [17]. According to another Japanese study, RF RDN is associated with a reduced risk of strokes, myocardial infarctions, and heart failures. In addition, RF RDN resulted in an increase of 0.36 QALYs at an incremental cost of ¥923,723 (\$10905.77), resulting in an ICER of ¥2,565,236 (\$30285.99) per QALY [24]. A Dutch study found that RF-RDN resulted in 0.8 risk reductions for stroke, 0.88 risk reduction for myocardial infarction, 0.89 risk reduction for angina pectoris and coronary artery disease, 0.72 risk reductions for heart failure, 0.96 risk reductions for end-stage renal disease, and 0.93 risk reductions for all-cause mortality. With RF-RDN, lifetime costs increased by €4.137 (\$5250) and QALYs increased by 0.61, resulting in ICER €6.784 (\$8609.14) per QALY [20].

A cost-effectiveness study of RFRDN in Canada by McFarlane et al. found that RFRDN increased QALYs by 0.51. Its ICER was \$11,809 per QALY, which is below the Canadian WTP threshold. In Canada, RFRDN was found to be a cost-effective strategy for managing blood pressure [16]. Study results from

Tab. I. Study design and setting overview.

Row	First author (Year of publication)	Country	Population	Population	Clinical Outcome	Comparators
1	Ribichini, Flavio L. (2026)	Italy	UH And RH	On average 55 years of age	Stroke, MI, AP/CHD, HF, ESRD CVD ACD, QALYs	RF RDN and standard of care (SOC)
2	Xursandov, I. (2025)	Uzbekistan	RH	Age group between 18 and 75 years	QALYs change in office blood pressure, non-fatal mi, non-fatal stroke, cv mortality	RDN Group Pharmacotherapy Group
3	Taylor, R. S. (2025)	United States	RH	136 patients aged 18 to 75 years	LYs, QALYs	Ultrasound RDN plus SoC versus SoC alone
4	S. Taylor (2025)	Belgium, France and the Netherlands	RH	Patients aged 18-75 years	LYs, QALYs	Ultrasound RDN plus SoC compared with SoC alone
5	McFarlane, P. A. (2025)	Canada	UH	On average, 55 years old with a baseline Office-based systolic blood pressure of 163 mmHg, and were on treatment with one to three anti-hypertensive medications	QALYs, stroke, MI, AP/CHD HF, ESRD, CVD, ACD	Radiofrequency renal denervation (RF RDN) vs. SoC
6	Lian, D. (2025)	China, Japan, and Thailand	UH	Initial age of 50 years	AMI, HF, sudden cardiac death, ischemic stroke, hemorrhagic stroke, transient ischemic attacks ESRD, Lys and QALY	Netrod RDN treatment plus antihypertensives compared with antihypertensives alone
7	Kahan, T. (2025)	Sweden	UH	Average 55 years of age, 19.9% female, with a baseline office SBP of 163 mmHg	Stroke, MI, AP/CHD HF, ESRD, CVD, ACD, QALY	RF RDN vs. SoC
8	Huang, H. C. (2025)	Taiwan	UH	Average age of participants was 55 years and the average baseline Office-based systolic blood pressure was 163 mmHg	Stroke, MI, AP/CHD, HF, ESRD, CVD, ACD, QALYs	RDN with standard-of-care (SoC) against SoC only
9	Daemen, J. (2025)	Netherlands	UH	Mean age 55 years, and prescribed one to three antihypertensive medications	QALYs	RF RDN vs. SoC
10	Taylor, R. S. (2024)	UK	RH	Patients aged -75 years with office BP ≥140/90 mmHg	Lys, QALYs, ESRD, CHD/ AP, MI, HF, stroke, recurrent stroke, mortality	Addition of the Paradise uRDN System compared with SoC alone
11	Sharp, A. S. P. (2024)	UK	UH	55 years of age with a baseline oSBP of 163 mmHg	Stroke, MI, AP/CHD, HF, ESRD CVD, ACD, QALYs	RF RDN vs. SoC
12	Rodríguez-Leor, Oriol (2024)	Spain	UH	, on average, aged 55 years, with a baseline office SBP of 163 mmHg	Stroke, MI AP/other CHD, HF ESRD, CVD, ACD Lys and QALYs	RF RDN in addition to SoC
13	Kario, K. (2024)	Japan	UH	Averaged 55 years of age, with a baseline SBP of 163 mmHg	QALYs, stroke, MI, and HF	RF RDN against SoC

Economic evaluation (model)	Perspective	Time horizon	Discount rate (%)	Sensitivity analysis	Willingness to pay
CUA (Markov model)	Payer perspective	Lifetime	3.0% per annum	Multi-way sensitivity and PSA	€25,000 per QALY
CUA (Markov model)	NR	10 years	0 and 6	DSA and PSA	\$5,000 per QALY
CEA and CUA (Markov model)	US health care system	Lifetime	3	One-way sensitivity analysis, scenario assessments and PSA	\$50,000 to \$100,00 and 0 per QALY
CEA and CUA (Markov model)	Health care system	Lifetime	For the French model, costs, QALYs and LYs were discounted at 2.5% annually up to 10 years, and 1.5% annually	One-way sensitivity analysis, PSA and scenario analyses	Belgium: WTP €40,000, France: WTP €50,000 and Netherlands: WTP €20,000
CUA (Markov model)	Publicly-funded Canadian healthcare payer's perspective	10-year and lifetime horizon	1.5	One-way sensitivity analyses, scenario analyses and PSA	\$50,000 per QALY
CEA and CUA (Markov model)	Healthcare system	30-year horizon(lifetime)	At 2% (Japan), 3% (Thailand), and 5% (China) per year	Univariate, PSA and scenario analyses	\$37,624 for Mainland China, \$101,849 for Japan, and \$21,894 for Thailand
CUA (Markov model)	Healthcare payer, with the societal perspective explored as a scenario	10-year and lifetime	3	One- and multi-way, and PSA	SEK 500,000 per QALY gained
CUA (Markov model)	Societal perspective	10-year and lifetime	3	One-way sensitivity analysis, scenario and PSA	Taiwan 1,000,000 TWD and 3,000,000 TWD per QALY
CUA (Markov model)	Societal perspective	10-year and lifetime	costs and effects were discounted 3.0% and 1.5%, respectively	DSA and PSA	€20,000 per QALY gained
CEA and CUA (Markov model)	Payer	Lifetime	3.5	One-way and PSA	£20,000-£30,000 (€23,214-€34,821) per QALY
CUA (Markov model)	UK healthcare payer perspective (National Health Service (NHS)	10-year and lifetime	3.5	Scenario analyses One-way and PSA	£20-30,000 per QALY gained
CUA (Markov model)	Spanish National Health System perspective	10-year and lifetime	3	DSA and PSA	€25,000 per QALY gained
CUA (Markov model)	public healthcare payer's perspective	Lifetime	2	DSA and PSA	¥5000,000 per QALY gained

Tab. I (follows). Study design and setting overview.

Row	First author (Year of publication)	Country	Population	Population	Clinical Outcome	Comparators
14	Kandzari, D. E. (2024)	United States	UH	On average 55 years old and had a baseline OSBP of 163 mm Hg	QALYs, stroke, MI, and cardiovascular death	RF RDN against SoC
15	Chowdhury, E. K. (2018)	Australia	RH	Aged 60 years at baseline, and without prior cardiovascular disease	Life year gained, QALY gained	RDN compared with (SoC)
16	Bulsei, J. (2018)	France	RH	Patients with resistant hypertension (DENERHTN) trial	mmHg reduction in daytime ambulatory SBP, risk of CV events or death	RDN with standardized stepped-care antihypertensive treatment (SSAHT) compared to SSAHT alone
17	Henry, T. L. (2015)	Netherlands	RH	Patients with resistant hypertension	LY, QALYs, AP, MI, HF, stroke, ESRD	RDN was compared with SoC
18	Gladwell, D. (2014)	UK	RH	Average age of 58 years, 43% were female, 16% were smokers, and 34% had an existing diagnosis of diabetes mellitus. Patients had a reported baseline SBP of 178 mmHg	LY, QALYs, stroke ESRD, HF, AP/CHD, MI	RDN vs. SoC
19	Dorenkamp, Marc (2013)	Germany	RH	With a baseline office SBP of 160 mmHg, 30-99 years of age free from prior CVD or renal disease.	Stroke, MI, ESRD, HF, Lys, HF, QALYs	RDN vs. best medical therapy (BMT)
20	Geisler, B. P. (2012)	United States	RH	The mean baseline SBP was 178 mm Hg mean age of 58 (55 to 61) years, were 43% female, had a diabetes mellitus prevalence of 34%, and a current smoker prevalence of 16%	Stroke, MI, all CHD, HF, ESRD, QALYs	RDN plus the existing SoC-3 or more antihypertensive medications
CEA: cost-effectiveness analysis; CUA: cost-utility analysis; QALYs: quality-adjusted life years; LYs: life years, RDN: renal denervation; MI: myocardial infraction, HF: Heart failure; ESRD: End-stage renal disease; AP: angina pectoris, CHD: coronary heart disease; PSA: probabilistic sensitivity analysis; DSA: deterministic sensitivity analysis, NR: not reported						

Taiwan also showed that RFRDN results in incremental costs of NT \$216,381 and QALY of 0.25 [19]. Sharp et al. reported, in a cost-effectiveness study conducted in the UK health system for patients with UH, that RFRDN led to a 10-year reduction in the relative risk of clinical events (strokes, MI, and heart failure) compared with the control group. This intervention resulted in an increase of 0.35 QALY at an incremental cost of £4,763 (\$7,515.98) and an ICER of £13,842 (\$21,274.49) per QALY [22]. Treatment costs for UH were highest in the United States

and Japan, and lowest in Thailand and China. In the United States, the difference between the two treatments was \$11,275; in Japan, it was \$10,905; and in Thailand and China, it was \$7,051 and \$7,250, respectively (Fig. 3). QALY estimates were highest in Japan and Canada, with a difference of 0.36 and 0.51, respectively. The lowest estimates were found in Thailand and China, with a difference of 0.37 (Fig. 5). Taiwan had the highest ICER (63,802.35), while Canada had the lowest (\$10,055.5) (Fig. 8).

Economic evaluation (model)	Perspective	Time horizon	Discount rate (%)	Sensitivity analysis	Willingness to pay
CUA (Markov model)	Medicare payer perspective	Lifetime	3	1-way sensitivity, multiway sensitivity, threshol, and PSA	\$50,000 per QALY and \$150,000 per QALY
CEA and CUA (Markov model)	Australian health system	20-year and lifetime	5	One-way sensitivity analyses and PSA	Australian dollar (AUD) 50,000 per life year gained or per QALY
CEA (DENERHTN) trial	French healthcare perspective (compulsory health insurance, complementary health insurance and patient co-payments)	6 months	Not applicable	PSA	Threshold of e1 540/ mmHg reduction
CUA and CEA (Markov model)	Payer perspective	Lifetime	Costs: 4.0% LYs and QALYs: 1.5%	Scenario analysis, one-way sensitivity analysis and PSA	E10,000-80,000/QALY
CEA and CUA (Markov model)	Healthcare payer	Lifetime	3.5	DSA and PSA	£20,000 per QALY
CEA and CUA (Markov model)	Payer's perspective	Lifetime	3	One-way and PSA	E35 000/QALY
CUA (Markov model)	Societal perspective	10-year and lifetime	3	DSA and PSA	\$50,000 per QALY

FINDINGS OF COST-EFFECTIVENESS OF RDN IN PATIENTS WITH RESISTANT HYPERTENSION

Taylor et al examined the cost-effectiveness of ultrasound RDN (uRDN) plus standard care compared with standard care from a US health system perspective using a Markov model. The effectiveness inputs for this study were derived from the RADIANCE-HTN TRIO trial. Based on the results of this study, uRDN reduced systolic blood pressure by 5.8 mmHg compared to standard care alone. On average, patients who received

uRDN gained 15 years of life and 12.01 QALYs. On the other hand, patients receiving standard care gained 14.29 years of life and 11.42 QALYs. The uRDN intervention, however, was associated with higher lifetime costs than standard care alone (\$110,476 vs. \$102,875 per patient, ICER=\$129,000 per QALY) [14]. According to the results of the study by Weber et al in the US, the Vessix system for RDN is cost-effective compared with pharmacotherapy. There was an ICER of \$18,819 per life year gained, which is below the US WTP [44].

Tab. II. The characteristics of conference abstracts included in the present study.

First author (Year of publication)	Country	Population	Compared interventions	Type of economic evaluation (Model)	Perspective	Time horizon	Willingness to pay	Main findings (US\$2024)
Schmieder, R. E. (2025)	UK, Spain, Netherlands, Belgium, Sweden, and the Czech Republic	Uncontrolled hypertension	RF RDN as an adjunct treatment option	CUA (Markov model)	NC	Lifetime	£20,000, €25,000, €20,000, €40,000, SEK 500,000, and 1,200,000 Kc per QALY gained in the UK, Spain, Netherlands, Belgium, Sweden, and Czech Republic settings, respectively	For Group 1, incremental costs, QALYs, and resulting ICERs with RF RDN were: UK: £1,451 (\$2,113.41), 0.82 QALYs, £1,760 (\$2,563.47) per QALY gained. Spain: €2,338 (\$3,825.44), 0.82 QALYs, €2,849 (\$4,661.54) per QALY gained. Netherlands: -€3,447 (\$4,344.29), 1.33 QALYs, dominant. Belgium: €686 (\$941.40), 1.23 QALYs, €556 (\$763.00) per QALY gained. Sweden: SEK 24,791 (\$2,901.98), 1.03 QALYs, SEK 24,134 (\$2,825.07) per QALY gained. Czech Republic: 154,604 Kc (\$11,601.76), 1.01 QALYs, 152,604 Kc (\$11,451.68)
Eusse, C. A. (2025)	Colombia	Resistant hypertension	RF RDN	CUA (Markov model)	Healthcare system	Lifetime	Three times the Colombian gross domestic product (GDP) per capita per QALY gained	Compared to a sham control and over a patient's lifetime, RF RDN led to a 0.37 QALY gain at an incremental cost of \$4,100 (\$3,986.90), yielding an ICER of \$11,017 (\$10,713.10) per QALY gained, below the WTP threshold of \$23,750 (\$23,094.87) per QALY
Ryschon, A. M. (2024)	Belgium	Uncontrolled hypertension	RF RDN	CUA (Markov model)	Healthcare payer	10 years and lifetime	€40,000 per QALY gained	Compared to sham therapy, RF RDN led to an incremental QALY gain of 0.57 at an incremental cost of €5,218 (\$6465.92), yielding an ICER of €9,089 (\$11262.70) per QALY gained, substantially below willingness-to-pay thresholds referenced for Belgium
Pietzsch, J. B. (2024)	Netherlands	Uncontrolled hypertension	RF RDN	CUA (Markov model)	NC	10 years and lifetime	€20,000 per QALY gained	Over a lifetime horizon, the therapy added 0.61 QALYs with an incremental cost of €3,828 (\$4857.87), yielding an ICER of €6,277 (\$7965.74) per QALY gained, below the willingness-to-pay threshold of €20,000 per QALY gained
Lobo, M. D. (2024)	UK	Uncontrolled hypertension	RDN	CUA (Decision-analytic model)	NHS healthcare system (payer)	10 years and lifetime	£20-30,000 per QALY gained	RDN resulted in an increase in health benefit over a patient's lifetime, adding 0.35 QALYs (0.44 based on ON MED OUS data) at a concurrent cost increase of £4779 (\$6886.17), resulting in an ICER of £13,629 (\$19638.33) per QALY gained
Kahan, T. (2023)	Sweden	Uncontrolled hypertension	RF-RDN	CUA (Markov model)	Swedish healthcare perspective	10 years and lifetime	SEK 500,000 per QALY gained	RDN resulted added 0.43 QALYs at a concurrent cost increase of SEK61,791 (\$7271.23) over lifetime, resulting in an ICER of SEK143,887 (\$16931.84) per QALY gained
Feldman, R. (2023)	Canada	Uncontrolled hypertension	RF-RDN	CUA (Markov model)	Payer perspective	10 years and lifetime	\$50,000 per quality-adjusted life year (QALY) gained	RF RDN added 0.38 QALYs (13.69 vs. 13.31) at a concurrent cost increase of \$8,935 (\$7608.25) (\$63,708 (\$54248.09) vs. \$54,772 (\$46638.98)), resulting in an ICER of \$23,442 (\$19961.13) per QALY gained

Tab. II (follows). The characteristics of conference abstracts included in the present study.

First author (Year of publication)	Country	Population	Compared interventions	Type of economic evaluation (Model)	Perspective	Time horizon	Willingness to pay	Main findings (US\$2024)
Sharp, A. S. P. (2022)	UK	Uncontrolled hypertension	RDN	CUA (Decision- analytic model)	NHS healthcare system (payer)	Lifetime	£20-30,000 per QALY gained	RDN resulted in an increase in health benefit over a patient's lifetime, adding 0.48 QALYs (0.52 based on 3-year data) at a concurrent cost increase of £3,428 (\$5409.36), resulting in an ICER of £7,169 (\$11312.62) per QALY gained (for 6 months, base-case analysis)
Kirtane, Ajay (2022)	UK	Resistant hypertension	Paradise Ultrasound RDN System compared with standard of care (SoC)	CUA (State- transition model)	NC	NC	£20,000 to £30,000 (\$27,346 to \$41,019)	A mean reduction in Office SBP of 8.5 mmHg with ultrasound RDN resulted in an average improvement in both absolute life years (LYs) and quality-adjusted life years (QALYs) gained compared with SoC (15.82 vs. 15.41 LYs and 12.68 vs. 12.34 QALYs). The overall cost per QALY gained with ultrasound RDN is estimated at £14,798 (\$23351.12)
Arbel, Yaron (2022)	Israel	Resistant hypertension	RDN compared to a usual care	CUA (Markov model)	HMO perspective	Lifetime	NC	Patients that underwent RDN had reduced event rates and that lead to an increased median survival of 18.2 years compared to 17.0 years for usual care. The discounted lifetime incremental cost-effectiveness ratio was \$16,119 (\$17090.27) per QALY
Pietzsch, J. B. (2018)	Germany	Uncontrolled hypertension	Catheter-based renal denervation (RDN)	CUA (Decision- analytic model)	NC	Lifetime	€100,000/QALY	In the base case, RDN had a lifetime additional clinical benefit of 0.31 QALYs (17.3 vs. 17.0 yrs). Concurrent discounted costs were €5,347 (\$8498.64) higher for RDN (€25,876 (\$41127.87) vs. 20,529 (\$32629.23)), resulting in a lifetime ICER of €33,741 (\$53628.66) per QALY gained
Pietzsch, J. B. (2016)	US	Uncontrolled hypertension	DN plus best medical therapy versus best medical therapy alone	CUA (Decision- analytic model)	NC	Lifetime	\$100k/QALY gained	Projected ICERs: \$13,326 (\$16999.66) per QALY
Weber, M (2014)	US	Resistant Hypertension	Vessix System for renal denervation (RDN) compared to best medical therapy (BMT)	CEA (Markov model)	NC	10 years and lifetime	NC	Incremental cost per life years gained: 10 years: \$18,819 (\$24490.08). Lifetime: \$2,637 (\$3431.66)
Tilden, D. (2014)	Australia	Resistant Hypertension	RDN plus standard of care (SOC) vs SOC alone	CUA (Markov model)	Payer	Lifetime	NC	RDN was associated with higher incremental costs \$5,951.04 (\$5297.69) and additional QALYs (0.4296) resulting in an incremental cost per QALY of \$13,852 (\$12331.23)
Sapoval, M. (2014)	Germany	Resistant hypertension	Vessix System for renal denervation (RDN)	CUA (Markov model)	NC	Lifetime (10 years)	35,000€/QALY	The incremental cost per life year gained (LYG) was €5,899 and per QALY gained was €7,986 (\$13564.41)
Kang, H. Y. (2014)	South Korea	Resistant Hypertension	standard of care (SOC) alone with 'SOC plus RDN.	CUA (Markov model)	National Health Insurance	Lifetime	Per-capita GDP in Korea in 2012 26 million KRW	The incremental cost-utility ratio (ICUR) was 19.69 million (\$27592.94) KRW per QALY gained

Tab. II (follows). The characteristics of conference abstracts included in the present study.

First author (Year of publication)	Country	Population	Compared interventions	Type of economic evaluation (Model)	Perspective	Time horizon	Willingness to pay	Main findings (US\$2024)
Henry, T. (2014)	Netherlands	Resistant Hypertension	RDN was compared with standard of care (SoC)	CUA (Markov model)	Health care payer	NC	€10,000-80,000 per QALY	RDN resulted in an increase in QALYs of 0.89 at an incremental cost of €1,315 (\$2082.40) per patient resulting in an ICER of just €1,474 (\$2334.18). RDN therapy was cost effective
Valencia, J. E. (2013)	Colombia	Resistant arterial hypertension	RDN compared with standard of care (SC)	CUA (Markov model)	Payer perspective	Lifetime	NC	RDN achieved higher QALY's (10.27 vs. 9.72) at a higher cost during their lifetime [COP\$91406.781 (\$116.13) vs. COP\$80799.285 (\$102.65)]. ICER of COP\$19301.843 (\$24.52)
Sadri, H. (2013)	Canada	Resistant hypertension	RDN compared to optimal pharmacotherapy (OPT)	CUA (Markov model)	Health care system	Lifetime	\$25,000 and \$50,000/QALY	RDN increased QALYs by 0.60 and LYs by 0.65 compared to OPT. ICERs for RDN were \$5,648 (\$6098.01)/QALY and \$5,171(\$5583.01)/LY
Jugrin, A. V. (2013)	Belgium	Resistant hypertension	RDN as compared to current standard of care (SoC)	CUA (Markov model)	Payer perspective	Lifetime	20,000€ /QALY	Incremental cost-utility ratio (ICUR) of €3,020 (\$4878.94)/QALY. Catheter-based RDN procedure could be a cost-effective strategy
Ceballos, R. M. (2013)	Mexico	Resistant Hypertension	RDN compared to standard of care (SoC)	CEA (Markov model)	Public payer perspective	Lifetime	One GDP/capita of MXN\$ 139,900 (US\$ 10,630) per additional life year	Lifetime ICER was estimated at US\$ 14,750 (\$19553.89 per LY gained, and had an incremental cost of MXN \$117,916 (\$156319.73) compared to SoC
Pietzsch, J. B. (2012)	UK	Resistant hypertension	Catheter-based renal denervation (RDN)	CUA (Markov model)	UK National Health Service perspective (payer)	Lifetime	NC	ICER: £4,870/QALY (\$2869.08). RDN reduces and delays cardiovascular events and is a cost-effective therapy
Pietzsch, J.B. (2012)	US	Resistant hypertension	RDN	CUA (Markov model)	NC	Lifetime	\$50-100K/QALY	ICERs were well below commonly accepted willingness-to-pay thresholds (\$50-100K/QALY)

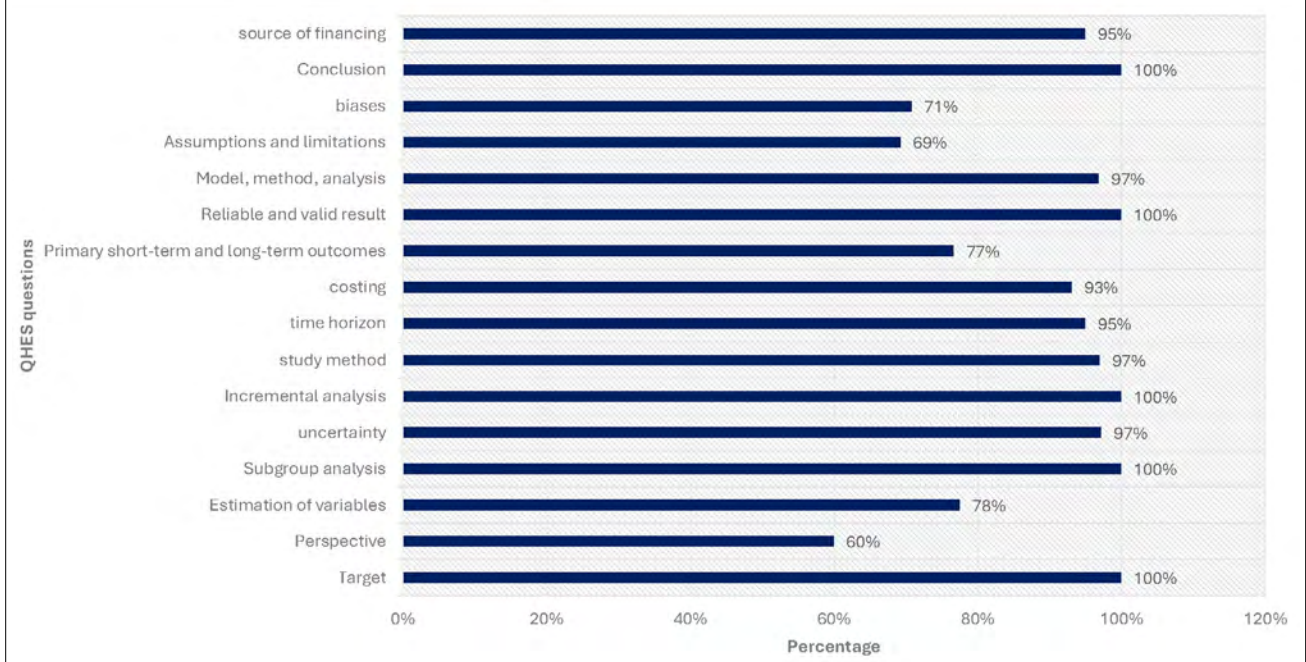
PSA: Probabilistic sensitivity analysis; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; NC: No clear; QALY: Quality-adjusted life years; RDN: radiofrequency renal denervation.

According to Henry et al., RDN was found to be cost-effective from a payer's perspective in the Netherlands. As compared to standard care, RDN generated 0.89 additional QALYs and cost €2,600 (\$4,356.98) more. In terms of QALYs, the ICER was €2,914 (\$4,883.17) [28]. Another cost-effectiveness study conducted in the Netherlands showed that URDN resulted in an incremental cost of €1,594 (\$2,108.31) when compared with SOC, and the difference in life years and QALYs was estimated to be 1.21 and 1.0, respectively. The ICER per life year gained was €1,321 (\$1,747.23) and the ICER per QALY gained was €1,654 (\$2,187.67) [15].

In Germany, Dorenkamp et al evaluated the cost-effectiveness of RDN for men and women with resistant hypertension at different ages. A payer perspective was used in this study. This study found that the cost-effectiveness ratio increased with age, indicating that RDN was more cost-effective in the younger age groups. In addition, RDN's cost-effectiveness was most

affected by its effectiveness in reducing systolic blood pressure, the number of non-responders to treatment, and the procedure's cost [30]. In addition, Taylor et al. in the UK found that RDN improved mean life years and QALY compared with standard care alone (0.63), with an ICER of £5,600 (\$5,937.43) per QALY [21]. The results of another UK study showed that uRDN generated 12.68 QALYs, while standard care generated 12.34. This study reported an ICER of £14,798 (\$23,351.12) [40]. In France, URDN in patients with resistant hypertension resulted in an improvement in life years by 1.18 and QALY by 0.9. ICER was €6,261 (\$7,248.75) per QALY and €4,996 (\$6,582.13) per life year gained. In Belgium, URDN improved life years by 1.22 and QALYs by 0.97 (ICER per QALY=€4,426 (\$5,674.46) [15].

Patients with resistant hypertension in Uzbekistan had a different cost pattern than those in other countries, with standard care costing \$1,700 more than RDN. In contrast, RDNs cost more than standard care in

Fig. 2. Results of quality assessment of the methodology of studies using QHES checklist.

the UK and other countries (for example, in the UK the difference was reported to be \$5,856). Among the countries, the United States had the highest cost level, with \$117,132 for RDN and \$109,073 for standard care (Fig. 4). The Netherlands and Belgium had the highest QALY gains, while Uzbekistan had the lowest, with a difference of 0.4 between the two treatment strategies (Fig. 6). The Netherlands had the lowest ICER (\$2,187.5) and Australia had the highest (\$39,613) in patients with resistant hypertension (Fig. 7).

Discussion

The purpose of this systematic review was to examine the evidence on the cost-effectiveness of RDN in treating patients with RH and UH. RDN appears to be a cost-effective treatment option in many countries based on the results of the studies. In spite of the higher initial cost of RDN compared to standard medical treatment, the reduction in blood pressure and, consequently, the reduction in cardiovascular events can lead to increased QALYs. In particular, this treatment advantage can be seen in the prevention of heart failure (a 28% reduction in risk; relative risk [RR]=0.72) and stroke (a 20% reduction; RR=0.80), among other clinical outcomes. In addition, other clinical outcomes demonstrated consistent downward trends, including coronary artery disease and angina (an 11% reduction; RR=0.89), myocardial infarction (a 12% reduction; RR=0.88), and advanced renal disease (a 4% reduction; RR=0.96), suggesting that RDN may have a preventive and long-term impact on the management of high-risk patients [16, 18, 20, 22, 23,

25]. In addition, RDN treatment reduced cardiovascular mortality by 30% and all-cause mortality by 15%, emphasizing its clinical superiority for improving patient survival [31].

To simulate clinical and economic outcomes over a lifetime horizon, most of the studies included in this review used Markov decision models. The economic analysis of the studies was based on the assumption that the reduction in systolic blood pressure caused by RDN leads to a reduction in the risk of clinical events in the long term, as demonstrated by available epidemiological studies, due to the lack of clinical trials that directly assessed the impact of RDN on serious clinical outcomes, including death, stroke, or major cardiovascular events. In spite of these general results, different studies have reported varying cost-effectiveness rates. It is likely that these differences are caused by differences in intervention costs and demographic characteristics among patients across countries. However, most of these studies reported ICERs below WTP. The heterogeneity of study results may also be caused by differences in model assumptions, risk prediction equations, and cost sources. According to the reviewed studies, patient characteristics have a significant impact on RDN's economic outcomes. It was found that younger patients benefit the most economically from this intervention in a German study [30]. In younger patients, due to a longer life expectancy, lower blood pressure can prevent a greater number of cardiovascular events, increasing QALYs. As preventing costly events such as stroke and myocardial infarction results in significant savings in healthcare costs, targeting patients with

Tab. III. Findings of methodology quality assessment with QHES checklist.

Study (year of publication)	Target	Perspective	Estimation of variables	Subgroup analysis	Uncertainty	Incremental analysis	Study method	Time horizon
Ribichini (2026)	7	4	6	1	9	6	5	7
Xursandov, I. (2025)	7	0	8	1	9	6	2	3
Taylor, R. S. (2025)	7	2	6	1	9	6	5	6
S. Taylor (2025)	7	2	6	1	9	6	5	7
McFarlane, P. A. (2025)	7	2	6	1	9	6	5	7
Lian, D. (2025)	7	2	6	1	9	6	5	7
Kahan, T. (2025)	7	2	6	1	9	6	5	7
Huang, H. C. (2025)	7	2	6	1	9	6	5	7
Daemen, J. (2025)	7	4	6	1	9	6	5	7
Taylor, R. S. (2024)	7	4	6	1	9	6	5	7
Sharp, A. S. P. (2024)	7	4	6	1	9	6	5	7
Rodríguez-Leor, Oriol (2024)	7	2	6	1	9	6	5	7
Kario, K. (2024)	7	4	6	1	9	6	5	7
Kandzari, D. E. (2024)	7	2	6	1	9	6	5	7
Chowdhury, E. K. (2018)	7	2	6	1	9	6	5	7
Bulsei, J. (2018)	7	2	8	1	4	6	5	7
Henry, T. L. (2015)	7	2	6	1	9	6	5	7
Gladwell, D. (2014)	7	2	6	1	9	6	5	7
Dorenkamp, Marc (2013)	7	2	6	1	9	6	5	6
Geisler, B. P. (2012)	7	2	6	1	9	6	5	6

higher cardiovascular risk can also increase the cost-effectiveness of RDN. RDN’s cost-effectiveness may be affected by assumptions about baseline cardiovascular risk, according to economic modeling studies. As an example, in a study by Chowdhury et al., it was reported that this intervention was only cost-effective when the 10-year risk of cardiovascular disease exceeded a certain threshold (approximately 13.2%) [26]. Many studies have shown that the cost-effectiveness of RDN varies greatly based on certain variables. An important factor is the magnitude and persistence of the reduction in systolic blood pressure following intervention [26, 30, 31]. In addition, the proportion of patients who do not respond to treatment [30], the cost of RDN treatment [17, 19,

20, 22-26, 28-30, 55], and the degree of reduction in the risk of cardiovascular events have been reported as other determinants of economic outcomes [15, 16, 19-22, 24, 25, 55]. As a result of these findings, appropriate patient selection, along with reduced costs associated with RDN, may increase RDN’s economic value. Despite the promising results, some limitations should be considered when interpreting the findings of this review. The majority of available studies are based on economic modeling, and long-term real-world data on RDN’s effectiveness and sustainability are still limited. As well, many models have extrapolated results from short-follow-up clinical trials to a lifelong time horizon, which may introduce uncertainty. Cost-effectiveness estimates may be affected if real-world treatment effects decline over

Costing	Primary short-term and long-term outcomes	Reliable and valid result	Model, method, analysis	Assumptions and limitations	Biases	Conclusion	Source of financing	Total
8	5	7	8	5	4	8	3	93
4	2	7	8	0	0	8	0	65
8	5	7	8	6	6	8	3	93
8	5	7	8	5	4	8	3	91
8	5	7	8	6	5	8	3	93
8	5	7	8	4	4	8	3	90
8	5	7	8	5	4	8	3	91
8	5	7	8	5	6	8	3	93
8	5	7	8	6	5	8	3	95
8	5	7	8	6	5	8	3	95
8	5	7	8	6	6	8	3	96
8	5	7	8	5	3	8	3	90
8	5	7	8	6	4	8	3	94
8	5	7	8	6	6	8	3	94
6	3	7	8	6	5	8	3	89
3	2	7	3	2	2	8	3	70
8	5	7	8	5	4	8	3	91
8	5	7	8	2	2	8	3	86
8	5	7	8	5	4	8	3	90
8	5	7	8	6	6	8	3	93

time. The lack of rigorous monitoring or assessment of patient compliance with antihypertensive drug therapy is an important limitation of the studies included in this review. The effectiveness of RDN compared to standard medicine could be affected by nonadherence to drug regimens in treatment-resistant hypertension. It is assumed in many economic models that patients in the intervention and comparison groups take their medications similarly. In real-world settings, adherence may vary. In the absence of accounting for this variable, the cost-effectiveness ratio can be overestimated or underestimated, with consequent changes in the clinical effects. According to the available evidence, RDN could be a potentially cost-effective treatment option for patients with resistant or uncontrolled hypertension, particularly when used in

patients with higher cardiovascular risk. It is, however, important to conduct studies based on real-world data and long-term follow-up to better assess the sustained clinical and economic effects of this intervention at the health policy level.

Conclusion

Based on the studies included in this systematic review, RDN has been reported as a cost-effective intervention in most cost-effectiveness models. To more accurately determine the economic value of RDN, further economic studies with long-term clinical data and in different health system settings are necessary.

Tab. IV. Intervention cost and output results.

ICER (US \$2,024)	Mean of LYG/QALY		Total cost (US \$2,024)	Comparators		First author (Year of publication)
	QALY	LYG				
Reference group	14.13	-	€33.900 (\$54,666.47)	SOC		Ribichini, Flavio L. (2026)
Incremental Cost per QALY: €8.282 (\$13,355.39)	14.54	-	€37.318 (\$60,178.26)	RF RDN		
Incremental Cost per QALY: \$4,150 (\$4035.52)	6.85	-	\$12,500 (\$12,155.20)	RDN Group		Xursandov, I. (2025)
	6.45	-	\$14,200 (\$13,808.30)	Pharmacotherapy Group		
Incremental Cost per QALY: \$129,900 (\$13,677.30)	12.01	15	\$110,476 (\$117,132.83)	Ultrasound RDN plus SoC		Taylor, R. S. (2025)
Incremental Cost per LYG: \$10,645 (\$11,286.42)	11.42	14.29	\$102,875 (\$109,073.83)	SoC alone		
Incremental Cost per QALY: €4.426 (\$5,674.46)	14.17	17.94	€44.087 (\$56,522.80)	Soc alone	Belgium	S. Taylor (2025)
Incremental Cost per LYG: €3.528 (\$4,523.16)				URDN + Soc		
Reference group	15.14	19.15	€48.378 (\$62,024.18)	URDN + Soc	France	
Incremental Cost per QALY: €6.261 (\$7,248.75)	13.77	17.43	€48.795 (\$64,286.48)	Soc alone		
Incremental Cost per LYG: €4.996 (\$6,582.13)				URDN + Soc	The Netherlands	
Reference group	14.71	18.61	€54.692 (\$72,055.67)	URDN + Soc		
Incremental Cost per QALY: €1.654 (\$2,187.67)	14.18	17.94	€55.478 (\$73,378.28)	URDN + Soc		
Incremental Cost per LYG: €1.321 (\$1,747.23)						
Reference group	15.15	19.15	€57.072 (\$75,486.59)	URDN + Soc	Soc	McFarlane, P. A. (2025)
Reference group	15.30		\$67,940 (\$57,851.69)			
Incremental Cost per QALY: \$11,809 (\$10,055.50)	15.81		\$73,971 (\$62,987.15)	RDN		
Incremental Cost per QALY: \$19,049 (\$19,480.52)	13.27	14.27	\$17,260 (\$17,650.99)	RDN group	Mainland China	Lian, D. (2025)
Incremental Cost per LYG: \$22,046 (\$22,545.4)				Control group		
Reference group	12.90	13.95	\$10,170 (\$10,400.38)	Control group	Japan	
Incremental Cost per QALY: \$15,821 (\$16,179.40)	13.27	14.27	\$34,592 (\$35,375.62)	RDN group		
Incremental Cost per LYG: \$18,310 (\$18,724.78)				Control group	Thailand	
Reference group	12.90	13.95	\$28,703 (\$29,353.22)	Control group		
Incremental Cost per QALY: \$18,525 (\$18,944.65)	13.27	14.27	\$10,994 (\$11,243.05)	Control group		
Incremental Cost per LYG: \$21,410 (\$21,895.01)						
Reference group	12.90	13.95	\$4,099 (\$4,191.86)	Control group	Soc	Kahan, T. (2025)
Incremental Cost per QALY: \$139,280 (\$15,764.57)	14.34	-	\$43,4362 (\$49,163.78)			
Reference group	14.79	-	\$49,7498 (\$56,309.90)	RDN		

Tab. IV (follows). Intervention cost and output results.

ICER (US \$2,024)	Mean of LYG/QALY		Total cost (US \$2,024)	Comparators	First author (Year of publication)
	QALY	LYG			
Incremental Cost per QALY: \$85,0932 (\$63,802.35)	14.90	-	\$41,3050 (\$30,970.23)	Soc	Huang, H. C. (2025)
Reference group	15.15	-	\$62,9432 (\$47,194.42)	RDN	
Incremental Cost per QALY: €6.784 (\$8,609.14)	17.49	-	€46.769 (\$59,351.52)	Soc	Daemen, J. (2025)
Reference group	16.88	-	€42.632 (\$54,101.52)	RDN	
Incremental Cost per QALY: £5,600 (\$5,937.43)	11.49	14.37	£31,261 (\$33,144.16)	uRDN+ Soc	Taylor, R. S. (2024)
Incremental Cost per LYG: £4,578 (\$4,853.85)	12.12	15.14	£34,784 (\$36,879.94)	SoC alone	
Reference group	13.40	-	£19,223 (\$31,122.73)	Soc	Sharp, A. S. P. (2024)
Incremental Cost per QALY: £13,482 (\$21,274.49)	13.76	-	£24,484 (\$38,638.71)	Rf RDN	
Reference group	13.63	15.8	€21.045 (\$36,052.07)	Soc	Rodríguez-Leor, Oriol (2024)
Incremental Cost per QALY: €15.057 (\$25,794.06)	13.99	16.08	€26.381 (\$45,193.14)	Rf RDN	
Reference group	17.98	-	¥6,886,843 (\$81,308.25)	Soc	Kario, K. (2024)
Incremental Cost per QALY: ¥2,565,236 (\$30,285.99)	18.34	-	¥7,810,566 (\$92,214.02)	Rf RDN	
Incremental Cost per QALY: \$32,732	12.83	-	\$96,416	Rf RDN	Kandzari, D. E. (2024)
Reference group	12.49	-	\$85,141	Soc	
Reference group	11216.9	11630.8	\$26,273,976 (\$22,083,806.05)	Soc	Chowdhury, E. K. (2018)
Incremental Cost per QALY: \$47,130 (\$39,613.71) Incremental Cost per LYG: \$49,519 (\$41,621.72)	11401.5	11806.4	34,970,545 (\$29,393,447.47)	RDN	
ICER: €1.450 (\$2,186.94) / mmHg reduction in SBP	Difference reduction daytime in SBP: 5.9 mm Hg			RDN	Bulsei, J. (2018)
				Soc	
Reference group	15.13	16.87	€20.861 (\$34958.04)	Soc	Henry, T. L. (2015)
Incremental Cost per QALY: €2.914 (\$4,883.17) Incremental Cost per LYG: €3.335 (\$5,588.66)	16.02	17.65	€23.461 (\$39,315.02)	RDN	
Reference group	12.16	13.59	[quale valuta?] 17,432.15	Soc	Gladwell, D. (2014)
Incremental Cost per QALY: £4,805 (\$9,507.55) Incremental Cost per LYG: £5887 (\$11648.47)	12.77	14.09	[quale valuta?] 23,289.03	RDN	



Tab. IV. Intervention cost and output results.

ICER (US \$2,024)	Mean of LYG/QALY		Total cost (US \$2,024)	Comparators		First author (Year of publication)	
	QALY	LYG					
Reference group	13.28	14.50	€30.474 (\$53,764.62)	BMT	Men, 50	Dorenkamp, Marc (2013)	
Incremental Cost per LYG: €1.576 (\$2,780.50) Incremental Cost per QALY: €1.512 (\$2,667.59)	14.52	15.69	€32.349 (\$57,072.65)	RDN			
Reference group	10.93	12	€27.149 (\$47,898)	BMT	Men, 60		
Incremental Cost per LYG: €2.615 (\$4,613.59) Incremental Cost per QALY: €2.642 (\$4,661.22)	11.91	12.99	€29,738 (\$52,466)	RDN			
Reference group	8.18	9.04	€22.601 (\$39,874.46)	BMT	Men, 70		
Incremental Cost per LYG: €4.166 (\$7,349.98) Incremental Cost per QALY: €4.292 (\$7,572.28)	8.84	9.72	€25.434 (\$44,872.66)	RDN			
Reference group	15.75	16.84	€29.593 (\$52,210.29)	BMT	Women, 50		
Incremental Cost per LYG: €1.619 (\$2,856.37) Incremental Cost per QALY: €1.560 (\$2,752.27)	16.86	17.91	€31.325 (\$55,266.02)	RDN			
Reference group	13.24	14.25	€26.961 (\$47,566.7)	BMT	Women, 60		
Incremental Cost per LYG: €2.349 (\$4,144.29) Incremental Cost per QALY: €2.323 (\$4,098.42)	14.12	15.12	€29.005 (\$51,172.90)	RDN			
Reference group	10.18	10.98	€39.013,49 (\$39,013.49)	BMT	Women, 70		
Incremental Cost per LYG: €4.118 (\$7,265.30) Incremental Cost per QALY: €4.260 (\$7,515.83)	10.76	11.58	€24.584 (\$43,373.02)	RDN			
Dominated	12.07	17.07	\$110,349 (\$154,784.19)	Soc			Geisler, B. P. (2012)
-	13.17	18.37	\$108,580 (\$152,392.85)	RDN			
QALY: Quality-adjusted life years; LYG: Life years gained; ICER: incremental cost-effectiveness ratio; SOC: Standard of care; RDN: Renal denervation; BMT: best medical therapov; Rf RDN: Radiofrequency Renal Denervation; uRDN: Ultrasound Renal Denervation							

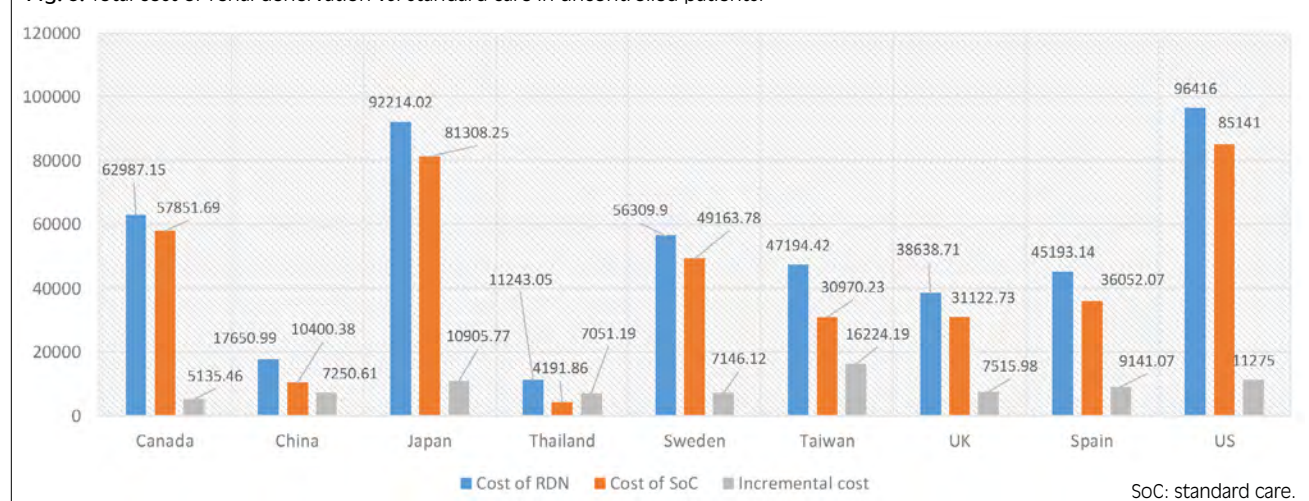
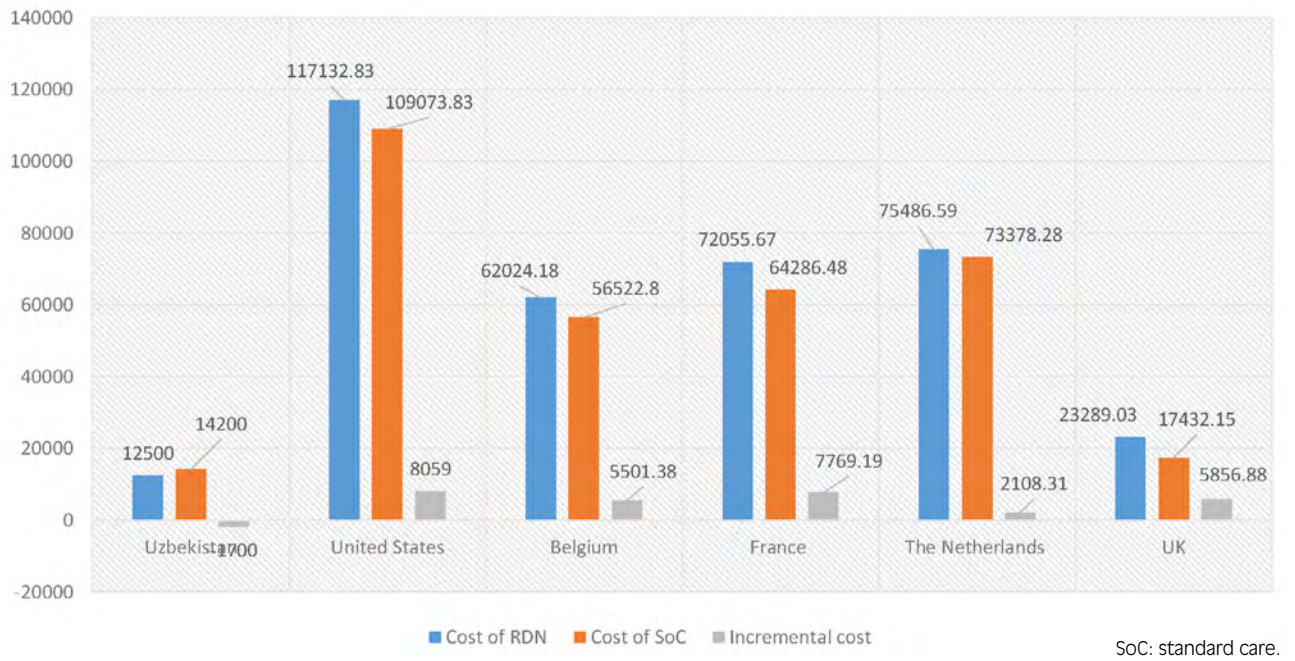
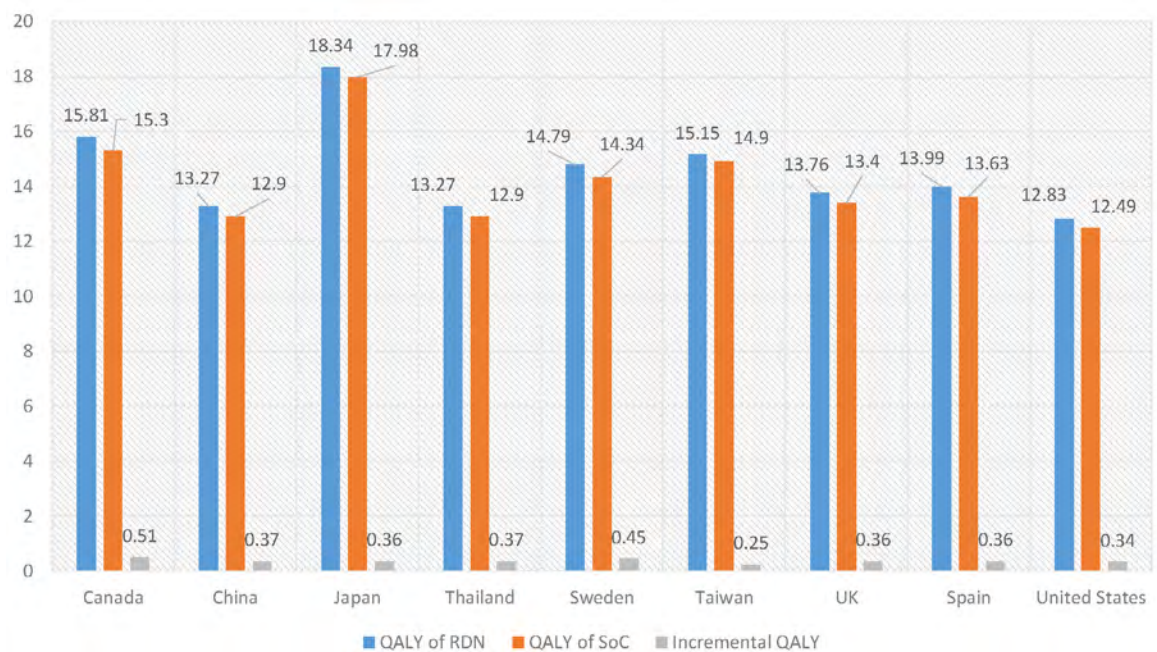
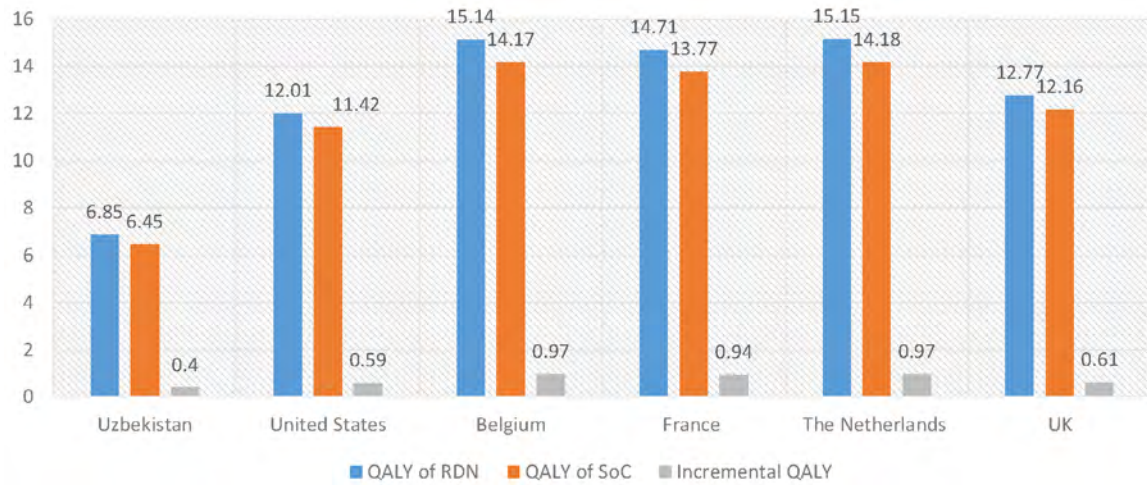
Fig. 3. Total cost of renal denervation vs. standard care in uncontrolled patients.

Fig. 4. Total cost of renal denervation vs. standard care in resistant patients.**Fig. 5.** QALYs of renal denervation vs. standard care in uncontrolled hypertension patients.

QALYs: quality-adjusted life-years; SoC: standard care.

Fig. 6. QALYs of renal denervation vs. standard care in resistant patients.

QALYs: quality-adjusted life-years; SoC: standard care.

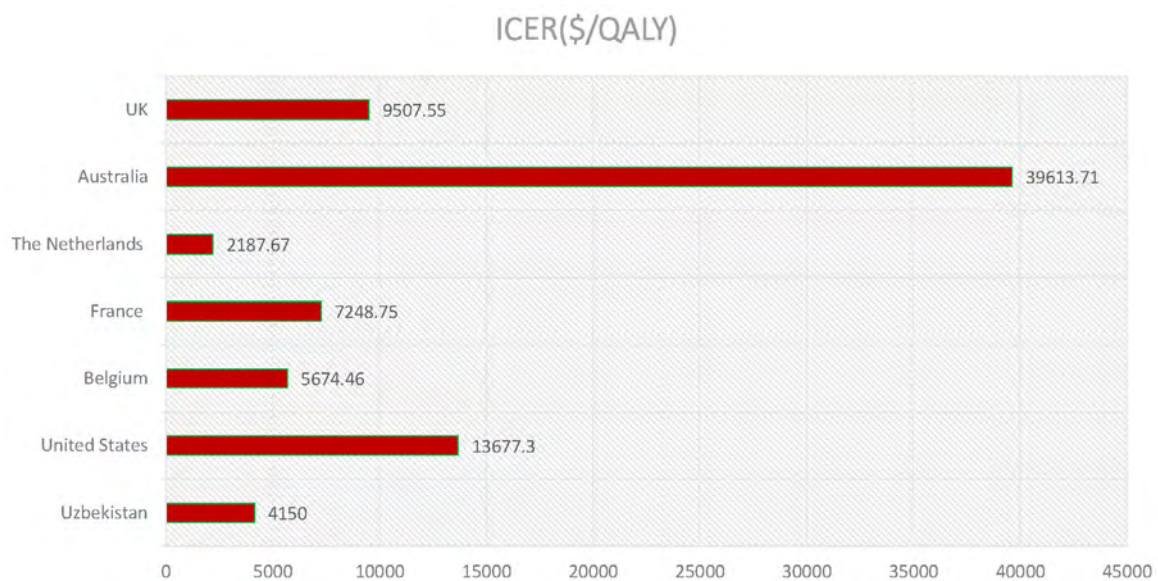
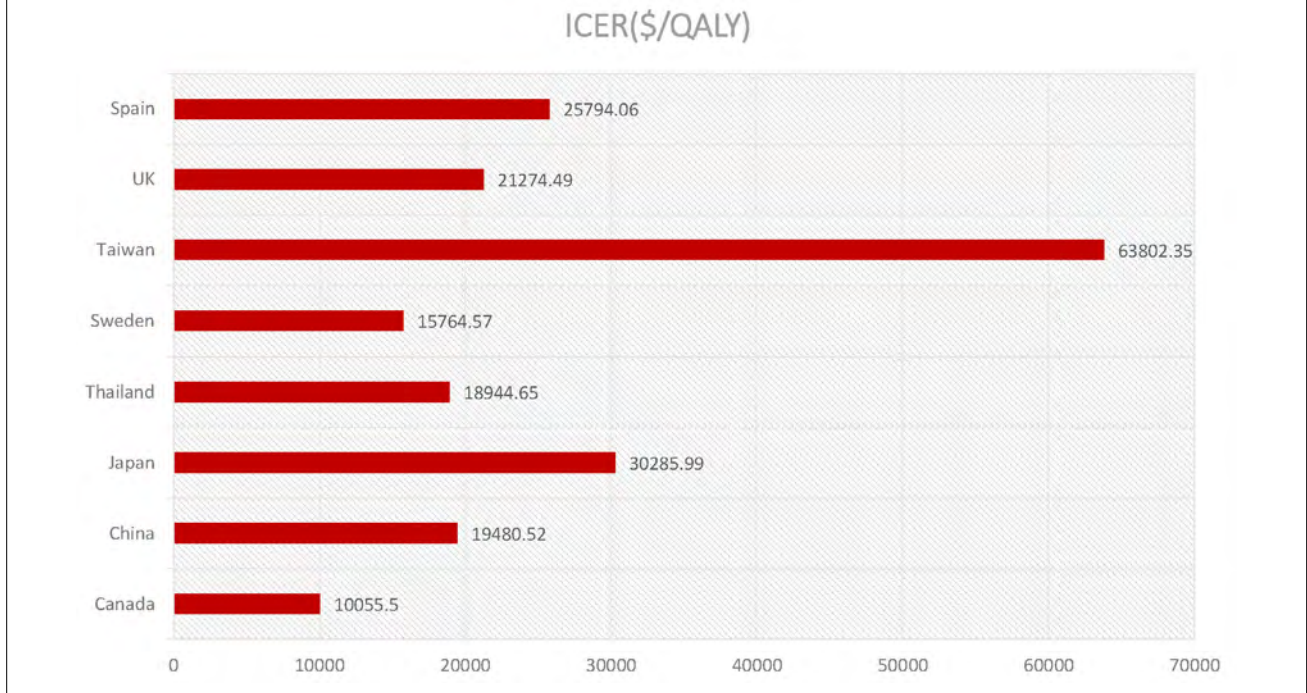
Fig. 7. Incremental cost per QALY of renal denervation vs. standard care resistant patients.

Fig. 8. Incremental cost per QALY of renal denervation vs. standard care in uncontrolled patients.

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Availability of data and materials

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Consent for publication

Not applicable.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Authors' contributions

AS and HO contributed to the conception and design

of the study. AS and AKH independently screened the articles, while HO served as the third reviewer to resolve disagreements. AS, MT, HO, and AKH contributed to data interpretation. AS, MT, HO, and AKH drafted the manuscript and critically revised it for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Bundibugyo Virus Disease in the Democratic Republic of the Congo and Uganda: A Neglected Public Health Threat

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Keywords

Bundibugyo virus • Bundibugyo virus disease • BDBV • Democratic Republic of the Congo
Uganda • viral hemorrhagic fever • emerging infectious diseases

Dear Editor,

Bundibugyo virus disease (BVD) is a rare haemorrhagic fever caused by the Bundibugyo virus, a genetically distinct species within the ebolavirus group [1]. BVD was first identified in Uganda in 2007. Since then, it has been reported only three times. The most recent outbreak began in April-May 2026 in Ituri Province, eastern Democratic Republic of the Congo (DRC). The outbreak later crossed the border into Uganda [1]. On 17 May 2026, the World Health Organization (WHO) designated this outbreak, the DRC's 17th Ebola-related outbreak since 1976, as a Public Health Emergency of International Concern (PHEIC) [2]. By 25 July 2026, the DRC had recorded 3,200 confirmed cases and 1,405 deaths, with 773 patients being isolated and 571 having recovered; Ituri Province alone accounted for 2,848 cases and 1,184 deaths [3]. These totals already exceed the two previous BVD outbreaks combined (131/42 in Uganda, 2007-08; 38/13 in DRC, 2012) [4].

This outbreak is important for reasons beyond the number of cases. It is the first BVD outbreak to be declared a PHEIC. This decision was linked to the documented spread of the virus across the border into Uganda. There were also cases that were transported for medical care to Germany, France, and the United States [1, 3, 5]. Nosocomial transmission has also been an important feature of the outbreak. It was first recognised after the death of a nurse in Mongbwalu, highlighting ongoing gaps in infection prevention and control [6]. Unlike Zaire ebolavirus, Bundibugyo virus has no licensed vaccine or approved therapeutic, leaving responders dependent on non-pharmaceutical measures [7].

Several factors may explain the resurgence of BVD. Ongoing armed conflict, population displacement, and artisanal mining have created highly mobile communities. This movement makes it more difficult to trace contacts and control the spread of infection [8]. Genomic evidence also suggests that the current outbreak may have resulted from a new spillover from an animal reservoir. In addition, limited investment in filovirus diagnostic capacity has created further challenges. GeneXpert, which is mainly optimised for detecting Zaire ebolavirus, did not detect Bundibugyo

virus effectively. This contributed to delays in confirming cases and isolating infected individuals [9].

Current prevention relies mainly on early case detection, isolation, contact tracing, safe burials and community engagement. However, these measures remain difficult to implement effectively in a conflict-affected setting. The outbreak has also exposed major gaps in diagnostic capacity, although WHO added the first molecular test specifically for Bundibugyo virus to its Emergency Use Listing in July 2026 [7, 10, 11].

Recent studies have highlighted important gaps in preparedness for non-Zaire filoviruses. These include limited diagnostic capacity and the need to develop effective medical countermeasures more quickly. In response, investigational treatments, including remdesivir and monoclonal antibodies such as MBP-134, are being evaluated. Vaccine candidates are also being developed and tested [7, 12].

We recommend: (1) improving filovirus diagnostics to enable pan-ebolavirus detection; (2) sustained and protected funding for contact tracing and infection control in conflict zones; (3) faster development of Bundibugyo-specific vaccines and therapeutics, alongside evaluation of cross-protection; (4) stronger cross-border coordination between DRC, Uganda and neighbouring states; and (5) conflict-sensitive risk communication adapted to the context of eastern DRC. The 2026 outbreak highlights that non-Zaire ebolaviruses remain a neglected but significant threat requiring sustained investment.

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Ethics Approval and Consent to Participate

Not applicable. This Letter to the Editor is based solely on publicly available data and does not involve human participants or identifiable individual information.

Consent for Publication

Not applicable.

Data Availability

All data referenced in this Letter to the Editor are publicly available from the cited sources.

Conflicts of interest statement

The author declares no conflict of interest.

Authors' contributions

ZK: Conceptualization, Methodology, Literature review, Investigation, Writing-Original Draft, Writing-Review & Editing, and Final approval of the manuscript.

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Google Trends and Wikipedia Queries as Proxies for Measles Surveillance

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Keywords

Infodemiology • Infoveillance • Measles • Infectious Diseases • Italy

Summary

Introduction. The increasing digitalization of information behaviors has created new opportunities in public health, promoting the development of infodemiology and infoveillance as complements to traditional epidemiological surveillance. This study aimed to assess the correlation and temporal association between official measles surveillance data published by the Italian National Institute of Health (ISS), Google Trends (GT) search volumes, and Wikipedia page views related to measles in Italy.

Methods. A retrospective ecological study with a time-series design was conducted using measles cases reported in Italy from January 2013 to November 2025. Monthly data from GT and Wikipedia were aggregated and compared with the monthly incidence reported in ISS bulletins. Linear regressions were performed to evaluate associations.

Results. The results showed a statistically significant associations between reported measles cases and both GT searches and Wikipedia page views. Linear regression analyses confirmed significant associations between digital indicators and official surveillance data, suggesting that online user activity closely reflects measles epidemiological trends.

Conclusion. These findings indicate that GT and Wikipedia may serve as useful and timely tools to complement traditional measles surveillance. Although caution is needed due to methodological limitations and potential information bias, integrating digital data could enhance early outbreak detection and support more rapid public health responses.

Introduction

In recent years, public healthcare has undergone a profound transformation driven by the progressive digitalization of the population's information behaviour, with increasing use of online platforms for health-related information searches. This is the context for infodemiology and infoveillance, two innovative approaches that apply the principles of epidemiology to the study of the production, dissemination, and use of health information in digital environments. Infodemiology, introduced by Gunther Eysenbach in the early 2000s, is defined as the science that analyses the distribution and determinants of information in digital contexts with the aim of supporting policy making and decision-making processes in public health [1, 2]. It is based on the assumption that online information flows significantly influence individual and collective behaviour, with potential direct impacts on population health outcomes. Within this theoretical framework, infoveillance represents the most operational dimension of infodemiology, configuring itself as a continuous and real-time information surveillance system, based on the analysis of online searches, social media and digital contents [2]. Numerous studies have demonstrated how these data sources can anticipate the progress of health events compared to traditional surveillance systems,

offering timely indicators relating to infectious diseases, health behaviours and risk perception in the general population [3-5]. The COVID-19 pandemic has further highlighted the crucial role of these tools in monitoring and combating the “infodemic”, *i.e.* the overabundance of information, often inaccurate or misleading, which can compromise the effectiveness of institutional healthcare responses [6]. At the same time, the evolution of digital platforms and the availability of large volumes of user-generated data from search engines like Google and social networks have expanded the application possibilities of digital epidemiological surveillance. Tools like Google Trends allow us to analyse the relative search volume (RSV) of specific terms or topics, providing indirect proxies for the population's attention, interest, and concerns [7, 8]. Several studies have highlighted a statistically significant correlation between online search trends and data from official surveillance systems for numerous infectious diseases [9-11], especially in contexts characterised by delays or incompleteness of traditional reporting systems. From this perspective, measles represents a particularly relevant case study. Despite the availability of a safe and effective vaccine, measles remains one of the most contagious infectious diseases and a significant cause of childhood morbidity and mortality globally, especially when vaccination coverage is insufficient [10, 12]. In Europe and Italy,

where the disease is subject to mandatory notification, epidemic outbreaks persist, particularly associated with poor adherence to vaccinations [12-14]. Traditional measles surveillance, based on clinical and laboratory reports, is often burdensome and characterized by a time delay in data availability; for this reason, the integration with digital data from the web and social media appears to be a promising strategy to improve early detection and monitoring of the disease progression [9-11, 15, 16]. Overall, infodemiology and infoveillance emerge as key tools for digital public health, capable of complementing traditional epidemiological surveillance systems, improving institutional communication, and strengthening the capacity to respond to health emergencies. However, their use requires careful consideration of methodological limitations, algorithmic biases, data representativeness, and ethical implications related to privacy protection and the responsible use of information [17]. In this scenario, harmonizing analysis methods and multidisciplinary integration are fundamental steps to fully exploit the potential of these innovative public health tools. This study was conducted with the primary objective of evaluating the temporal association between data from Google Trends (GT), Wikipedia searches, and conventional surveillance data relating to measles infection, reported in the bulletins of the Italian National Institute of Health (ISS). Specifically, the study aims to explore the applicability of digital surveillance tools as a support to traditional systems for monitoring communicable diseases, with specific reference to measles.

Materials and Methods

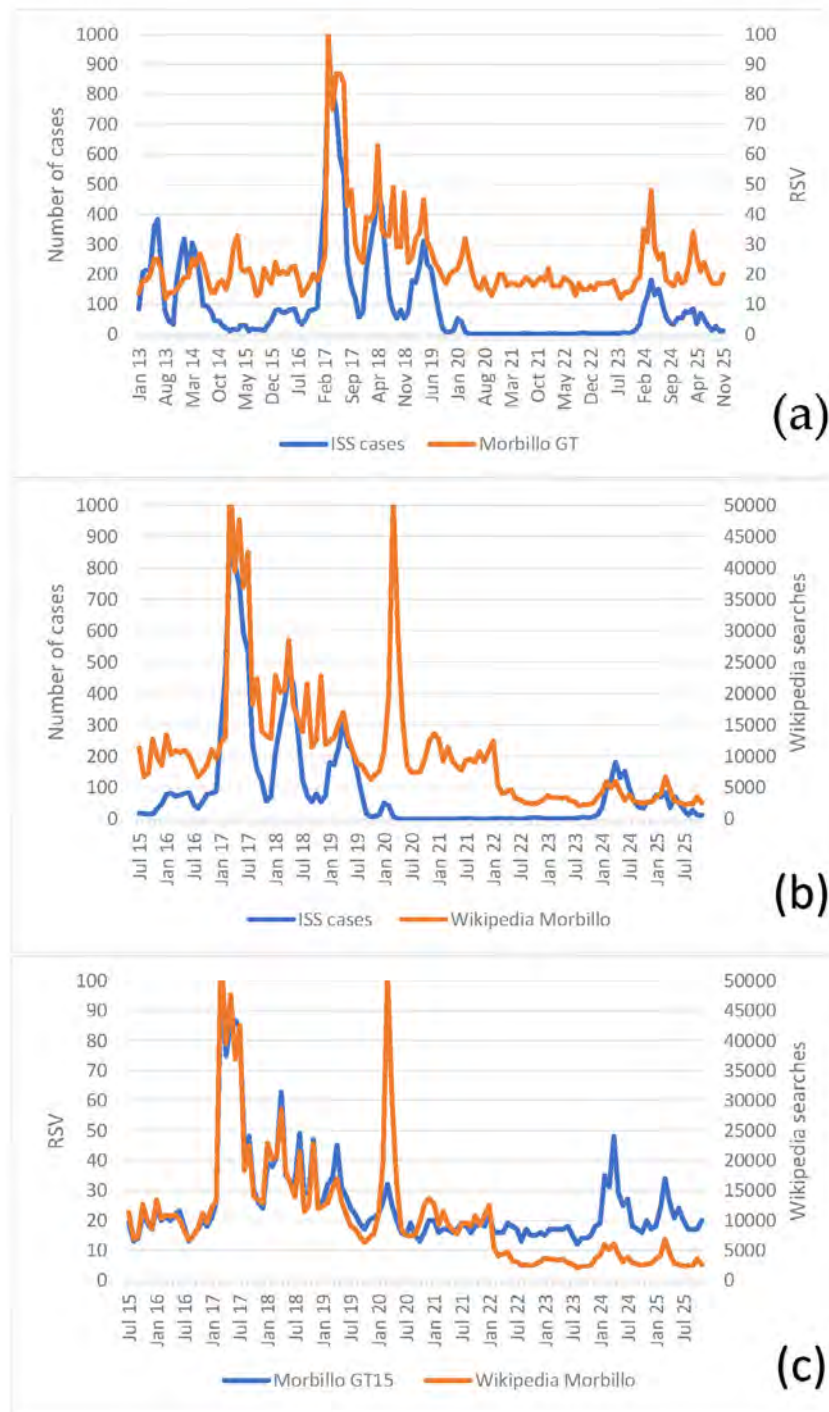
A retrospective ecological study with a time-series design was conducted. Measles cases were selected between January 2013 and November 2025. The ISS publishes a monthly bulletin containing the number of measles cases classified as possible, probable, and confirmed during the previous months [18]. Internet search data were obtained from Google Trends (GT) [11]. Google Trends provides a relative search volume (RSV), calculated as the proportion of searches for a specific term relative to the total number of searches performed in a given location and time period, normalized on a scale from 0 to 100. Data were extracted on December 31, 2025 using the Italian search terms in the “Health” category: “Morbillo” (Measles in English) and “Sintomi Morbillo” (Measles Symptoms in English), for the period between January 1, 2013 (when data became available) and November 30, 2025. Data were aggregated on a monthly basis. The resulting dataset, referred to as GT, included all available monthly RSV values during the study period. Since Wikipedia Trends data were available only from July 1, 2015, a second Google Trends dataset was created by selecting only RSV values from July 2015 to November 2025, corresponding to the period covered by Wikipedia data. This restricted dataset is referred to as GT15 throughout the manuscript and was used to

ensure temporal comparability between Google Trends and Wikipedia indicators. The files were downloaded in Comma-Separated Values (CSV) format. Wikipedia Trends [19] provides information on the number of views of specific Wikipedia pages over time. Data were extracted as daily values and subsequently aggregated on a monthly basis. The following Wikipedia pages were considered: “Morbillo” (Measles in English), “Vaccino del Morbillo” (Measles vaccine in English), “Vaccinazione MPR” (MMR Vaccination in English), “Esantema” (Exanthema in English), and “Macchie di Koplik” (Koplik spots in English), for the period between July 1, 2015 (when data became available) and November 30, 2025. Data from Wikipedia and Google Trends were temporally aligned with the monthly incidence of measles cases reported in the ISS epidemiological bulletins. Linear regression analyses were performed to evaluate the temporal associations between digital indicators and official measles surveillance data. Dependent variables included the monthly number of measles cases reported by the Italian National Institute of Health (ISS), Google Trends relative search volume (RSV) values for the terms “Morbillo” and “Sintomi Morbillo”, and monthly views of the Wikipedia page “Morbillo”. Independent variables included the selected Google Trends search terms, the analyzed Wikipedia pages, and, where applicable, ISS measles cases. Regression coefficients (β), 95% confidence intervals (95% CI), and corresponding *p-values* were calculated for each model. Statistical significance of individual regression coefficients was assessed using Student’s *t*-test. Potential autocorrelation was evaluated using the Durbin-Watson (DW) statistic. The DW test is used to detect autocorrelation in the residuals (prediction errors) of regression models [20, 21]. The DW statistic ranges between 0 and 4; values substantially lower than 2 indicate positive serial correlation, whereas values close to 2 suggest the absence of autocorrelation. Scatterplots with fitted linear regression lines and corresponding 95% confidence intervals were generated to visually represent the relationships between measles surveillance data and digital indicators. The coefficient of determination (R^2) was calculated to assess the proportion of variance explained by each linear model. The statistical significance level was set at 0.05. All analyses were conducted using STATA statistical software, version 13.

Results

The raw data on ISS measles cases, Google Trends relative search volume (RSV) for the term “Morbillo”, and views of the “Morbillo” Wikipedia page are presented in Figure 1. Figure 2 shows the scatterplots and the corresponding linear and exponential regression models describing the relationships between ISS cases, Google Trends search terms, and Wikipedia page views. In most analyses, linear models provided a better fit to the observed data compared with exponential models. Table I reports the results of the linear regression analyses,

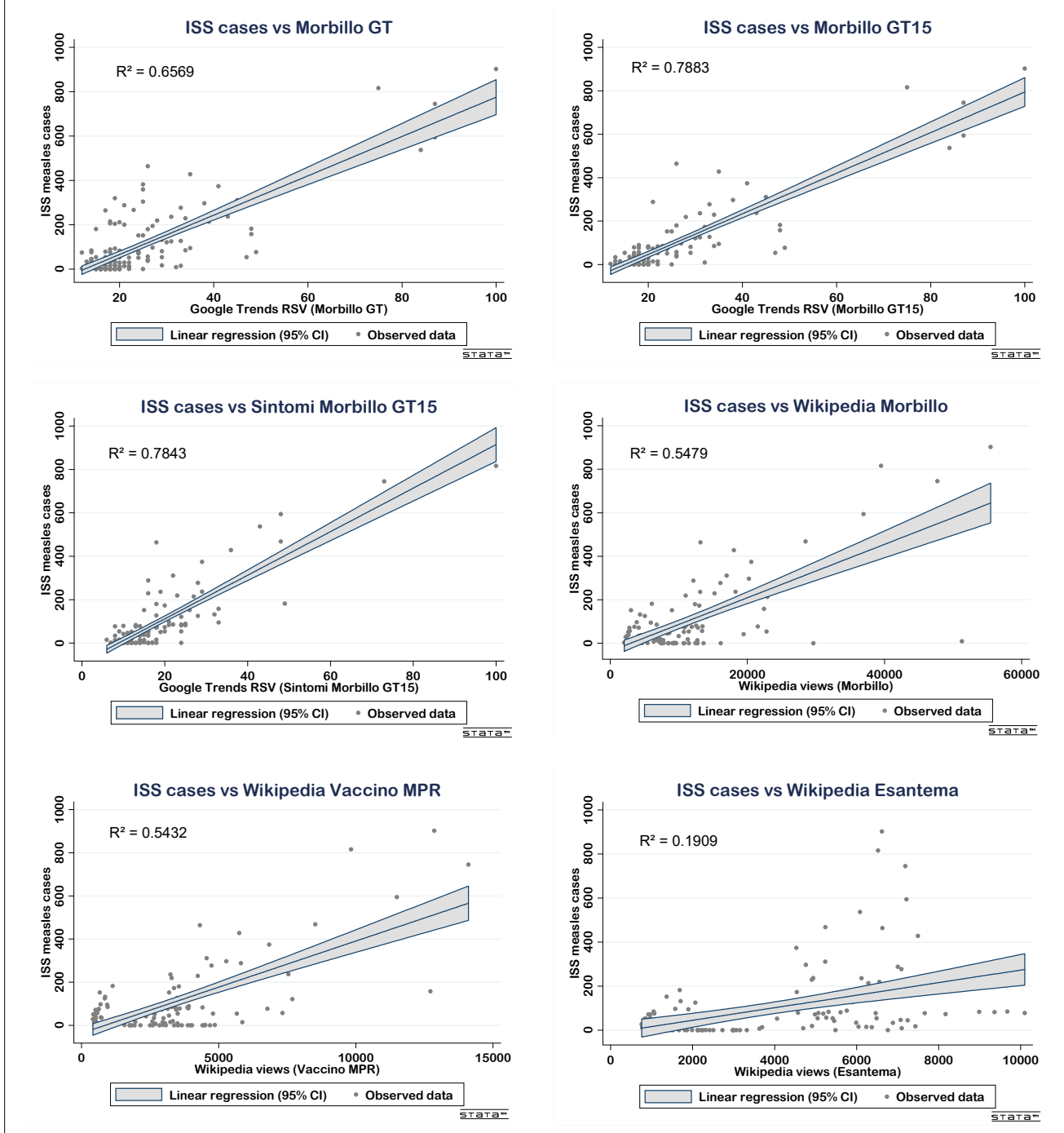
Fig. 1. Raw data for the number of ISS and RSV measles cases from GT (a). Raw data for the number of ISS cases and the number of searches for the measles Wikipedia page (b). Raw RSV measles data from GT15 and the number of searches for the measles Wikipedia page (c).



considering ISS measles cases, Google Trends (GT and GT15) values for “Morbillo”, and views of the “Morbillo” Wikipedia page as dependent variables. All models showed statistically significant positive associations between digital indicators and measles surveillance data, with all *p-values* <0.001. When ISS measles cases were considered as the dependent variable, Google Trends indicators showed a strong positive association with surveillance data. The search term “Morbillo GT” was

associated with ISS cases ($\beta=8.86$, 95% CI: 7.84-9.98), while the restricted dataset “Morbillo GT15” showed a slightly stronger association ($\beta=9.34$, 95% CI: 8.48-10.21). Similarly, searches for “Síntomi Morbillo” were positively associated with ISS cases, both for the complete dataset ($\beta=9.72$, 95% CI: 8.66-10.79) and for GT15 ($\beta=10.03$, 95% CI: 9.09-10.98). Wikipedia indicators also showed significant positive associations with ISS measles cases. The strongest association was observed for

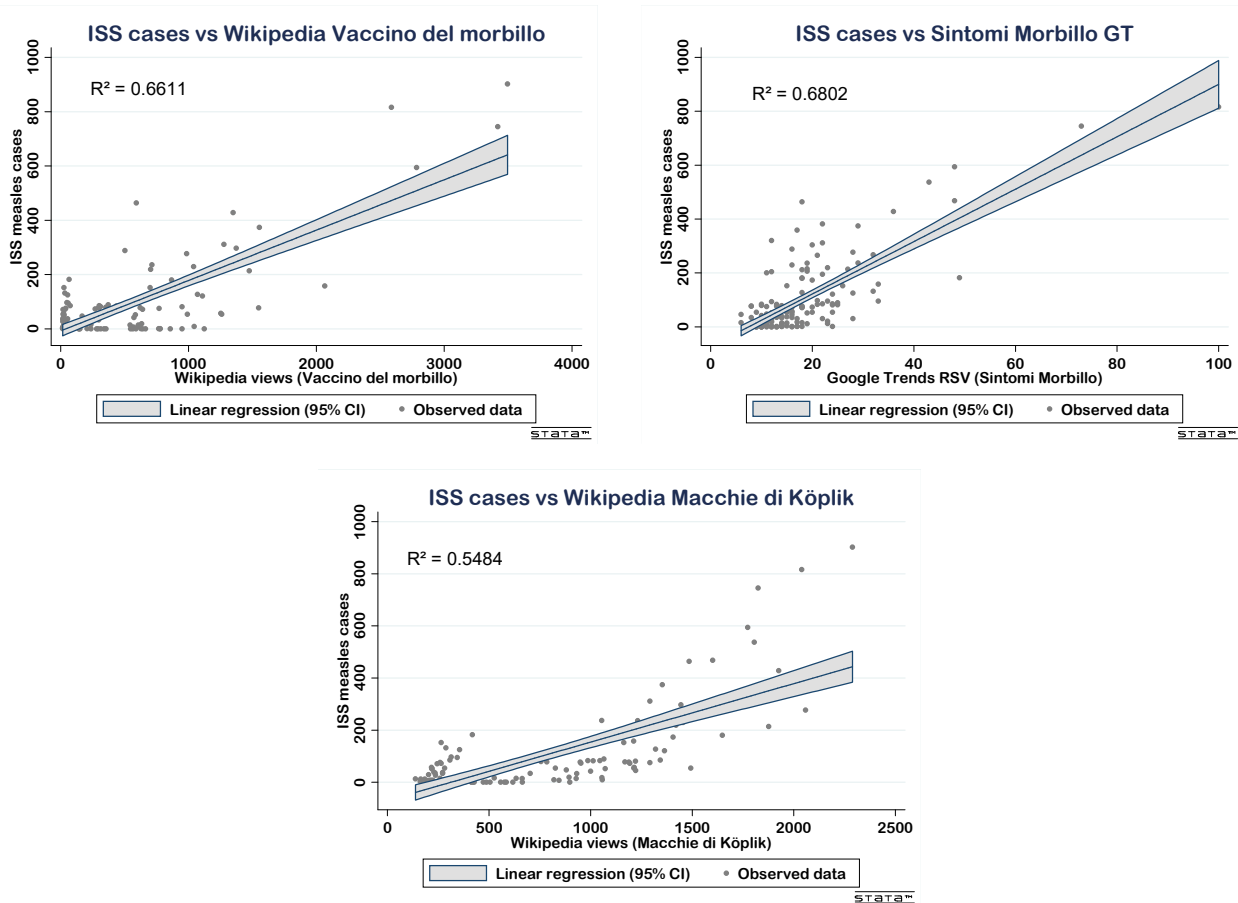
Fig. 2. Scatterplots showing the associations between official measles surveillance data (ISS cases) and digital indicators. Linear regression lines with corresponding 95% confidence intervals are shown. The corresponding R^2 are shown in the figures



“Macchie di Koplik Wikipedia” ($\beta=0.22$, 95% CI: 0.18-0.26), followed by “Vaccino del Morbillo Wikipedia” ($\beta=0.18$, 95% CI: 0.16-0.21), “Vaccino MPR Wikipedia” ($\beta=0.04$, 95% CI: 0.03-0.05), “Esantema Wikipedia” ($\beta=0.02$, 95% CI: 0.01-0.03), and “Morbillo Wikipedia” ($\beta=0.012$, 95% CI: 0.010-0.014). To identify the digital indicators most strongly associated with official measles surveillance data, Internet-based variables were ranked according to the magnitude of the regression coefficients

(β) obtained from models using ISS cases as the dependent variable. Among Google Trends variables, the highest coefficients were observed for “Sintomi Morbillo GT15”, followed by “Sintomi Morbillo GT”, “Morbillo GT15”, and “Morbillo GT”. Among Wikipedia variables, the ranking was led by “Macchie di Koplik Wikipedia”, followed by “Vaccino del Morbillo Wikipedia”, “Vaccino MPR Wikipedia”, “Esantema Wikipedia”, and “Morbillo Wikipedia” (Tab. II). Further analyses showed that ISS

Fig. 2 (follows). Scatterplots showing the associations between official measles surveillance data (ISS cases) and digital indicators. Linear regression lines with corresponding 95% confidence intervals are shown. The corresponding R^2 are shown in the figures



measles cases were significantly associated with Google Trends activity for “Morbillo” ($\beta=0.07$, 95% CI: 0.06-0.08) and “Morbillo GT15” ($\beta=0.08$, 95% CI: 0.07-0.09). In addition, “Sintomi Morbillo GT” was strongly associated with “Morbillo GT” ($\beta=0.92$, 95% CI: 0.83-1.01), while “Sintomi Morbillo GT15” was significantly associated with “Morbillo GT15” ($p < 0.001$), confirming the consistency between general measles-related searches and symptom-related searches. Positive associations were also observed between Wikipedia indicators and “Morbillo GT15”. These included “Morbillo Wikipedia” ($\beta=0.001$, 95% CI: 0.0011-0.0015), “Vaccino del Morbillo Wiki” ($\beta=0.019$, 95% CI: 0.017-0.021), “Vaccino MPR Wiki” ($\beta=0.004$, 95% CI: 0.003-0.004), “Esantema Wiki” ($\beta=0.002$, 95% CI: 0.001-0.003), and “Macchie di Koplik Wiki” ($\beta=0.019$, 95% CI: 0.015-0.023). ISS cases were also associated with “Morbillo Wikipedia” activity ($\beta=44.62$, 95% CI: 37.39-51.86). Similarly, “Morbillo GT15” ($\beta=527.67$, 95% CI: 464.67-590.67) and “Sintomi del Morbillo GT15” ($\beta=453.25$, 95% CI: 362.01-544.49) significantly predicted Wikipedia searches for “Morbillo”. Overall, these findings demonstrate consistent positive relationships between online search activity, Wikipedia page views, and official measles surveillance data. Durbin-Watson statistics were calculated for all linear regression

models to assess residual autocorrelation. The obtained values ranged from 0.21 to 1.22, indicating the presence of positive autocorrelation in the residuals across most models. These findings suggest that the observations were not fully independent over time, which is consistent with the time-series nature of the analyzed data. Therefore, the observed associations should be interpreted with caution, as residual autocorrelation may have influenced the estimated regression coefficients and their statistical significance.

Discussion

The study of the application of GT and Wikipedia in the surveillance of communicable diseases in Italy has a high relevance for public health, as suggested by numerous previous studies [7, 8]. Measles outbreaks remain a global health problem, and surveillance is an essential tool for their control. However, traditional monitoring approaches based on conventional reporting systems present some critical issues, including time lags in data availability and potential underestimation of cases due to underreporting.

In 2009, Eysenbach defined infodemiology and

Tab. I. Linear regression analyses showing regression coefficients (B), 95% confidence intervals (C.I. 95%), *p*-values for individual regression coefficients (Student's *t*-test), and Durbin-Watson statistics.

Independent variable: Morbillo GT				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin Watson
ISS cases	8.86	7.84-9.98	<0.001	0.56
Independent variable: Morbillo GT15				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin Watson
ISS cases	9.34	8.48-10.21	<0.001	0.93
Independent variable: Sintomi Morbillo GT				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
ISS cases	9.72	8.66-10.79	<0.001	0.67
Independent variable: Sintomi Morbillo GT15				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
ISS cases	10.03	9.09-10.98	<0.001	0.92
Independent variable: Morbillo Wikipedia				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
ISS cases	0.012	0.010-0.014	<0.001	0.43
Independent variable: Vaccino del Morbillo Wikipedia				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
ISS cases	0.18	0.16-0.21	<0.001	0.44
Independent variable: Vaccino MPR Wikipedia				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
ISS cases	0.04	0.03-0.05	<0.001	0.37
Independent variable: Esantema Wikipedia				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
ISS cases	0.02	0.01-0.03	<0.001	0.21
Independent variable: Macchie di Koplik Wikipedia				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
ISS cases	0.22	0.18-0.26	<0.001	0.25
Independent variable: ISS cases				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo GT	0.07	0.06-0.08	<0.001	0.82
Independent variable: Sintomi Morbillo GT				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo GT	0.92	0.83-1.01	<0.001	1.06
Independent variable: ISS cases				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo GT15	0.08	0.07-0.09	<0.001	1.22
Independent variable: Sintomi Morbillo GT15				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo GT15	0.94	0.84-1.03	<0.001	1.05
Independent variable: Morbillo Wikipedia				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo GT15	0.001	0.0011-0.0015	<0.001	0.51
Independent variable: Vaccino del Morbillo Wiki				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo GT15	0.019	0.017-0.021	<0.001	0.52
Independent variable: Vaccino MPR Wiki				
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson

Tab. I (follows). Linear regression analyses showing regression coefficients (B), 95% confidence intervals (C.I. 95%), *p*-values for individual regression coefficients (Student's *t*-test), and Durbin-Watson statistics.

	Independent variable: Morbillo GT			
Morbillo GT15	0.004	0.003-0.004	<0.001	0.55
	Independent variable: Esantema Wiki			
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo GT15	0.002	0.001-0.003	<0.001	0.51
	Independent variable: Macchie di Koplik Wiki			
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo GT15	0.019	0.015-0.023	<0.001	0.66
	Independent variable: ISS cases			
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo Wikipedia	44.62	37.39-51.86	<0.001	0.73
	Independent variable: Morbillo GT15			
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo Wikipedia	527.67	464.67-590.67	<0.001	0.52
	Independent variable: Sintomi del Morbillo GT15			
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo Wikipedia	453.25	362.01-544.49	<0.001	0.61
	Independent variable: Vaccino del Morbillo Wiki			
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo Wikipedia	12.38	11.31-13.45	<0.001	0.84
	Independent variable: Vaccino MPR Wiki			
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo Wikipedia	2.92	2.58-3.26	<0.001	0.81
	Independent variable: Esantema Wiki			
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo Wikipedia	2.34	1.78-2.91	<0.001	0.64
	Independent variable: Macchie di Koplik Wiki			
Dependent variable	Coef.	C.I. 95%	<i>p</i> -value	Durbin-Watson
Morbillo Wikipedia	13.78	11.64-15.92	<0.001	0.83

infoveillance as “the science of the distribution and determinants of information in an electronic medium, especially the Internet, or in a population, with the ultimate goal of informing public health and public policy.” [1]. This emerging approach has been widely used to explore public interest in communicable diseases, such as influenza [3], and for the early detection of infectious epidemics [22].

Measles is one of the most contagious vaccine-preventable diseases ($R_0=12-18$) [12]. The inherent delays in traditional surveillance systems can limit the ability of health authorities to intervene promptly. Data from Google Trends and Wikipedia are collected and processed in near real time, allowing for significantly faster information availability than traditional systems. [9]. In this study, statistical analyses highlighted a clear temporal association between ISS surveillance data and search trends on Google and Wikipedia. In particular, associations were observed on a monthly basis, suggesting that this approach could

provide a useful time frame for more timely public health interventions. However, it cannot be ruled out that a weekly or daily analysis could allow for even earlier case reporting, as reported in other studies. [23, 24].

An additional methodological aspect to consider is the presence of positive residual autocorrelation, as indicated by the Durbin-Watson statistics. This finding is consistent with the temporal nature of the analyzed data and suggests that consecutive monthly observations were not fully independent. Consequently, although the observed associations between digital indicators and official surveillance data were statistically significant, the regression estimates should be interpreted with appropriate caution.

This study has some limitations. First, the influence of mass media (television, radio, and print) may lead to an increase in online searches regardless of actual case trends [25]. Furthermore, Google Trends does not provide sufficiently granular data to accurately identify the geographic location of outbreaks. Further limitations

Tab. II. Ranking of Internet-based indicators according to the strength of their association with ISS measles cases.

Data source	Internet variable (independent variable)	Ranking
Google Trends	Sintomi Morbillo GT15	1
Google Trends	Sintomi Morbillo GT	2
Google Trends	Morbillo GT15	3
Google Trends	Morbillo GT	4
Wikipedia	Macchie di Koplik Wikipedia	1
Wikipedia	Vaccino del Morbillo Wikipedia	2
Wikipedia	Vaccino MPR Wikipedia	3
Wikipedia	Esantema Wikipedia	4
Wikipedia	Morbillo Wikipedia	5

GT: Google Trends general dataset

GT15: Google Trends dataset restricted to the period July 2015–November 2025

arise from changes over time in the GT interface and algorithms, which are not fully documented and could influence the results. Therefore, the interpretation and generalization of the results should be made with caution. Another limitation is the presence of residual autocorrelation in the regression models, as indicated by the Durbin-Watson statistics. This reflects the time-series nature of the data and may have affected the independence of observations and the estimated standard errors. Therefore, although linear regression was considered appropriate for this exploratory analysis, future studies should consider applying dedicated time-series approaches, such as autoregressive or other longitudinal models, to better account for temporal dependence.

Previous experiences, such as Google Flu Trends, have shown how the use of big data for epidemiological forecasting can lead to significant overestimations, as occurred in the 2012–2013 influenza season. [26]. In the case of measles, online search volume is likely influenced more by media attention than by direct patient experience, given the relative rarity of cases. This makes digital surveillance potentially more sensitive, but also more susceptible to bias. A prudent and integrated use of these tools, alongside traditional surveillance systems, is therefore necessary.

Conclusion

In summary, the Italian healthcare system operates in a context characterized by limited resources, which necessitates the adoption of innovative strategies to improve efficiency and sustainability. Investing in technological innovation represents a strategic lever to strengthen the National Health Service and improve its capacity to respond to the population's needs. The results of this study suggest that surveillance systems based on Google Trends and Wikipedia could play a complementary role in public health by providing dynamic, near-real-time indicators of the spread of infectious diseases. The integration of these tools

with traditional surveillance systems could support policymakers in implementing preventive measures and targeted communication strategies [27, 28]. Although this field of research is still relatively young, its rapid expansion is expected, facilitated by the increasing availability of data and increased computational power [29]. Online searches, conducted in real time, could serve as an early warning system, signaling sudden changes in the population's interests and therefore deserving attention from health authorities [30]. Looking ahead, this approach could be used as a supplementary tool for epidemic forecasting and for a more efficient allocation of health resources [31, 32].

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None.

Conflicts of Interest statement

The authors declare no conflicts of interest.

Authors' contributions

OES: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, visualization, supervision, project administration.

OES, ASP, CV, DG, SP, AF: Original draft preparation, writing, review and editing.

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

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INFECTIOUS DISEASE

Assessment of Antimicrobial Consumption Patterns in Adult and Pediatric Patients in Intensive Care Units Using DDD, DOT, and WHO AWaRe Classification: A Point Prevalence Study from Central India

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Keywords

Antibiotic consumption • Central India • Intensive care units • Point prevalence survey • Stewardship

Summary

Introduction. *Inappropriate use of antimicrobials is the primary driver of antimicrobial resistance, which threatens modern medicine. Monitoring antimicrobial consumption is the initial step for planning and guiding antimicrobial stewardship initiatives. This pilot study aimed to evaluate antimicrobial consumption patterns among adult and pediatric patients and to identify factors influencing antimicrobial use in the intensive care units (ICUs) of a tertiary care hospital in Central India.*

Methods. *This hybrid point-prevalence survey was conducted across five ICUs of a tertiary care hospital in March 2025. The survey included all ICU-admitted patients on the day of the survey. Antimicrobial prescription data, laboratory investigations, and clinical-demographic data were retrieved from medical records. The WHO Anatomical Therapeutic Chemical and WHO-AWaRe classification systems were used to categorize the antimicrobials used. Antibiotic consumption was evaluated using the Defined Daily Dose methodology, and factors associated with*

antimicrobial use were analyzed using descriptive statistics and logistic regression.

Results. *Among 88 patients, 79 (89.77%) received at least one antimicrobial. Of 188 antimicrobials prescribed, antibacterials accounted for the highest consumption (96.3%). The most commonly prescribed antibiotics included cefotaxime, metronidazole, and meropenem. The highest (65%) consumption of antimicrobials was from the “Watch group”, with empirical therapy as the primary indication, accounting for 63.29% of prescriptions, of which 63.29% were appropriate. No significant differences were observed in consumption patterns between pediatric and adult patients.*

Conclusion. *The high consumption of antimicrobials in ICUs is predominantly from the Watch category, with higher use for empirical therapy, indicating an urgent need for robust antimicrobial and diagnostic stewardship.*

Introduction

Antibiotics are key players in fighting against infections. However, their injudicious use, particularly in critical care settings, has rapidly driven the selective pressure for antimicrobial resistance (AMR) [1]. AMR threatens modern medicine due to limited treatment options, resulting in increased mortality and morbidity, longer hospital stays, and increased medical expenses [1, 2]. Each year, over 700,000 deaths are linked to AMR, and if prompt action is not taken, it could result in 10 million fatalities and a potential cost to the global economy of up to \$100 trillion by 2050 [3]. Furthermore, AMR is expected to have a greater impact on low- and middle-income countries (LMICs) [2, 4].

Gathering information on current antibiotic consumption patterns in hospitals is crucial for developing effective antibiotic stewardship policies and strategies to guide and control antibiotic misuse, combat AMR, and identify areas for improvement [5,

6]. However, there are limited reports on rates and patterns of antibiotic consumption from LMICs. A point prevalence survey (PPS) is a practical tool for collecting data on antimicrobial use and identifying areas that need corrective action. Additionally, conducting repeated PPS is beneficial for evaluating the impact of the corrective actions implemented in identified problematic areas [7, 8].

In this study, we aimed to determine the characteristics of antimicrobial prescribing practices, including consumption rates, clinical appropriateness, the most prevalent antibiotic classes, and risk factors for increased antimicrobial use among adult and pediatric patients hospitalized in ICUs. This pilot study will provide a snapshot of antimicrobial use patterns in the Intensive Care Units (ICUs) at a tertiary care hospital in Central India, helping to identify areas for improvement, formulate robust antimicrobial stewardship initiatives, and inform the design of more extensive, definitive studies in the future.

Materials and Methods

STUDY DESIGN AND SETTING

This hybrid point-prevalence cohort study (cross-sectional enrolment with longitudinal follow-up) was conducted in the 143-bed ICUs of a tertiary care hospital in Central India in March 2025. The study was approved by the Institutional Ethics Committee (No. 3687 EC/Pharmac/GMC/NGP).

STUDY POPULATION AND DATA COLLECTION

All patients admitted to the Neonatal ICU (NICU), Pediatric ICU (PICU), Medicine ICU (MICU), Surgery ICU (SICU), and Plastic Surgery ICU (Pl-SICU) before or on the day of the survey (March 25, 2025) were included in the study. Surgery ICU included post-LSCS patients, post-operative patients, and trauma/accident injury patients. The data of clinical and demographic details, invasive devices, comorbid conditions, relevant laboratory or microbiological reports, retrospective (from the day of admission to the day of survey) and prospective data (from the day of survey till discharge) on the antibiotic consumption (drug name, dosages, administration route, frequency, culture and antimicrobial sensitivity tests, duration of treatment, and total number of dosages till discharge) of the patients were collected from their records. The drugs classified as systemic antibiotics fall under the J01 category of the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, which includes antibacterials for systemic use, excluding antimycobacterial drugs [9].

A set of quality indicators for initiating antimicrobial therapy was evaluated from patients' medical records, including documented reasons, whether the treatment was empirical or targeted, based on microbiological results from clinical specimens or other microbiological results, such as bacterial antigen or antibody testing or biomarker data, such as C-reactive protein (CRP) and procalcitonin levels, adherence to established Indian Council of Medical Research treatment guidelines, and documentation of review or cessation of antimicrobial therapy after culture report. Furthermore, if the choice of antimicrobial was based on a microbiological culture and susceptibility report, information on the targeted organisms was also gathered. For surgical prophylaxis, we recorded any single dose of an antimicrobial agent administered within 24 hours before 8:00 a.m. on the day of the survey. Clinical appropriateness was evaluated by two independent investigators based on these records and antimicrobial stewardship principles.

The following patients were excluded from this study: those treated in outpatient departments; patients who were discharged before 8:00 a.m. on the day of the survey but remained in the hospital awaiting transportation; patients undergoing treatment or surgery who were either discharged or expected to be discharged on the same day; individuals using topical or ophthalmic antibiotics; and patients whose treatment was discontinued before 8:00 a.m..

DATA ANALYSIS

Antimicrobial use was documented based on the number of patients receiving parenteral antimicrobials for either therapeutic or prophylactic purposes, as well as the total number of therapies or prophylactic measures administered. Descriptive statistics, including frequency, percentages, and means or ranges, were used to summarise the data. Furthermore, the number of antimicrobials designated for systemic use was classified according to the WHO ATC classification system [9].

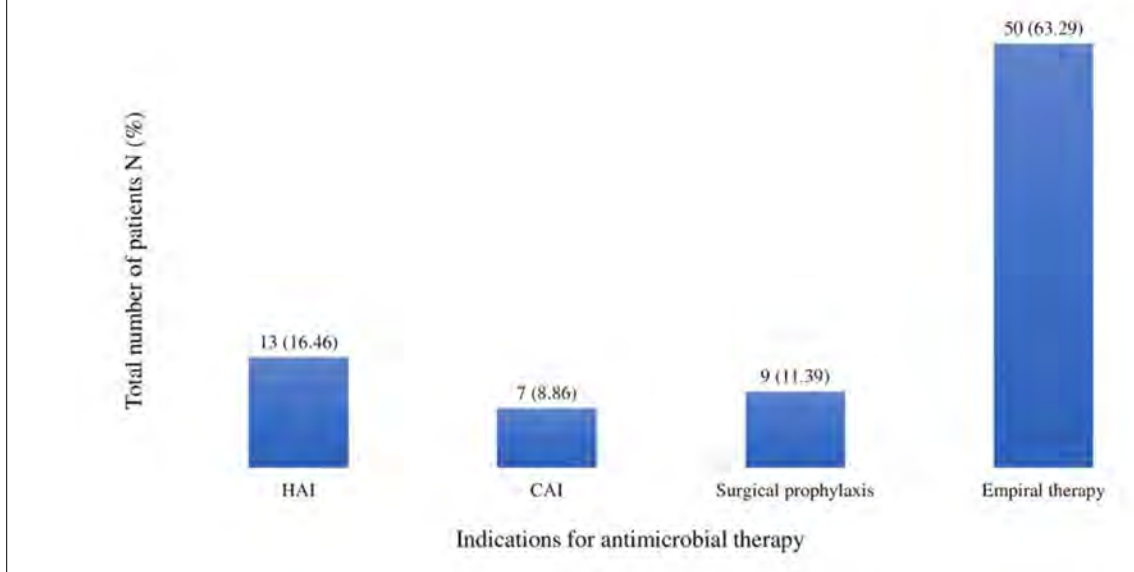
All statistical analyses were performed using Microsoft Excel 2024 and the Statistical software STATA version 14.0. Antibiotic consumption in adult patients was measured using the WHO Antimicrobial Consumption Tool and reported as Defined Daily Doses (DDDs) and days of therapy (DOTs). To calculate the total DDD consumed per pack, we used product and pack size data from prescriptions and the hospital pharmacy, along with DDD data for the corresponding formulations from the WHO ATC/DDD index [10]. In the <18-year age group (NICU and PICU), the DOT is used to measure antibiotic use because it is independent of weight- and age-related dose differences. The antibiotics were categorized according to the updated WHO 2025 list in compliance with the Access, Watch and Reserve (AWaRe) system [11], and we used data from the Central Drugs Standard Control Organization (CDSCO) to determine the approval status [12]. The McCabe score system is used to classify the severity of underlying medical conditions [13].

Using univariate analysis, the demographic and clinical characteristics of patients receiving antimicrobials were assessed for statistical significance using the chi-squared (χ^2) test. Antimicrobial DOT rates for individual antimicrobial agents were compared between pediatric and adult patients using Poisson regression and negative binomial regression. The Pearson chi-square test was applied to compare the clinical appropriateness of antimicrobials prescribed in adult and pediatric patients. A *p-value* of <0.05 was considered statistically significant. STATA version 14.0 software was used for statistical analysis.

Results

Of the 88 patients admitted to the five established ICUs, with 769 patient-days of hospitalization, 79 received one or more types of parenteral antimicrobial therapy on the day of the PPS.

Out of the total 188 antimicrobials prescribed, according to ATC classification, 181 (96.28%) were antibacterial (J01), 4 (2.13%) were antiviral (J05), and 3 (1.6%) were antifungal (J02) for systemic use. Most antimicrobials (123/188, 65%) were used for empirical therapy followed by therapeutic purposes (49/188, 26%) and surgical prophylaxis (16/188, 8.5%) (Tab. I). Of 79 prescriptions, the most common indications were empirical therapy (50/79, 63.29%), followed by hospital-associated infections (HAI) (13/79, 16.46%), with $\chi^2=27.61$ and

Fig. 1. Patient-level indications for antimicrobial therapy among the 79 patients receiving antimicrobials.**Tab. I.** Prescription-level antimicrobial utilization according to indication and WHO AWaRe classification (N = 188 antimicrobial prescriptions).

WHO AWaRe Group; N (%)*	Antimicrobial agents	ATC Code	All indication N (%)	Therapeutic N (%)	Empirical Therapy N (%)	Surgical prophylaxis N (%)
Access; 63 (35)	Amoxicillin-clavulanate	J01CR02	4 (2.13)	2 (4.08)	2 (1.63)	0 (0)
	Amikacin	J01GB06	7 (3.72)	2 (4.08)	5 (4.07)	0 (0)
	Gentamicin	J01GB03	7 (3.72)	1 (2.04)	6 (4.88)	0 (0)
	Doxycycline	J01AA02	5 (2.67)	2 (4.08)	3 (2.44)	0 (0)
	Clindamycin	J01FF01	2 (1.10)	1 (2.04)	1 (0.81)	0 (0)
	Metronidazole	J01XD01	37 (19.68)	10 (20.41)	22	5 (31.25)
	Nitrofurantoin	J01XE01	1 (0.53)	1 (2.04)	0 (0)	0 (0)
Watch; 117 (65)	Piperacillin-tazobactam	J01CR05	25 (13.30)	5 (10.20)	17 (13.82)	3 (18.75)
	Cefotaxime	J01DD01	42 (22.34)	7 (14.29)	30 (24.39)	5 (31.25)
	Ceftriaxone	J01DD04	10 (5.32)	2 (4.08)	7 (5.69)	1 (6.25)
	Cefixime	J01DD08	1 (0.53)	0 (0)	1 (0.81)	0 (0)
	Azithromycin	J01FA10	3 (1.60)	0 (0)	3 (2.44)	0 (0)
	Ciprofloxacin	J01MA02	5 (2.66)	3 (6.12)	2 (1.63)	0 (0)
	Levofloxacin	J01MA12	5 (2.66)	2 (4.08)	2 (1.63)	1 (6.25)
	Meropenem	J01DH02	14 (7.45)	4 (8.16)	9 (7.32)	1 (6.25)
	Vancomycin	J01XA01	12 (6.38)	4 (8.16)	8 (6.50)	0 (0)
Reserve; 1 (0.6)	Colistin	J01XB01	1 (0.53)	0 (0)	1 (0.81)	0 (0)
NA	Fluconazole	J02	3 (1.60)	1 (2.04)	2 (1.63)	0 (0)
NA	Acyclovir	J05	4 (2.13)	2 (4.08)	2 (1.63)	0 (0)
	Total		188 (100)**	49 (100)	123 (100)	16 (100)

ATC: Anatomical Therapeutic Chemical; NA: Not available (Fluconazole and Acyclovir not yet included in AWaRe classification). *AWaRe classification is only applied for antibacterial drugs (Total=181); Green color-Access group antibacterial; Yellow color- Watch group antibacterial; Red color- Reserve group antibacterial. **Each antimicrobial prescription was considered a separate observation; therefore, the total number of prescriptions (N = 188) exceeds the number of patients receiving antimicrobials (N = 79), as individual patients could receive more than one antimicrobial agent.

p-value <0.001 (Fig. 1). In 13 HAI cases, the isolated organisms were *K. pneumoniae* (n=3), methicillin-resistant *Staphylococcus aureus* (MRSA) (n=3), *Acinetobacter baumannii* (n=3), *Enterococcus faecium* (n=2), *Pseudomonas aeruginosa* (n=2), *Escherichia coli* (n=1), and *Citrobacter koseri* (n=1). Among 7

community-associated infections, 4 were *Escherichia coli*, and 3 were *Staphylococcus aureus*. All the isolated organisms were multidrug-resistant (MDR).

The total antimicrobial consumption among adult ICU patients was 356.2 DDD over 281 patient-days, corresponding to 126.77 DDD per 100 patient-days

Tab. II. Antimicrobial consumption pattern in adults using the WHO-Defined Daily Dose method (N=43).

Antimicrobials	Route	No. of Treatment Days	No. of patients, N (%) (N=43) *	Total DDD for each antimicrobial	DDD/100 patient days
Piperacillin-tazobactam	IV	61	16 (37.21)	51.9	18.47
Cefotaxime	IV	99	25 (58.14)	51.9	18.47
Ceftriaxone	IV	1	1 (2.33)	1.1	0.39
Meropenem	IV	36	9 (20.93)	18.20	6.48
Azithromycin	IV	10	3 (6.98)	10	3.56
Ciprofloxacin	IV	15	4 (9.30)	11.5	4.09
Levofloxacin	IV	7	3 (6.98)	13.5	4.8
Doxycycline	IV	13	3 (6.98)	26	9.2
Metronidazole	IV	128	26 (60.47)	122	43.42
Amoxicillin-clavulanate	IV	19	3 (6.98)	8.98	3.19
Vancomycin	IV	22	4 (9.30)	21.5	7.65
Nitrofurantoin	Oral	7	1 (2.33)	7	2.49
Fluconazole	Oral	1	1 (2.33)	2	0.71
Acyclovir	IV	12	2 (4.65)	6.53	2.32
Total DDD/ 100 Patient Days= Total DDD of antimicrobial/ Total patient days x 100 = 356.2/281 x 100= 126.77					

The data are presented as a number (N); LD- Loading dose; *DDD is calculated only for adult patients aged >18 years. Pediatric patients were excluded from DDD analysis.

DDD-Daily Defined Dose; IV-Intravenous; TDS-Thrice a day; BD-Twice a day; OD-Once a day; QID- Quarter in Die.

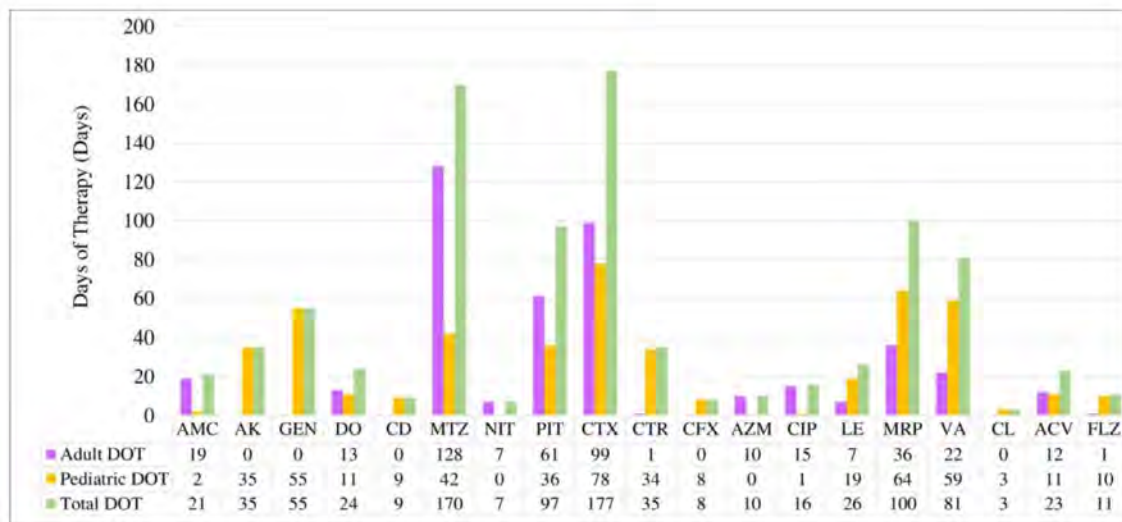
(range: 0.39 to 43.42 DDD per 100 patient-days) (Tab. II). Overall, the “Watch group” of antibiotics comprised a significant (65%) proportion of antibiotic consumption (DDD: 0.39 to 19.93 DDD per 100 patient-days), followed by the “Access group” (35%) with a DDD range of 2.49 to 43.42 DDD/100 patient-days. Only 0.5% of consumption was from the “Reserve category” (Tabs. I, II). In terms of days of therapy (DOT), overall antimicrobial consumption was 1180.75 DOT/1000 patient-days, as 908 antimicrobial DOT were used over 769 patient-days. In Adult patients, 431 DOT were used over 281 patient-days, corresponding to 1533.81 DOT/1000 patient-days; while pediatric patients (NICU and PICU) accounted for 477 DOT over 488 patient-days, corresponding to 977.46 DOT/1000 patient-days. This indicates that, descriptively, antimicrobial consumption measured as DOT/1000 patient-days was 1.6 times higher in adult ICUs than in pediatric ICUs. For antimicrobial level analysis, we applied a Poisson regression model, in which substantial overdispersion (Pearson $\chi^2/df=25.32$) was observed. Therefore, we used a negative binomial regression model with log(patient-days) as an offset, which showed no statistically significant difference in DOT rates at the antimicrobial level between pediatric and adult ICUs. In adults, the most commonly prescribed antimicrobials were metronidazole (128 DOT), cefotaxime (99 DOT), piperacillin-tazobactam (61 DOT), and meropenem (36 DOT). However, in pediatric patients, the most frequently prescribed were cefotaxime (78 DOT), meropenem (64 DOT), vancomycin (59 DOT), and gentamicin (54 DOT), (Fig. 2). Thus, three out of the four most commonly used antimicrobials were from the “Watch group”.

Antimicrobial prescriptions were evaluated for clinical appropriateness, of which 63.29% were appropriate, 25.32% were potential overuse, and 11.39% were

inappropriate, with no significant difference observed between pediatric and adult patients (*p-value*: 0.45) (Tab. III). Among 79 patients on antimicrobials, 22 (27.85%) received a single antimicrobial, 30 (37.97%) received two, 14 (17.72%) received three, and 13 (16.46%) received more than three antimicrobials. Based on the McCabe score, 11 patients (12.5%) had a rapidly fatal disease, 16 patients (18.18%) had an ultimately fatal disease, 50 patients (56.82%) had a non-fatal disease, and 11(12.5%) patients had an unknown status. All patients with rapidly fatal disease, as well as most patients with ultimately fatal disease, were receiving empirical antimicrobial therapy (Tab. IV). Potential overuse was observed in most patients with rapidly fatal disease, ultimately fatal disease, and surgical prophylaxis in craniotomy patients. Based on the microbiological culture report and biomarker assay, empirical therapy was modified in 86% (43/50) of patients. In the remaining 7 (14%) patients, the empirical regimen was continued without change following clinical review because it was considered appropriate in 5 patients according to culture and antimicrobial susceptibility test report, while in two patients with ultimately fatal illness, broad-spectrum therapy was continued despite negative culture and biomarker results (Fig. 3).

The demographic and clinical characteristics of patients who received antimicrobial therapy are presented in Table IV. Univariate analysis revealed that antimicrobial consumption was significantly higher among patients older than one year and adults. Increased usage was observed in the MICU, followed by the SICU and PICU, and among patients with urinary and central venous catheters (CVCs). It was also observed in those with two or more invasive devices and in those with ICU stays longer than 7 days (Range: 7-33 days). However, the lowest antimicrobial consumption was observed in

Fig. 2. Adult versus pediatric antimicrobial utilization based on Days of Therapy (DOT).



Negative Binomial Regression (Pediatric v/s adult)
Incidence Rate Ratio: 1.14
95% Confidence Interval: 0.81-1.61
P-value: 0.445

AMC; Amoxicillin-clavulanate; AK-Amikacin; GEN; Gentamicin; DO; Doxycycline; CD; Clindamycin; MTZ; Metronidazole; NIT; Nitrofurantoin; PIT; Piperacillin-tazobactam; CTX; Cefotaxime; CTR; Ceftriaxone; CFX; Cefixime; AZM; Azithromycin; CIP; Ciprofloxacin; LE-Levofloxacin; MRP; meropenem; VA; Vancomycin; CL-Colistin; ACV; Acyclovir; FLZ; Fluconazole.

Tab. III. Categorization of Antimicrobial Prescriptions Based on Clinical Appropriateness.

Category	Criteria	Adult (>18 years) N (%)	Paediatric (<18 years) N (%)	Total N (%)	χ^2 : 0.92, p-value: 0.63
Appropriate	Empiric therapy with appropriate indication, dose, route, frequency, and duration according to ICMR treatment guidelines, combination justified, targeted therapy based on culture-sensitivity report, PK-PD parameters considered, biomarkers (CRP, procalcitonin) suggestive of infection	22 (57.89)	28 (68.29)	50 (63.29)	
Potential overuse	Too many broad-spectrum agents used together, unnecessary duplication, or very broad combinations in mild/moderate illness, surgical prophylaxis >24hr	11 (28.95)	9 (21.95)	20 (25.32)	
Inappropriate use	No indication for antibiotics/ treating non-infectious causes with antibiotics (e.g., viral illness), or wrong antibiotic class (e.g., dual β -lactams), unsuitable routes or dosing intervals.	5 (13.16)	4 (9.76)	9 (11.39)	
Total		38 (100.0)	41 (100.0)	79 (100.0)	

Note: Data are presented as n (%). The Pearson chi-square test is used to compare adult and pediatric patients. A p-value of <0.05 was considered statistically significant.

PK-PD: Pharmacokinetic-Pharmacodynamic

the ≤ 1 -year age group, in the NICU, and among those with ICU stays of less than 4 days. Multivariable logistic regression was not applied because very few patients did not receive antimicrobials, preventing a stable estimation of the model.

Discussion

AMR is a complex issue influenced by various interconnected factors. The inappropriate and overuse of antimicrobials are major contributors to AMR [2].

Research indicates a strong correlation between antibiotic consumption and the rise of resistant pathogens [14, 15]. To tackle this challenge, the World Health Organization (WHO) has established a Global Action Plan that includes a standardized methodology for PPS to optimize antimicrobial use and combat AMR [16]. Notably, India is the world's leading consumer of antibiotics. Evaluating antimicrobial usage patterns in a hospital setting is crucial for effectively managing and mitigating antibiotic overuse, thereby tackling AMR [6]. This research provides critical insights into patterns of antimicrobial consumption in pediatric and adult

Tab. IV. Univariate analysis for the association of various risk factors with the consumption of antibiotics.

Variables	Total Surveyed Patients, N (%) (N=88)	Patients Receiving Antibiotics, N (%) (N=79)	p-value
Age group			
≤1 years	27 (30.68)	19 (70.37)	0.0058
2-18 years	18 (20.45)	17 (94.44)	
19-25 years	2 (2.27)	2 (100)	
26-54 years	22 (25)	22 (100)	
55-64 years	4 (4.55)	4 (100)	
≥65 years	15 (17.05)	15 (100)	
Gender			
Female	35 (39.77)	33 (94.29)	0.2562
Male	53 (60.23)	46 (86.79)	
ICU Type			
Medicine ICU	26 (29.55)	26 (100)	0.0007
Neonatal ICU	25 (28.41)	17 (68)	
Paediatric ICU	13 (14.77)	13 (100)	
Surgery ICU	16 (18.18)	16 (100)	
Plastic Surgery ICU	8 (9.09)	7 (87.5)	
McCabe Score			
Rapidly fatal	11 (12.5)	11 (100)	0.2038
Ultimately fatal	16 (18.18)	15 (93.75)	
Non-fatal	50 (56.82)	42 (84)	
Unknown	11 (12.5)	11 (100)	
Central vascular catheter			
Yes	29 (32.95)	29 (100)	0.0264
No	59 (67.05)	50 (84.75)	
Urinary catheter			
Yes	37 (42.05)	37 (100)	0.007
No	51 (57.95)	42 (82.35)	
Mechanical Ventilation			
Yes	33 (37.5)	32 (96.97)	0.0844
No	55 (62.5)	47 (85.45)	
No. of devices			
1	22 (25)	21 (95)	0.0319
2	9 (10.23)	9 (100)	
>2	19 (21.59)	19 (100)	
None	38 (43.18)	30 (78)	
Outcome			
Death	30 (34.1)	30 (100)	0.0228
Transfer out/ Discharged	58 (61.36)	49 (83.33)	
ICU stay (days)			
<4	16 (18.18)	13 (81.25)	0.1376
4-7	36 (40.90)	31 (86.11)	
>7	36 (40.90)	35 (97.22)	

Note: Data are presented as number (n) and percentage (%). Percentages were calculated row-wise using the total number of patients in each sub-group as the denominator. A p-value of <0.05 was considered statistically significant.

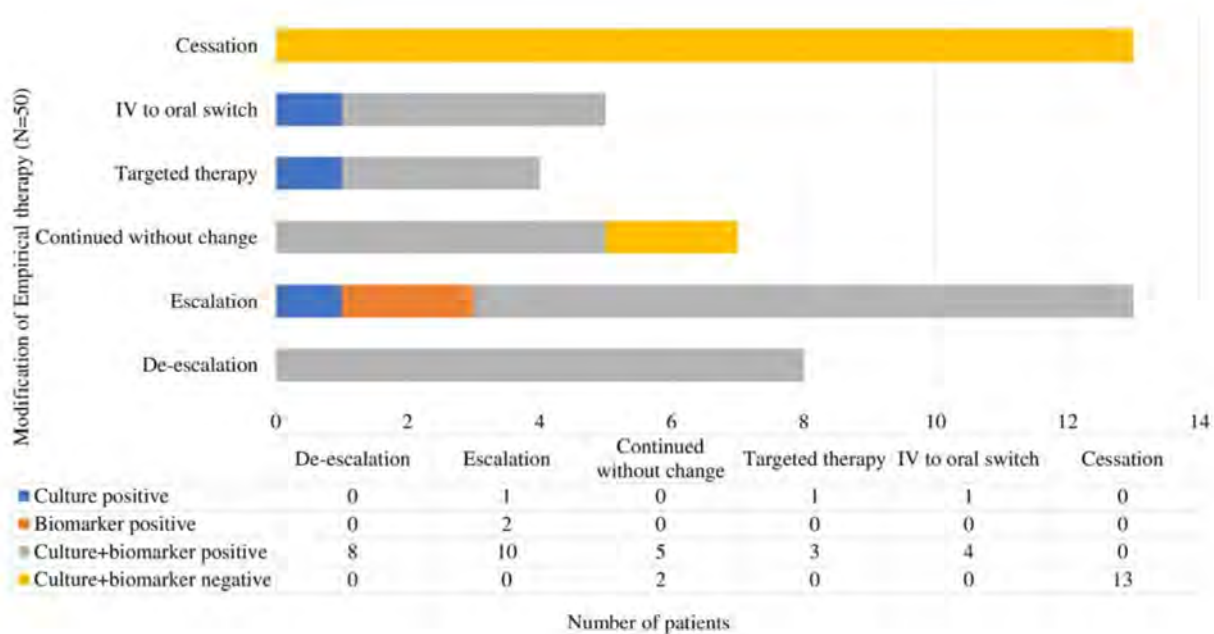
patients admitted to ICUs of a tertiary care teaching hospital, using a PPS methodology.

This study revealed a high prevalence of antimicrobial consumption in ICUs, with 79 of 88 cases (89.77%). A high prevalence of antimicrobial use in ICUs was also

reported in other PPS studies [17, 18]. A comparatively low prevalence (47.3-77.6%) was observed in similar hospital-based studies (which included both ICUs and wards) across different regions [19-23]. Our institute is a tertiary-care referral hospital in this area, with most referred patients being critically ill, having invasive devices, and several comorbidities; most admitted patients had rapidly progressive or ultimately fatal disease, and post-operative patients with suspected sepsis requiring empirical broad-spectrum antimicrobials. However, these consistently increasing rates of antimicrobial consumption highlight the critical need for effective stewardship interventions in high-dependency areas, such as ICUs.

In our cohort, the majority of prescribed agents for systemic use were antibacterials, with a small percentage of antivirals and antifungals (Tab. I). This aligns with findings from a PPS conducted by Porto et al., which reported that antibacterials accounted for over 89.9% of all antimicrobials used [22]. The most commonly prescribed antibiotics in our ICUs included cefotaxime, metronidazole, meropenem, piperacillin-tazobactam, and vancomycin (Tab. I, Fig. 3). This pattern is consistent with the studies from other countries, which reported that third-generation cephalosporins, β -lactam/ β -lactamase inhibitor combinations, and carbapenems were the predominant agents used [22, 24-26]. Cephalosporins are commonly prescribed for ICU patients because of their broad-spectrum activity against a wide range of pathogens and their well-tolerated nature, with a lower risk of adverse effects compared to other antibiotic classes. Additionally, piperacillin-tazobactam has favorable pharmacokinetic properties, including good tissue penetration and a prolonged half-life [27]. This makes them suitable choices for treating severe infections in critically ill patients, where achieving adequate drug concentrations is crucial for successful treatment. Furthermore, the use of broad-spectrum β -lactams or their combination aligns with the high rates of MDR Enterobacterales infections and the need for empirical treatment of sepsis in our patient cohort. Due to the high prevalence of MRSA in our institute, vancomycin is the preferred choice for gram-positive coverage in empirical therapy. Higher use of metronidazole was observed in our ICUs, mainly for gastrointestinal infections, aspiration pneumonia, and intra-abdominal surgeries. However, it was also found to be potentially overused in combination with β -lactam/ β -lactamase inhibitor combinations and/or carbapenems, reflecting unnecessary duplication of anaerobic coverage, which does not add value to therapeutic outcomes. It underscores a significant area for improvement in clinical practice, emphasizing the need for more judicious use of these medications to avoid unnecessary complexity in treatment regimens and potential adverse effects.

The increased usage of broad-spectrum “Watch” group antibiotics in this study (117/181, 65%) raises significant concerns, especially considering the WHO’s recommendations to limit their use to combat the emergence of AMR. A similar high prevalence (37.4%-

Fig. 3. Modifications of Empirical Antimicrobial Therapy Following Microbiological and Biomarker-Guided Assessment (N=50).

"continued without change" represents an active, guideline-concordant clinical decision following antimicrobial susceptibility test report review, rather than an absence of review or stewardship intervention.).

71.7%) of Watch antibiotics has been observed in hospital settings across other low- and middle-income countries (LMICs) [24, 28-32]. A multicenter review of AWaRe surveillance in LMICs analyzed that the higher proportions of Watch antibiotics in tertiary and teaching hospitals are often attributed to common practices in empiric treatment and to limitations in rapid diagnostic capabilities [32]. Analysis of the high use of Watch antimicrobial agents in our ICUs revealed concerns about treatment failures with Access antibiotics, availability and prescriber familiarity with Watch antibiotics, and the high prevalence of MDR organisms (MDROs) in ICUs. Similar contributing factors were also reported in a multicentric study in India [33].

In this PPS, DDD consumption in ICUs ranges from 0.39 to 43.42 DDD/100 patient-days, with varying levels of consumption observed for each antimicrobial. The highest DDDs were for metronidazole 500 mg (DDD=110), cefotaxime 1 g (DDD=41), and piperacillin-tazobactam 4.5 g (DDD=41.1), which are comparable to Wahlang et al.'s study, which reported high DDD consumption for these three antimicrobials [24]. Coenen et al. reported European surveillance data, in which DDD consumption ranged from 1.8 to 12.4 DDD/100 bed-days [34]. Mittal et al.'s study from North India reported that total antibiotic consumption in inpatient departments ranged from 60.22 to 102.42 DDD per 100 bed-days during 2017-2023 [6]. In terms of DOT/patient-days, antimicrobial utilization in pediatric patients was 0.98 DOT/patient-days, comparable to antimicrobial consumption in pediatric populations reported in other studies [35-37]. In adults, high antimicrobial DOTs were

for metronidazole, cefotaxime, piperacillin-tazobactam, and meropenem. However, in pediatric patients, cefotaxime, meropenem, vancomycin, and gentamicin were used. Similar patterns were reported in global-PPS conducted in Canadian hospitals [23].

The empirical antimicrobial therapy prescribed in our ICUs was significantly higher (n=50, 63.29%), comparable to other LMICs [2, 15] but higher than rates reported in higher-income countries [38, 39]. Most (52%, 26/50) patients receiving empirical therapy were classified as rapidly fatal and ultimately fatal disease based on the McCabe Score, influencing clinicians to initiate empirical therapy (Tab. IV). However, empirical treatments were reviewed based on biomarker and microbiological culture-susceptibility reports, except in two patients with ultimately fatal disease (Fig. 3). Moreover, in the potentially overused category, most of the prescriptions contained multiple therapies (n=13), overlapping β -lactam (n=5) and anaerobic coverage (n=5), and prolonged surgical prophylaxis (n=4). Only 20/79 (25.32%) of prescriptions were intended to treat HAIs and community-acquired infections, which are predominantly caused by MDROs. The prevalence of these MDROs further supports the observed tendency for empirical treatment escalation (26%, 13/50) in our ICUs. Prolonged surgical prophylaxis (>24 hours) and the use of multiple antimicrobials in craniotomy patients were contrary to current guideline recommendations [40]. This overuse of empirical antimicrobials and prolonged surgical prophylaxis creates unnecessary selective pressure, highlighting the urgent need to strengthen diagnostic stewardship and local prophylaxis guidelines.

Therefore, implementing continuous audit and feedback mechanisms may help to optimize prescribing behavior. In univariate regression analysis, antimicrobial use was significantly associated with age group, ICU type, presence of urinary and central venous catheters (CVCs), number of invasive devices, and patient outcome (Tab. IV). Similar drivers were also reported by Barbadoro et al. [20]. Higher antimicrobial use in patients with invasive devices and certain ICUs likely reflects more severe illness and a higher risk of HAIs.

During this study, we analyzed several key areas to improve antimicrobial stewardship and patient outcomes in our setup: establish protocols to limit the overuse of 3rd-generation cephalosporins, revise perioperative guidelines to avoid unnecessary long-term prophylaxis, and increase targeted therapy based on cultures. Enhancing medical documentation of antimicrobial changes will support better decision-making, while ongoing education and training for junior physicians, along with monitoring, will ensure compliance. Promoting collaboration among healthcare teams will provide comprehensive care and optimize antibiotic use, ultimately improving patient safety and combating antibiotic resistance. The findings call for stringent compliance with the WHO AWaRe classification framework, adoption of restrictive antibiotic policy, implementation of regular PPS, and enhanced diagnostic stewardship to facilitate appropriate de-escalation and cessation practices.

The study's limitations include its hybrid PPS, single-center design, small sample size, and reliance on a single-day PPS, which limit its ability to capture temporal fluctuations or variations in antibiotic duration. Although patients were enrolled using a PPS approach, antimicrobial consumption data were collected both retrospectively and prospectively to calculate DDDs and DOTs and to assess treatment modifications. This hybrid design differs from a traditional single-day PPS, which may limit the direct comparison of antimicrobial consumption metrics with other PPS studies. DDDs calculated in this study used patient-days as the denominator; therefore, they cannot be compared with those from other studies using bed-days as the denominator. Due to the small sample size and a high prevalence of antimicrobial use, findings of univariate analysis should be interpreted cautiously. This analysis was intended to identify potential factors associated with antimicrobial prescribing rather than establish independent predictors. Larger multicentric studies employing multivariable regression analyses are warranted to validate these observations and identify independent risk factors of antimicrobial use in ICUs. Despite these constraints, this is the first PPS study of antimicrobial consumption and prescribing patterns in this part of India, and it offers an essential baseline for developing antimicrobial stewardship initiatives within the institution and will assist in planning future adequately powered multicentre studies, including sample size estimation and refinement of the study methodology.

Conclusion

The high consumption of antimicrobials in ICUs is predominantly from the Watch category, with higher use for empirical therapy, indicating an urgent need for robust antimicrobial and diagnostic stewardship. The use of CVCs and ICU admissions >7 days were identified as key drivers of increased antimicrobial use in our ICUs. Implementing regular PPS, followed by an audit and comprehensive awareness training for clinicians, is imperative to address this issue. Future studies with large sample sizes are needed for more robust comparison between adult and pediatric antimicrobial consumption.

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Conflict of interest statement

None to declare.

Authors' contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript. NSB wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. NSB: Conceptualization, Data acquisition, Methodology, Investigation, Formal analysis, Writing and editing of the original draft. SPC: Supervision, Project Administration, Review of the original draft. AR: Data acquisition. SSZ: Conceptualization, Resources, Project Administration, Supervision, Review of the original draft. AVR: Resources, Project Administration, Supervision, Review of the original draft. MMT: Resources, Project Administration, Supervision, Review of the original draft. BBG: Resources, Project Administration, Supervision, Review of the original draft.

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HEALTH PROMOTION

Digital Health Literacy and Health-Seeking Behaviour Among Hospital Outpatients: Evidence from Traditional, Professional and Online Search Patterns

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Keywords

Digital competence • Health information literacy • Health-seeking behaviour • Outpatients • Preventive medicine

Summary

Introduction. Digital health literacy may shape how patients seek health information in increasingly digitalized environments where patients use computers, smartphones, tablets and AI-supported search tools to access health information. This study examined the association between digital health literacy competencies and traditional, professional and online health-seeking behaviour among hospital outpatients.

Methods. A cross-sectional descriptive-correlational survey was conducted with 400 volunteer outpatients aged 18 years and older at a training and research hospital in Türkiye. Participants were recruited equally from pulmonology, internal medicine, obstetrics and gynaecology, ophthalmology and cardiology clinics using quota-based convenience sampling. Data were collected using demographic questions, the Health-Seeking Behaviour Scale and the Digital Health Literacy Competency Scale for Citizens. Non-parametric group comparisons and Spearman correlation analyses were performed using SPSS 26.

Results. Traditional health-seeking behaviour had the highest mean score, followed by professional and online health-seeking behaviour. Online health-seeking behaviour was positively correlated with health information literacy ($r_s=.446$, $p<.001$) and digital competence ($r_s=.493$, $p<.001$). Online health-seeking behaviour, health information literacy and digital competence decreased with age and increased with education. Women reported higher online health-seeking behaviour and digital competence than men.

Conclusion. Digital health literacy competencies were most clearly associated with online health-seeking behaviour; while traditional and professional sources remained important. Outpatient clinics may be useful settings for practical, age-sensitive and education-sensitive digital health literacy support.

Introduction

Digital technologies have changed how patients access health information, arrange appointments, review test results, and communicate with health services. These developments have expanded health literacy beyond reading and understanding written health materials. Patients are increasingly expected to locate, evaluate, and apply health information in digital environments, often before they meet a clinician or after they leave an outpatient clinic [1, 2].

Digital health literacy refers to the competencies required to access, understand, evaluate, and use health information through digital technologies. It includes the ability to judge the quality of digital information, identify reliable sources, and use online information in ways that support appropriate health decisions [3, 4]. These competencies are relevant to patient engagement, decision-making, communication with health professionals, and effective use of health services [5, 6]. The importance of digital health literacy has increased because digital health information is abundant but uneven in quality. Patients may encounter official portals,

hospital websites, social media posts, commercial platforms, personal blogs, or artificial intelligence-supported search tools. Access to information alone therefore does not guarantee informed decision-making. Patients also need the ability to compare sources, understand uncertainty, recognize misinformation, and decide when professional consultation is required.

Türkiye provides a relevant setting for examining this issue because digital access is widespread but not uniformly converted into digital health competence. National ICT statistics show that internet use among individuals aged 16-74 increased to 88.8% in 2024, while household internet access reached 96.4% [14]. Mobile connectivity is also extensive; early-2024 estimates reported 80.69 million cellular mobile connections, equivalent to 93.8% of the population, indicating that smartphones are a major route into digital environments [15]. At the same time, PCs, tablets and smartphones differ in usability, screen size, privacy, and ability to complete formal health-service tasks. Artificial intelligence is also becoming part of the digital information environment: even where organizational adoption remains uneven, AI-supported search, recommendation and conversational

tools may increasingly influence how patients formulate questions, interpret symptoms and evaluate online health information [16, 17].

Health-seeking behaviour is also central to patient engagement. Individuals may respond to health concerns by consulting family members or trusted social contacts, seeking support from health professionals, or searching for information online [7, 8]. These pathways can be conceptualized as traditional, professional, and online health-seeking behaviours. In digitalized health environments, these forms do not necessarily replace one another. Patients may use digital information while continuing to rely on professional and informal sources. Hospital outpatients are an important group for studying these relationships. Unlike general population samples, outpatients are already interacting with the health system and may have immediate health concerns, diagnostic needs, chronic disease follow-up, or prior service-use experiences. They may also use digital platforms before, during, or after outpatient encounters to interpret symptoms, prepare questions, use appointment systems, or understand test results.

This outpatient context is particularly relevant for health literacy research because it connects information behaviour with real service use. A person attending an outpatient clinic may have searched the internet before the visit, may ask a clinician to confirm information obtained from relatives or online sources, and may use digital systems afterward to follow results or recommendations. For this reason, outpatient settings provide an opportunity to understand digital health literacy as part of a broader pattern of health-seeking rather than as an isolated technical skill.

Previous studies have examined health literacy, eHealth literacy, digital literacy, and health information-seeking behaviour in different populations [3, 8, 9]. However, the association between digital health literacy competencies and multiple forms of health-seeking behaviour among hospital outpatients remains insufficiently clarified. This distinction matters because digital health engagement may complement, rather than replace, face-to-face and socially embedded health-seeking practices.

The aim of this study was to examine the relationship between digital health literacy competencies and traditional, professional, and online health-seeking behaviours among adult hospital outpatients. The primary expectation was that higher digital health literacy competencies would be positively associated with online health-seeking behaviour. Differences according to gender, age, education, occupation, and outpatient clinic type were examined as exploratory subgroup analyses.

CONCEPTUAL FRAMEWORK

This study conceptualizes digital health literacy as an overarching construct that includes both health information literacy and digital competence. Health information literacy refers to the ability to understand, evaluate, and apply health-related information, whereas digital competence refers to the ability to use digital

tools and digital environments to obtain, assess, and manage health information.

This distinction is important because digital health literacy is frequently reduced to internet use or technical access. In this study, the Health-Seeking Behaviour Scale and the Digital Health Literacy Competency Scale for Citizens were therefore treated as two different but related measurements. The Health-Seeking Behaviour Scale captures the practical behaviour of seeking help or information through traditional, professional and online channels. By contrast, the Digital Health Literacy Competency Scale for Citizens captures the competence needed to understand health information and to use digital tools when managing online health information. Health-seeking behaviour was treated as a multidimensional construct consisting of traditional, professional, and online domains. Traditional health-seeking refers to informal and socially embedded practices, professional health-seeking refers to consulting health professionals, and online health-seeking refers to searching digital sources for health information. These are actions or behavioural pathways, not technical skills. The three health-seeking domains may overlap in everyday patient behaviour. Online searching may lead a patient to seek professional help, professional advice may encourage a patient to use a digital portal, and family members may guide older adults in using online systems. Therefore, higher online health-seeking should not automatically be interpreted as lower professional care use, and higher traditional health-seeking should not be interpreted as resistance to digital health. The relationships among these domains require cautious interpretation.

This framework avoids treating digital health engagement as a replacement for professional or traditional health-seeking. Instead, it examines whether digital health literacy is associated most strongly with online health-seeking while recognizing that outpatients may combine multiple sources of information and support. This approach is suitable for outpatient settings, where patients are simultaneously exposed to clinical advice, social support, and digital information.

Methods

STUDY DESIGN AND SETTING

This cross-sectional descriptive-correlational study was conducted among adult outpatients at Samsun Training and Research Hospital in Türkiye. The selected outpatient clinics were pulmonology, internal medicine, obstetrics and gynecology, ophthalmology, and cardiology. These clinics were selected because they were the five departments with the highest number of outpatient visits according to hospital records during the study period from August 9, 2024, to December 9, 2024. The study was designed to describe digital health literacy competencies and health-seeking behaviour patterns and to examine associations among their subdimensions. Because the design was cross-sectional, the analyses

identify associations at one point in time and do not establish causal direction. This design was considered appropriate for an outpatient survey intended to generate evidence on patient information behaviour in a clinical service environment.

PARTICIPANTS AND SAMPLING

The study population consisted of patients aged 18 years and older who applied for outpatient care at the selected clinics. Patients younger than 18 years, emergency department patients, and patients attending clinics outside the five selected departments were excluded. The five selected clinics had 245,923 outpatient visits during the reference period.

The minimum required sample size was calculated as 385 participants, and 400 volunteers were included to account for possible incomplete responses. Participants were recruited using quota-based convenience sampling. Eighty participants were recruited from each clinic, corresponding to 20% of the sample per clinic. This balanced design enabled exploratory clinic comparisons but should not be interpreted as a probability sample of all outpatients.

The quota approach was used to avoid the dominance of a single high-volume clinic in the sample. However, because patients were recruited voluntarily and not randomly selected from all eligible outpatient visits, the sample should be understood as a balanced outpatient sample rather than a representative hospital-wide sample. Clinic-based comparisons are therefore reported as exploratory findings.

DATA COLLECTION

Data were collected through a face-to-face questionnaire administered by the researcher in outpatient clinic settings. Eligible patients were invited to participate voluntarily. Before completing the questionnaire, participants were informed about the study purpose, voluntary participation, and confidentiality of responses. The same questionnaire and data collection procedure were used across all five clinics.

Face-to-face data collection was preferred because the study included participants with different ages and education levels and because some patients may have had limited familiarity with digital questionnaires. This approach helped ensure that participants could complete the survey in a consistent manner. At the same time, the face-to-face procedure may have introduced social desirability bias, especially in questions concerning digital skills or health-seeking practices. This possibility is acknowledged in the limitations.

MEASURES

The questionnaire included demographic questions, the Health-Seeking Behaviour Scale, and the Digital Health Literacy Competency Scale for Citizens. Demographic variables included gender, age, education level, occupation, and outpatient clinic type. Residential area was not included as a questionnaire variable; therefore, urban-rural comparisons could not be performed.

Health-seeking behaviour was measured using the Health-Seeking Behaviour Scale developed by Kırac and Öztürk [7]. The scale includes 12 items and three subdimensions: traditional, professional, and online health-seeking behaviour. Items are scored on a five-point Likert-type response format; therefore, scale values are ordinal/discontinuous at the item level. Traditional health-seeking reflects reliance on informal sources and previous experiences; professional health-seeking reflects consulting health professionals; and online health-seeking reflects the use of digital or internet-based sources for health information.

Digital health literacy competencies were measured using the Digital Health Literacy Competency Scale for Citizens, adapted by İder [13]. The scale includes 26 items and two subdimensions used in this study: health information literacy and digital competence. Health information literacy reflects the ability to understand, evaluate, and use health-related information. Digital competence reflects the ability to use digital tools and digital environments to access and evaluate health information. Thus, this scale measures competence, whereas the Health-Seeking Behaviour Scale measures behavioural actions.

RELIABILITY AND STATISTICAL ANALYSIS

Internal consistency coefficients were calculated for the scale scores in the present sample. Cronbach alpha was .953 for the Digital Health Literacy Competency Scale for Citizens and .698 for the Health-Seeking Behaviour Scale. The latter value was interpreted cautiously as marginal but acceptable for exploratory analysis. Reliability was therefore described as the internal consistency of the scores obtained in this sample rather than as a fixed property of the instruments.

Data were analysed using SPSS 26. Descriptive statistics summarized participant characteristics and scale scores. Because the Health-Seeking Behaviour Scale uses five-point Likert-type responses and the relevant variables did not meet normality assumptions, inferential analyses were based on nonparametric methods. Mann-Whitney U tests were used for two-group comparisons, Kruskal-Wallis tests for comparisons involving more than two groups, and post hoc comparisons for significant Kruskal-Wallis results. Spearman rank correlation coefficients examined associations among scale subdimensions. Medians and ranges were emphasized in group comparisons, while means and standard deviations were retained only as conventional descriptive summaries of aggregated scale scores.

Statistical significance was set at $p < .05$; p values smaller than .001 were reported as $p < .001$. The primary analysis focused on the relationship between digital health literacy competencies and online health-seeking behaviour. Comparisons by gender, age, education, occupation, and clinic type were treated as exploratory subgroup analyses. Because multivariable adjustment was not performed, subgroup findings and correlations were interpreted as associations rather than independent effects.

ETHICS

Ethical approval was obtained from Ondokuz Mayıs University, and institutional permission was obtained from Samsun Training and Research Hospital before data collection. Participation was voluntary, and informed consent was obtained from participants. No personally identifying information was reported in the manuscript.

Results

PARTICIPANT CHARACTERISTICS

A total of 400 outpatients participated in the study. Participants were recruited equally from five clinics, with 80 participants from each clinic. The sample included 234 women and 166 men. The largest age group was 18-33 years, followed by 34-49 years, 50-65 years, and 66 years and older. Most participants had completed high school or higher education. The occupational category labelled “other” included a large proportion of the sample and should therefore be interpreted cautiously. Participant characteristics are shown in Table I.

DESCRIPTIVE FINDINGS

Traditional health-seeking behaviour had the highest descriptive score ($M=4.69$, $SD=0.56$), followed by professional health-seeking behaviour ($M=3.40$, $SD=1.38$) and online health-seeking behaviour ($M=2.85$, $SD=1.04$). Health information literacy had a mean score of 5.15 ($SD=2.07$), and digital competence had a mean score of 4.29 ($SD=1.84$). Because the HBS

Tab. II. Descriptive Statistics for Scale Subdimensions.

Subdimension	Mean	SD	Minimum	Maximum
Online health-seeking	2.85	1.04	1.00	5.00
Traditional health-seeking	4.69	0.56	1.00	5.00
Professional health-seeking	3.40	1.38	1.00	5.00
Health information literacy	5.15	2.07	0.00	7.00
Digital competence	4.29	1.84	0.00	7.00

Note. HBS subdimensions are based on five-point Likert-type responses (1-5). DHLC subdimensions are scored on a 0-7 metric. Higher values indicate higher levels of the relevant behaviour or competence. Means and SDs are descriptive summaries of aggregated scale scores; nonparametric tests and median-based group summaries were used for inferential comparisons.

is based on a five-point Likert-type format and the analyses were nonparametric, these mean values should be interpreted as descriptive summaries rather than as evidence of interval-level measurement. Descriptive statistics and scale interpretation notes are shown in Table II.

GROUP DIFFERENCES

Women reported higher online health-seeking behaviour than men (median 3.00 vs. 2.33; $z=-3.395$, $p=.001$). Digital competence also differed by gender, with higher median scores among women than men (5.00 vs. 3.88; $z=-3.562$, $p<.001$). Health information literacy did not differ significantly by gender ($z=0.599$, $p=.549$).

Age-based comparisons showed significant differences in online health-seeking behaviour, professional health-seeking behaviour, health information literacy, and digital competence. Online health-seeking behaviour declined across age groups ($H=76.613$, $p<.001$), while professional health-seeking behaviour increased with age ($H=28.227$, $p<.001$). Traditional health-seeking behaviour did not differ significantly by age ($H=14.367$, $p=.065$). Digital competence showed a pronounced age-related difference ($H=167.790$, $p<.001$).

Education-based comparisons showed significant differences in online and professional health-seeking behaviour. Online health-seeking behaviour increased with education ($H=63.888$, $p<.001$), while professional health-seeking behaviour differed by education ($H=41.204$, $p<.001$), with lower median scores among participants with higher education. Health information literacy ($H=82.341$, $p<.001$) and digital competence ($H=142.043$, $p<.001$) also differed significantly by education level.

Occupation-based comparisons showed significant differences in online health-seeking behaviour, professional health-seeking behaviour, health information literacy, and digital competence. Retirees generally had lower online health-seeking behaviour, health information literacy, and digital competence scores than several other occupational groups. Clinic-based comparisons also showed significant differences

Tab. I. Participant Characteristics.

Characteristic	Category	n	%
Gender	Female	234	58.5
	Male	166	41.5
Age	18-33 years	160	40.0
	34-49 years	117	29.3
	50-65 years	89	22.3
	66 years and older	34	8.5
Education	Primary school	69	17.3
	Middle school	42	10.5
	High school	136	34.0
	Higher education	141	35.3
Occupation	Master's degree	12	3.0
	Civil servant	60	15.0
	Worker	49	12.3
	Retired	69	17.3
	Other	222	55.5
Clinic	Pulmonology	80	20.0
	Internal medicine	80	20.0
	Obstetrics and gynecology	80	20.0
	Ophthalmology	80	20.0
	Cardiology	80	20.0

Note. Percentages are based on $N=400$. Clinic quotas were fixed at 80 participants per clinic. Residential area (urban/rural) was not collected and could not be compared.

Tab. III. Selected Group Comparisons.

Variable	Comparison	Finding	Test statistic	<i>p</i>
Gender	Online health-seeking	Women > men	$z=-3.395$	.001
Gender	Digital competence	Women > men	$z=-3.562$	< .001
Age	Online health-seeking	Decreased with age	$H=76.613$	< .001
Age	Professional health-seeking	Increased with age	$H=28.227$	< .001
Age	Digital competence	Decreased with age	$H=167.790$	< .001
Education	Online health-seeking	Increased with education	$H=63.888$	< .001
Education	Digital competence	Increased with education	$H=142.043$	< .001

Note. Findings summarize the direction of statistically significant nonparametric comparisons. Median values are reported in the text for key two-group comparisons. H =Kruskal-Wallis statistic; z =Mann-Whitney U standardized statistic.

Tab. IV. Spearman Correlations Among Scale Subdimensions.

Variable	1	2	3	4	5
1. Online health-seeking	-				
2. Traditional health-seeking	.095	-			
3. Professional health-seeking	-.130**	-.038	-		
4. Health information literacy	.446***	.303***	-.172**	-	
5. Digital competence	.493***	-.021	-.197***	.548***	-

Note. Values are Spearman rank correlation coefficients (r_s), used because the scale distributions were non-normal and Likert-type scores are ordinal/discontinuous at the item level. ** $p<.01$; *** $p<.001$.

in online health-seeking behaviour, professional health-seeking behaviour, health information literacy, and digital competence. Because occupational and clinic comparisons were exploratory, they should be interpreted cautiously. Selected group comparisons are summarized in Table III.

CORRELATIONS AMONG SCALE DIMENSIONS

Spearman correlation analyses showed that online health-seeking behaviour was positively correlated with health information literacy ($r_s=.446$, $p<.001$) and digital competence ($r_s=.493$, $p<.001$). Online health-seeking behaviour was weakly and negatively correlated with professional health-seeking behaviour ($r_s=-.130$, $p=.009$). Traditional health-seeking behaviour was weakly and positively correlated with health information literacy ($r_s=.303$, $p<.001$) but not significantly correlated with digital competence ($r_s=-.021$, $p=.668$). Professional health-seeking behaviour was weakly and negatively correlated with health information literacy ($r_s=-.172$, $p=.001$) and digital competence ($r_s=-.197$, $p<.001$). Health information literacy was moderately and positively correlated with digital competence ($r_s=.548$, $p<.001$). Correlations are shown in Table IV.

Discussion

This study examined the relationship between digital health literacy competencies and health-seeking behaviour among hospital outpatients in Türkiye. The main finding was that digital health literacy was most clearly associated with online health-seeking behaviour. Participants with higher health information literacy and digital competence reported higher online health-seeking

scores. This finding is consistent with the expectation that patients who can understand health information and use digital tools are more likely to search for health information online. However, the cross-sectional design does not allow causal interpretation.

The positive correlations between online health-seeking behaviour and the two digital health literacy dimensions are meaningful for outpatient care in a setting where internet and mobile access are widespread [14, 15]. Patients who are able to interpret health information and use digital tools may be better positioned to search for information before visits, prepare questions, and follow up on recommendations after clinical encounters. At the same time, frequent online searching may itself contribute to the development of digital competence. The observed association should therefore be understood as reciprocal or mutually reinforcing rather than one-directional.

Traditional health-seeking behaviour had the highest descriptive score ($M=4.69$, $SD=0.56$), followed by professional health-seeking behaviour ($M=3.40$, $SD=1.38$) and online health-seeking behaviour ($M=2.85$, $SD=1.04$). Health information literacy had a mean score of 5.15 ($SD=2.07$), and digital competence had a mean score of 4.29 ($SD=1.84$). Because the HBS is based on a five-point Likert-type format and the analyses were nonparametric, these mean values should be interpreted as descriptive summaries rather than as evidence of interval-level measurement. Descriptive statistics and scale interpretation notes are shown in Table II.

The persistence of traditional health-seeking behaviour has practical significance. Digital health education programmes may be less effective if they assume that patients make decisions only as individual users of online information. In many cases, patients interpret health

information within family and social networks. Health educators may therefore need to design messages that encourage patients to verify informal advice, to discuss online or socially obtained information with health professionals, and to recognize when AI-supported tools provide general information rather than clinical judgement [17].

Professional health-seeking behaviour showed weak negative correlations with health information literacy and digital competence. This result should not be interpreted as evidence that digital health literacy reduces appropriate professional care. Several alternative explanations are possible. Individuals with higher digital health literacy may use online information to decide when consultation is necessary, while older adults or individuals with greater health needs may rely more strongly on professional care. In this study, professional health-seeking behaviour increased with age, which may reflect greater health service needs, chronic disease burden, or more frequent interaction with clinicians.

Age and education differences were especially important. Online health-seeking behaviour, health information literacy, and digital competence declined across older age groups, a pattern consistent with broader discussions of the digital divide [10-12]. Similar Turkish evidence has shown that younger adults report higher online health-information seeking than older adults [19]. Education was also strongly associated with online health-seeking behaviour and digital health literacy. These findings suggest that digital health literacy is shaped not only by access to technologies but also by broader educational and information-processing resources [2, 5].

The age-related pattern should be interpreted carefully. Lower digital competence among older outpatients does not mean that older adults cannot benefit from digital health tools. Rather, it suggests that the design and delivery of digital health support should consider usability, confidence, prior experience, and the need for guided practice. Older patients may benefit from demonstrations, printed step-by-step guides, caregiver involvement, and opportunities to ask questions about official digital platforms.

Gender differences showed higher online health-seeking behaviour and digital competence among women. This pattern may reflect differences in health information engagement, but the study did not measure caregiving roles, household health responsibilities, or motivations for seeking information. Occupation-based findings also require caution because retirement status overlaps with age, and the “other” category was large. Clinic-based differences should also be interpreted as exploratory because the sample was balanced by quota rather than randomly selected.

Overall, the findings contribute to the literature by showing that digital health literacy among outpatients is associated primarily with online health-seeking behaviour, while traditional and professional health-seeking remain visible parts of patients’ health

information practices. International studies describe a persistent digital divide in which older age, lower education and limited digital skills constrain the use of online health information [9, 10-12]. The present findings extend that discussion to hospital outpatients in Türkiye, where broad internet and mobile access creates opportunities for digital health engagement but does not eliminate differences in competence, confidence and preferred sources of help [14, 15].

PRACTICAL IMPLICATIONS FOR PREVENTIVE MEDICINE AND PUBLIC HEALTH

The findings have practical implications for health education in outpatient settings. Clinics can provide brief guidance on reliable digital health resources, appointment systems, laboratory result portals, and safe use of online health information. Older adults, retirees, and patients with lower education levels may benefit from simple, visual, and step-by-step support. Health educators should help patients connect online information-seeking with appropriate professional consultation rather than presenting digital information as an alternative to professional care.

Outpatient clinics may be suitable settings for short and low-cost digital health literacy activities. For example, waiting areas can display guidance on how to identify official health websites, use appointment and result systems, evaluate online claims, and discuss internet-based or AI-generated information with clinicians. Such guidance is particularly important because AI-supported search tools may provide fluent but incomplete or non-contextual health information; patients therefore need practical skills for verification, uncertainty recognition and appropriate professional consultation [18].

The high level of traditional health-seeking behaviour suggests that interventions should acknowledge the role of families and social networks. Educational messages can encourage patients to compare advice from relatives, friends, or online sources with professional recommendations. This approach may reduce the risk of misinformation while respecting the social nature of health decision-making.

Clinic-specific tailoring may also be useful. Patients in clinics with older or chronic disease profiles may need more assistance with digital follow-up, appointment management, medication information, and disease-specific resources. Rather than applying a single digital education model to all outpatients, clinics can adapt materials to patient age, education level, and service needs [19].

LIMITATIONS

This study has limitations. It was conducted in a single hospital and used a cross-sectional design, volunteer participation, and quota-based convenience sampling. The findings cannot establish causal relationships or be generalized to all outpatient populations. The data were self-reported and may be affected by recall or social desirability bias.

The analyses were based on nonparametric group comparisons and bivariate correlations, and multivariable regression was not performed. Therefore, the study cannot determine whether observed associations remain significant after simultaneous adjustment for age, education, gender, occupation, and clinic type. The 66 years and older group was relatively small, and the “other” occupational category limited interpretation of occupational differences.

The study did not directly measure several factors that may influence health-seeking behaviour, including chronic disease status, health anxiety, trust in information sources, internet access, digital device ownership, type of device used (PC, smartphone or tablet), caregiver support, frequency of internet use and use of AI-supported tools. It also did not collect information on whether participants lived in urban or rural areas; therefore, urban-rural comparisons could not be conducted. Future studies should include these variables and use multivariable or longitudinal designs to better explain how digital health literacy relates to health-seeking behaviour over time.

Conclusion

Digital health literacy competencies were positively associated with online health-seeking behaviour among hospital outpatients, while traditional health-seeking remained highly visible. Age and education differences suggest that digital health literacy support should be tailored to patients’ needs and capacities.

The findings indicate that digital health literacy should be understood as part of a broader health-seeking context that includes online, professional, and traditional sources. Outpatient clinics may provide useful settings for practical digital health literacy education. Such efforts should help patients find reliable information, evaluate online content critically, and use digital information in ways that complement appropriate professional care.

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Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

PT contributed to conceptualisation, supervision, manuscript revision and final approval of the article. MD contributed to data collection, thesis-based study development and preliminary analysis. Both authors reviewed and approved the final version of the manuscript.

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HEALTH PROMOTION

Factors associated with HPV vaccination coverage before pregnancy: a cross-sectional study in a cohort of Pregnant Women

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Keywords

HPV vaccination • Pregnant women • Vaccine hesitancy • Risk perception • Socio-demographic factors

Summary

Background. Human papillomavirus (HPV) infection is a major cause of cervical and other anogenital cancers. Despite the availability of effective vaccines, HPV vaccination coverage remains suboptimal in Italy, particularly among women of childbearing age. Pregnant women represent a key population for investigating vaccine hesitancy and its determinants. This study aimed to explore socio-demographic, behavioural, and perceptual factors associated with HPV vaccination coverage prior to pregnancy, using data from the NEHO cohort in Southern Italy.

Methods. A cross-sectional analysis was conducted on 567 pregnant women enrolled between 2018 and 2020 in the Priolo National Priority Site. HPV vaccination status was obtained from local immunization databases. Risk perception indices (HPI, EHPI, HRPI, RPI), and information sources were assessed via structured questionnaires. Logistic regression and Bayesian Weighted Quantile Sum (bWQS) models were used to identify

associations between vaccination status and independent variables.

Results. Only 7.4% of participants had HPV vaccination coverage prior to pregnancy. Vaccinated women were significantly younger, unmarried, and more likely to have lower educational levels. Higher scores on environmental and exposure hazard perception indices (HPI and EHPI) were positively associated with vaccination uptake. Vaccinated individuals were more likely to attribute health protection responsibility to national institutions and industry leadership. bWQS regression confirmed the relevance of risk perception in shaping vaccination behaviour, with EHPI contributing most to the overall effect.

Conclusion. The results of this study suggest that tailored public health strategies that address risk perception, institutional trust, and population-specific dynamics are essential to increase HPV vaccination coverage and reduce health inequalities.

Introduction

Human papillomavirus (HPV) refers to a group of viruses that cause the most prevalent sexually transmitted infection [1] and represents the second leading cause of cancer linked to an infectious agent [2], being strongly associated with anogenital and oropharyngeal malignancies [3, 4].

HPV-related cancers represent 5% of new global cancer cases [5]. Annually in Europe, there are an estimated 58,169 new cases of cervical cancer and 17,486 cervical cancer deaths [6]. In 2018, the Italian Health System incurred direct costs of €542.7 million for HPV-related diseases, which may increase by €16.2–€37.5 million with innovative cancer therapies [7].

HPV vaccination is a highly effective primary prevention strategy for reducing infections and HPV-related cancer [8]. Herd protection has been significantly observed when vaccination coverage exceeds 50% [9, 10].

Since their introduction in 2006, HPV vaccines have been endorsed by the World Health Organisation (WHO) as a critical public health measure, with official

recommendations beginning in 2009 [11]. In line with these efforts, the WHO has launched the global strategy for the elimination of cervical cancer as a public health problem, based on the so-called “90-70-90” targets: 90% of girls fully vaccinated with the HPV vaccine by age 15, 70% of women screened with a high-performance test by ages 35 and 45, and 90% of women identified with cervical disease receiving appropriate treatment. Achieving these targets is expected to drastically reduce the global burden of HPV-related cancers and underscores the central role of vaccination in comprehensive cancer prevention strategies [12].

Currently, three HPV vaccines are approved for use in the European Union: the bivalent vaccine Cervarix (GlaxoSmithKline Biologicals), the quadrivalent vaccine Gardasil (MSD Vaccins), and the nonavalent vaccine Gardasil 9 (MSD Vaccins), with the latter currently representing the main HPV vaccine in use [13].

In Italy, HPV vaccination has been actively provided free of charge to 11-year-old girls since 2007/2008. Recognizing the advantages of gender-neutral immunization campaigns, the programme was expanded to include 11-year-old boys and was implemented

nationwide by 2018. Additionally, catch-up vaccination is recommended for women up to the age of 26, especially during their initial cervical cancer screening [14]. Beyond this, HPV vaccination in Italy is also recommended for specific high-risk groups, including women treated for high-grade cervical intraepithelial neoplasia (CIN II or III), people living with HIV regardless of age, and men who have sex with men (MSM), who are at increased risk of HPV infection and related diseases [15].

Despite these efforts, HPV vaccination coverage in Italy remains below the 95% target for 12-year-olds set by the National Vaccination Prevention Plan. According to national data, coverage in the 2021 birth cohort is approximately 51% among girls and 45% among boys, with no Italian region reaching the recommended target established by the National Vaccination Prevention Plan [16].

The prevalence of HPV among pregnant women suggests a higher risk of infection compared to non-pregnant women [17, 18]. HPV infection has been detected in maternal and fetal tissues [19], possibly influenced by physiological and immunological changes occurring during gestation [20, 21].

While the relationship between HPV infection and pregnancy outcomes remains unclear [22], some studies suggest adverse effects such as preterm birth [23], spontaneous abortion [24], premature rupture of membranes [25], intrauterine growth restriction [26], low birth weight [27], hypertensive disorders and fetal death [28]. However, conflicting evidence exists, with some authors finding no significant association [29, 30]. Moreover, a population-level analysis has provided the first evidence that HPV vaccination reduces negative pregnancy outcomes, such as preterm birth and low birth weight, in vaccinated women [31].

Inequalities in HPV vaccination uptake are driven by several factors, including inadequate knowledge about HPV, which is strongly linked to lower vaccination rates. In fact, greater HPV-related knowledge is associated with more positive attitudes toward vaccination and a stronger intention to vaccinate [32]. Although HPV vaccination is ideally administered before sexual debut through school-based programmes, several factors influencing vaccination uptake in adolescents and young adults have been identified, including risk perception, vaccine cost, and healthcare provider recommendations [33], alongside low awareness of HPV infection, particularly among Italian adolescents and young women [34]. Socioeconomic disparities also play a significant role, as lower educational attainment, and socioeconomic status limit access to health information, reduce health-related knowledge, and contribute to unhealthy behaviours [35, 36]. Additional barriers to vaccination include fears of side effects, inconsistent advice from healthcare providers, limited access to reliable information [37, 38], as well as a lack of trust in the medical system [39, 40]. In this perspective, perception of environmental health hazards may reflect a broader cognitive framework related to health risk appraisal and preventive orientation,

potentially influencing attitudes toward preventive behaviours such as vaccination.

This study aims to analyse the factors influencing HPV vaccination coverage prior to pregnancy among women enrolled during pregnancy, with a focus on understanding and addressing disparities in vaccine uptake. Vaccine hesitancy is defined by the World Health Organisation Strategic Advisory Group of Experts (SAGE) as the delay in acceptance or refusal of vaccination despite availability of vaccination services. It is a complex and context-specific phenomenon, varying across time, place, and vaccines, and influenced by factors such as complacency, convenience, and confidence [41]. Pregnant women have recently been identified as a key population for studying vaccine hesitancy, mainly in relation to maternal immunizations such as influenza, Tdap and RSV vaccines, particularly in Western countries where hesitancy has grown significantly [42]. In this context, pregnancy offers a valuable opportunity to explore attitudes toward vaccination more broadly, including previous HPV vaccination behaviours.

By exploring these determinants, this research seeks to bridge gaps in the existing literature and provide actionable insights to inform targeted public health interventions.

Materials and Methods

STUDY DESIGN

This study was conducted using data collected within the NEHO cohort study [43], which employed an previously validated questionnaire and, between January 2018 and January 2020, voluntarily enrolled pregnant women residing in three National Priority Sites for Environmental Remediation (SIN) in Southern Italy, including Crotone, Priolo, and Milazzo, as well as in the corresponding Local Reference Areas (LRAs), characterized by similar geographic and socio-demographic features but were located outside the SIN boundaries. For the present study, 567 participants were selected from the NEHO cohort in the Priolo SIN and its associated LRAs. Vaccination data were retrieved from the provincial immunization database of the local Health Department, which systematically records all administered vaccines, regardless of the setting in which they were delivered (*e.g.*, school-based programmes, vaccination centers, pharmacies, or physicians).

STUDY VARIABLES

Information for this study was collected through questionnaires administered during the third trimester of pregnancy. The data included socio-demographic characteristics (age, marital status, educational level, place of residence, and overcrowding index) and lifestyle habits (alcohol consumption, folate supplementation, physical activity, smoking habits, and breastfeeding duration). HPV vaccination status was recorded as a binary variable (Yes/No).

Environmental and health risk perception was assessed

using four specific indices: Hazard Perception Index (HPI): assessment of perceived environmental hazards in the area of residence; Exposure Hazard Perception Index (EHPI): perception of exposure to these hazards; Health Risk Perception Index (HRPI): perception of health risks related to specific conditions, such as allergies, chronic respiratory diseases, infertility, and cancer; Risk Perception Index (RPI): a composite index integrating various perceptions of environmental and health risks. Participants were also asked about their beliefs regarding responsibility for public health protection. Specifically, they were asked whether they considered national institutions, local institutions, industry leadership, local health authorities (*e.g.*, ASP, general practitioners), and individual citizens to be responsible for safeguarding health. Responses were recorded as binary variables (yes/no) for each actor. In addition, participants were asked to indicate which sources they normally rely on to obtain information about environmental and health risks. These sources included national media, local media, healthcare professionals and organisations, scientists, factory workers, the internet, and personal networks (*e.g.*, family, friends, colleagues). Responses were also collected as binary variables for each information source.

STATISTICAL ANALYSIS

Descriptive statistics were computed for all variables, with categorical variables presented as frequencies and percentages, and continuous variables summarized using medians and interquartile ranges due to non-normal distributions. Associations between HPV vaccination status (Yes/No) and categorical variables (*e.g.*, socio-demographic characteristics, behavioural factors, beliefs about health protection, and information sources) were evaluated using the Chi-square test or Fisher's exact test, as appropriate. A multivariable logistic regression model was performed to explore independent associations with HPV vaccination status. To examine the association between HPV vaccination and all the risk indices, we employed a Bayesian Weighted Quantile Sum (bWQS) regression. The bWQS model estimates both the overall effect of the risk perception indices, EHPI, HPI and HRPI, on HPV vaccination and the individual contribution (weights) of each component to the mixture effect. We modeled HPV vaccination status as the outcome variable (binary), and included age, educational level and marital status as potential confounders. The weights of the indices were constrained to be non-negative and sum to 1, and all model parameters were estimated using Markov Chain Monte Carlo (MCMC) sampling. The model was implemented using the R package bWQS, with default chains and iteration parameters. Results were reported as regression coefficients (β), with corresponding p-values. Statistical significance was defined as $p < 0.05$. All analyses were performed using R software (version 4.3.2).

ETHICS AND REGULATION

All participants provided written informed consent after reading a detailed information sheet. The study was approved by the Ethics Committee "Catania 2" (July

11, 2017, No. 38/2017/CECT2) and was conducted in accordance with the Declaration of Helsinki, the General Data Protection Regulation (EU 2016/679), and Italian regulations on personal data protection.

Results

The analysis of the study population (N=567) revealed several associations between HPV vaccination and socio-demographic and behavioural factors, as shown in Table I. Among the participants, 42 individuals (7.4%) reported being vaccinated for HPV, while 525 (92.6%) were unvaccinated.

Vaccinated individuals were significantly younger than those unvaccinated (22.0 vs. 31.0 years, $p < 0.001$).

Tab. I. Main findings.

Variable	HPV Vaccination Status		p-value
	No (N=525, 92.6%)	Yes (N=42, 7.4%)	
Age	31.0 [28.0;34.0]	22.0 [20.0;28.8]	<0.001
Marital status:			<0.001
Married	330 (62.9%)	13 (31.0%)	
Unmarried	195 (37.1%)	29 (69.0%)	
Educational level:			0.041
High	119 (22.7%)	7 (16.7%)	
Medium	263 (50.1%)	16 (38.1%)	
Low	141 (26.8%)	19 (45.2%)	
Missing	2 (0.4%)	0 (0.0%)	
Crowding index	1.00 [0.75;1.33]	1.20 [0.75;1.50]	0.649
Risk perception:			
HPI	0.54 [0.36;0.71]	0.66 [0.49;0.78]	0.026
HRPI	0.62 [0.36;0.78]	0.75 [0.38;0.80]	0.297
EHPI	0.43 [0.29;0.57]	0.57 [0.43;0.71]	0.023
RPI	0.55 [0.38;0.70]	0.67 [0.46;0.79]	0.052
Habits during pregnancy			
Alcohol consumption:			1.000
No	516 (98.3%)	42 (100%)	
Yes	8 (1.5%)	0 (0.00%)	
Missing	1 (0.2%)	0 (0.0%)	
Folate supplementation:			1.000
No	8 (1.5%)	0 (0.00%)	
Yes	517 (98.5%)	42 (100%)	
Physical activity:			0.396
No	503 (95.8%)	42 (100%)	
Yes	22 (4.2%)	0 (0.00%)	
Smoking:			0.045
No	467 (88.9%)	33 (78.6%)	
Yes	56 (10.7%)	9 (21.4%)	
Missing	2 (0.4%)	0 (0.0%)	
Breastfeeding			0.672
No	263 (50.18%)	21 (50%)	
3 months	74 (14.1%)	6 (14.3%)	
6 months	113 (21.5%)	6 (14.3%)	
Missing	75 (14.3%)	9 (21.4%)	

Unmarried participants were more likely to be vaccinated compared to married ones (69.0% vs. 31.0%, $p<0.001$). Educational level also showed a significant association ($p=0.041$), with a higher proportion of vaccinated individuals having a low educational level (45.2%) compared to unvaccinated ones (26.8%). Conversely, individuals with medium and high educational levels were more prevalent among the unvaccinated group (50.1% and 22.7%, respectively) compared to the vaccinated group (38.1% and 16.7%).

Risk perception indices were assessed, with vaccinated individuals showing significantly higher scores for HPI ($p=0.026$) and EHPI ($p=0.023$), reflecting a greater perception of vulnerability and benefits related to vaccination. Differences in HRPI ($p=0.297$) and RPI ($p=0.052$) were not statistically significant, though trends suggested that vaccinated individuals generally had a higher perception of risk severity and response efficacy. Smoking habits were also significantly associated with vaccination status ($p=0.045$). A higher proportion of smokers was found among vaccinated individuals (21.4%) compared to unvaccinated ones (10.7%), while non-smokers were more prevalent in the unvaccinated group (88.9% vs. 78.6%). Other behavioural variables, including alcohol consumption ($p=1.000$), folate supplementation ($p=1.000$), physical activity ($p=0.396$), and breastfeeding duration ($p=0.672$), did not show statistically significant differences between vaccinated and unvaccinated groups. Tables II and III report participants' beliefs regarding

responsibility for health protection and sources of information on environmental and health risks. These analyses were conducted on the subsample of participants who answered these specific questions, corresponding to 450 out of 525 (85.7%) unvaccinated and 33 out of 42 (78.6%) vaccinated subjects. Participants' beliefs regarding responsibility for health protection showed significant associations with HPV vaccination status (Tab. II). Unvaccinated individuals were more likely to attribute this responsibility to national institutions compared to vaccinated participants (47.8% vs. 24.2%, $p=0.015$). A similar trend was observed with regard to industry leadership, with a higher proportion of unvaccinated individuals identifying this group as responsible, although the result did not reach conventional significance (45.6% vs. 27.3%, $p=0.063$). No significant associations emerged for local institutions (54.0% vs. 42.4%, $p=0.269$), individual citizens (41.6% vs. 48.5%, $p=0.551$), or local health services (50.7% vs. 48.5%, $p=0.951$). Nonetheless, vaccinated individuals tended to assign relatively less responsibility to these latter categories.

Regarding sources of information on environmental and health risks (Tab. III), a significant association was

Tab. II. Responsibility for Health Protection and HPV Vaccination Status.

Who is responsible for health protection?	HPV Vaccination Status		p-value
	No, n (%) N=450/525	Yes, n (%) N=33/42	
Industry leadership			0.063
No	245 (54.4%)	24 (72.7%)	
Yes	205 (45.6%)	9 (27.3%)	
National Institution			0.015
No	235 (52.2%)	25 (75.8%)	
Yes	215 (47.8%)	8 (24.2%)	
Local institutions			0.269
No	207 (46.0%)	19 (57.6%)	
Yes	243 (54.0%)	14 (42.4%)	
Individual citizens			0.551
No	263 (58.4%)	17 (51.5%)	
Yes	187 (41.6%)	16 (48.5%)	
Local health services (e.g., Local Health Authority, GPs)			0.951
No	222 (49.3%)	17 (51.5%)	
Yes	228 (50.7%)	16 (48.5%)	

Proportion refers to 450 unvaccinated (85.7% of the total unvaccinated group) and 33 vaccinated (78.6% of the total vaccinated group) participants without any missing data on these items.

Tab. III. Information Sources on Health Risks and HPV Vaccination Status.

Main sources of information on health risk	HPV Vaccination Status		p-value
	No, n (%) N=450/525	Yes, n (%) N=33/42	
National mass media			0.702
No	209 (46.4%)	17 (51.5%)	
Yes	241 (53.6%)	16 (48.5%)	
Local mass media			0.297
No	279 (62.0%)	24 (72.7%)	
Yes	171 (38.0%)	9 (27.3%)	
Healthcare organisations and professionals			0.642
No	345 (76.7%)	27 (81.8%)	
Yes	105 (23.3%)	6 (18.2%)	
Scientists			1.000
No	411 (91.3%)	31 (93.9%)	
Yes	39 (8.67%)	2 (6.06%)	
Factory workers			0.032
No	419 (93.1%)	27 (81.8%)	
Yes	31 (6.89%)	6 (18.2%)	
Internet			1.000
No	191 (42.4%)	14 (42.4%)	
Yes	259 (57.6%)	19 (57.6%)	
Personal networks			0.622
No	299 (66.4%)	20 (60.6%)	
Yes	151 (33.6%)	13 (39.4%)	

Proportion refers to 450 unvaccinated (85.7% of the total unvaccinated group) and 33 vaccinated (78.6% of the total vaccinated group) participants without any missing data on these items.

found with reliance on factory workers. Vaccinated individuals reported greater reliance on this group compared to unvaccinated participants (18.2% vs. 6.9%, $p=0.032$). While the remaining sources did not show statistically significant associations, some trends were noted. Unvaccinated participants reported slightly higher reliance on local media (38.0% vs. 27.3%, $p=0.297$), health professionals (23.3% vs. 18.2%, $p=0.642$), and personal networks such as family, friends, or acquaintances (33.6% vs. 39.4%, $p=0.622$). Minimal differences were observed for scientists (8.67% vs. 6.06%, $p=1.000$), national media (53.6% vs. 48.5%, $p=0.702$), and internet (57.6% in both groups, $p=1.000$). Logistic regression models (Tab. IV) were used to assess associations between HPV vaccination status and various risk perception indices, adjusted for age, marital status, and educational level.

Higher scores on the HPI were significantly associated with increased odds of HPV vaccination (OR=0.90; 95% CI: 0.827, 0.988; $p=0.026$), as were higher scores on the EHPI (OR=0.86; 95% CI: 0.780, 0.957; $p=0.005$). These results suggest that individuals perceiving more environmental hazards or exposure risks were more likely to be vaccinated. The HRPI did not reach

Tab. IV. Regression models.

	OR	CI - lower	CI - higher	p-value
HPI	0.90	0.827	0.988	0.026
Unmarried	0.97	0.920	1.017	0.193
Educational Level (High)	0.96	0.910	1.017	0.171
Educational Level (Low)	0.97	0.909	1.031	0.314
Age	1.01	1.006	1.017	<0.001
HRPI	0.27	0.048	1.313	0.113
Unmarried	0.62	0.245	1.539	0.305
Educational Level (High)	0.31	0.096	0.969	0.041
Educational Level (Low)	0.65	0.230	1.961	0.425
Age	1.26	1.137	1.417	<0.001
EHPI	0.86	0.780	0.957	0.005
Unmarried	0.97	0.925	1.022	0.270
Educational Level (High)	0.96	0.905	1.011	0.118
Educational Level (Low)	0.97	0.914	1.036	0.388
Age	1.01	1.008	1.018	<0.001
RPI	0.06	0.007	0.494	0.011
Unmarried	0.67	0.259	1.682	0.389
Educational Level (High)	0.29	0.090	0.937	0.036
Educational Level (Low)	0.60	0.209	1.823	0.347
Age	1.28	1.150	1.446	<0.001

Tab. V. Results from Bayesian Weighted Quantile Sum (bWQS) regression 3.2. Figures, Tables and Schemes

	OR	CI-lower	CI-higher
beta1	0.05	0.005	0.405
Age	1.29	1.186	1.448
Educational Level	0.54	0.310	0.880
Marital Status	0.63	0.247	1.538
W-EHPI	0.476	0.089	0.849
W-HRPI	0.229	0.010	0.584
W-HPI	0.295	0.009	0.654

statistical significance (OR=0.27; 95% CI: 0.048, 1.313; $p=0.113$), while the RPI showed a statistically significant association (OR=0.06; 95% CI: 0.007, 0.494; $p=0.011$), indicating that higher overall risk perception was also related to increased likelihood of HPV vaccination. Age was consistently associated with higher vaccination probability across all models ($p<0.001$). Marital status (unmarried vs. married) and low educational level were not significantly associated with vaccination in most models; however, higher educational level was negatively associated with HPV vaccination in the models including HRPI (OR=0.31; $p=0.041$) and RPI (OR=0.29; $p=0.036$), suggesting that individuals with higher education were less likely to be vaccinated.

To assess the combined effect of risk perception on HPV vaccination, we applied Bayesian Weighted Quantile Sum (bWQS) regression, incorporating the three risk perception indices as exposures. Given the high collinearity among the indices, bWQS provided an appropriate framework for estimating their joint contribution while accounting for inter-correlation (Fig. S1). The model was adjusted for potential confounders, including age, educational level and marital status (Tab. V). Results from bWQS analysis showed a negative association between the weighted mixture of risk perception indices and the likelihood of HPV vaccination (OR=0.05; 95% CI: 0.005; 0.405). Age and educational level confirmed the same trend observed for regressions with single indices (age: OR=1.29; 95% CI: 1.186; 1.448 - educational level: OR=0.54; 95% CI: 0.310; 0.880). Among the three indices, EHPI contributed the highest weight to the mixture ($w=0.476$), followed by HPI ($w=0.295$) and HRPI ($w=0.229$) (Fig. S2), suggesting it may play a more prominent role in shaping vaccination decisions. These findings underscore the importance of aggregated risk perception in influencing vaccine uptake behaviour.

Discussion

The findings of this study provide a comprehensive analysis of socio-demographic and behavioural factors associated with HPV vaccination coverage before pregnancy among women enrolled during pregnancy. Understanding these associations is crucial for developing targeted public health strategies to increase

vaccine coverage, particularly amidst challenges such as vaccine hesitancy and inequitable access to preventive healthcare. Vaccination behaviours are shaped by a complex interplay of individual, social, and cultural factors, and this study offers valuable insights into barriers and facilitators that influence health decision-making.

One key observation was the significant age disparity between vaccinated and unvaccinated individuals, with vaccinated participants being notably younger. This difference likely reflects greater exposure to vaccination campaigns during adolescence and early adulthood, critical periods for establishing preventive health behaviours, as well as a cohort effect related to the relatively recent introduction of the HPV vaccine. Indeed, younger women were more likely to be targeted by organised vaccination programmes, whereas older women may not have been offered vaccination in their youth and may have subsequently been lost to follow-up by the healthcare system. Moreover, younger individuals are often better informed about HPV and vaccination benefits [44] and are more receptive to new information due to higher cognitive adaptability [45]. Notably, age was a significant predictor across all risk perception indices in our regression analyses, suggesting that perceived vulnerability and awareness of health risks increase with age.

Marital status also emerged as a significant factor, with unmarried individuals demonstrating higher vaccination rates than married ones. This finding aligns with previous research indicating lower HPV vaccine uptake among married women compared to unmarried women [46-8]. Married women may perceive a lower risk of HPV due to assumptions of monogamy, reducing their perceived need for vaccination [46]. However, it is important to emphasize that even women with only one sexual partner face an 85% lifetime risk of HPV infection [49].

Educational attainment showed an inverse relationship with vaccination status. A larger proportion of vaccinated individuals had lower educational levels compared to the unvaccinated group. While higher education often correlates with better health literacy and vaccine uptake [50], this finding may reflect the success of targeted interventions that effectively reached lower-educated populations. Nevertheless, lower educational attainment is frequently associated with reduced HPV knowledge [51], underscoring the need for ongoing, inclusive public health campaigns. Moreover, logistic regression models revealed that higher educational level was significantly associated with lower odds of vaccination in the presence of certain risk perception variables, such as HRPI and RPI, suggesting that educational attainment may interact with cognitive risk evaluations in complex ways. This finding suggests a more complex relationship between education and vaccination behaviours. Individuals with higher education typically possess enhanced knowledge, superior information-processing skills, and greater risk awareness [52], which generally enable them to better assess threats and adopt effective preventive

strategies [53]. One possible interpretation is that among individuals with higher education, greater knowledge and information-processing skills may prompt more critical evaluation of vaccine-related information or diminished perceived personal risk, leading to lower acceptance of HPV vaccination despite awareness of potential risks. These findings imply that while higher educational attainment often facilitates access to health information, it does not necessarily translate into increased risk perception or consistent preventive action. Additionally, the younger age of vaccinated individuals may partly explain this inverse association, as younger participants often present lower educational levels due to ongoing studies.

Risk perception indices revealed vaccinated individuals had higher scores for HPI and EHPI, indicating the importance of personal health risk appraisal in vaccine decision-making. Though differences in HRPI and RPI were not statistically significant, trends suggested vaccinated individuals generally had greater awareness of HPV risks and the effectiveness of prevention measures. These findings are consistent with research showing that vaccinated individuals tend to perceive higher risks of cervical cancer and demonstrate greater engagement in preventive behaviours [54] and non-vaccinated women often cite a low perceived risk of HPV, influenced by factors such as lack of sexual activity or reliance on alternative prevention methods [42, 55, 56]. These associations were further supported by regression analysis: higher HPI, EHPI, and RPI scores were significantly associated with increased likelihood of HPV vaccination, reinforcing the relevance of perceived hazard and exposure in motivating preventive action.

An unexpected result was the association between smoking habits and vaccination status. Smokers were more prevalent among vaccinated individuals compared to non-smokers. This contrasts with literature suggesting smokers are less likely to engage in preventive health measures [57, 58]. The observed trend may reflect unique socio-behavioural dynamics within our population and highlights the importance of further research to clarify underlying mechanisms.

Other lifestyle factors, such as alcohol consumption, folate supplementation, physical activity, and breastfeeding duration, did not show statistically significant differences between vaccinated and unvaccinated individuals. While these variables are not directly related to HPV vaccination, their inclusion underscores the multifaceted nature of health behaviours in this specific phase of life. Indeed, many women tend to modify their habits before and during pregnancy, often reducing smoking, caffeine, and alcohol intake, and increasing their consumption of fruits and vegetables [59, 60]. However, a significant proportion continues to engage in unhealthy behaviours, despite available evidence and clinical recommendations promoting a healthy lifestyle. These behavioural patterns are shaped not only by medical advice but also by non-medical influences, including social, cultural, and psychological factors. In particular, psychosocial variables such as anxiety and stress have been negatively

associated with pregnancy outcomes [61], and may also influence adherence to preventive measures like vaccination.

Participants' beliefs regarding health protection responsibility showed relevant associations with HPV vaccination status. Vaccinated individuals were more likely to attribute responsibility for health protection to industry leadership and national institutions, suggesting that trust in these entities may positively influence vaccine uptake. Conversely, no significant differences emerged regarding local institutions, individual citizens, or local health services. However, trends indicated a higher attribution of responsibility to local institutions and individual citizens among vaccinated participants, although these did not reach statistical significance. This pattern nonetheless highlights the broader relevance of institutional trust in shaping vaccine acceptance [62].

Regarding sources of information on health risks, vaccinated participants reported a stronger reliance on factory workers, suggesting that, within this industrial-area population, informal workplace communication may serve as a significant channel for health information dissemination. This pattern likely reflects the strong social ties and trust-based relationships common in industrial work environments, where peer-to-peer dynamics and supportive workplace cultures – characterized by encouragement from both colleagues and supervisors – have been shown to foster healthier behaviours among employees [63]. No significant associations were found for other sources such as national media, local media, health professionals, scientists, internet, or personal networks. Nonetheless, a non-significant trend suggested greater reliance on national media and health professionals among vaccinated individuals, warranting further investigation.

This study underscores the complex interplay of socio-demographic and behavioural factors influencing HPV vaccination uptake. Identifying these patterns provides valuable insights into factors associated with HPV vaccination uptake and may help inform tailored, population-specific interventions aimed at addressing barriers to vaccination. The results highlight the importance of addressing misconceptions about HPV risk, particularly among married women and those with lower educational attainment. Importantly, our findings also demonstrate that individual cognitive risk perception – particularly regarding environmental hazards, perceived exposure, and overall risk – plays a significant role in vaccination decisions. Furthermore, exploring unique trends, such as the association between smoking and vaccination, can inform more effective, targeted public health strategies. Notably, participants' beliefs about who holds responsibility for health protection revealed important trends that may shape vaccination behaviours. Vaccinated individuals tended to place greater trust in industry leadership and national institutions as responsible for safeguarding public health, suggesting that confidence in authoritative bodies could enhance vaccine acceptance. Conversely, trust in local institutions, individual citizens, and local health services

did not significantly differ between groups, indicating these may be perceived as less influential or less relevant in vaccination decisions. Similarly, while various sources of health risk information such as national and local media, healthcare professionals, scientists, the internet, and personal networks showed no significant differences in trust levels, vaccinated participants reported a notably higher reliance on factory workers as informants. This unexpected finding points to potentially unique community dynamics or communication channels that could be leveraged to improve vaccine outreach. Ultimately, these findings contribute to the broader goal of reducing HPV-related morbidity and mortality through improved vaccination coverage and equitable access to preventive healthcare.

Strengths and Limitations

This study has several strengths. By leveraging data from the NEHO cohort, which includes a well-defined sample of women of reproductive age residing in areas with varying environmental and socio-demographic characteristics, the study provides a nuanced understanding of factors influencing HPV vaccination uptake. Although pregnant women are not a target group for HPV vaccination, this population represents a well-defined and accessible subgroup of young women, allowing a retrospective assessment of HPV vaccination status and its determinants in a public health-relevant population. The use of validated indices to measure risk perception (HPI, EHPI, HRPI, and RPI) further strengthens the reliability of the findings by capturing multidimensional aspects of participants' perceptions. Additionally, the study fills critical gaps in the literature by focusing on a population often overlooked in vaccine-related research and by exploring associations between sociodemographic factors, risk perceptions, and vaccination status.

However, the study is not without limitations. First, although the overall sample size was relatively robust (567 participants), only 42 women (7.4%) were vaccinated against HPV, which limits the statistical power to detect certain associations, reduces the precision of some estimates, and requires that the findings be interpreted with caution. The particularly low HPV vaccination rate observed in our sample compared to national and regional estimates cannot be fully explained by the available data and may reflect unmeasured contextual or population-specific factors. Therefore, caution is warranted when comparing these findings with broader surveillance data.

Second, the cross-sectional design prevents establishing causal relationships between the observed factors and HPV vaccination uptake.

Third, data on lifestyle habits and vaccination status were self-reported and may therefore be subject to recall bias or social desirability bias. In addition, the lack of information on several variables that could act as relevant confounders in the analysis of HPV vaccination uptake, such as household income, accessibility to nearby vaccination hubs, sexual activity and related habits, previous HPV infections or HPV-related cancers,

and adherence to routine cervical cancer screening, represents a further limitation. These variables were not included in the questionnaire because the NEHO cohort was originally designed to investigate environmental exposures and health risk perception rather than vaccination behaviours. Their absence may have limited our ability to fully capture the complexity of factors influencing HPV vaccination decisions.

Furthermore, the observed inverse association between educational level and HPV vaccination uptake may be partially influenced by a cohort or confounding effect related to age, as younger women are more likely both to be vaccinated and to have lower educational levels due to ongoing studies. This should be taken into account when interpreting the relationship between education and vaccination behaviour.

Finally, the study sample, while robust, may not fully generalize to populations outside the specific geographic and social contexts investigated. In particular, most participants resided in SInS and their corresponding LRAs, mainly involving medium-small sized urban areas. This environmental burden may have influenced participants' cognitive risk assessments, increasing their sensitivity toward environmental health risks and potentially affecting both their perceptions and reported behaviours. Consequently, findings regarding risk perception and vaccination decisions may not be entirely generalizable to populations living in larger cities or in less polluted or differently perceived environments.

POLICIES

This study underscores the critical role of socio-demographic and behavioural factors in shaping HPV vaccination coverage before pregnancy in women enrolled during pregnancy, providing valuable insights for targeted policy and public health interventions. Health behaviours are deeply influenced by individuals' perceptions of susceptibility, severity, benefits, and barriers related to a disease [64, 65]. Perceived benefits and barriers significantly impact decision-making processes [42]. To encourage early vaccination, it is crucial to widely disseminate information about the higher effectiveness of the HPV vaccine when administered at a young age.

Pregnant women have been recognized as an ideal target population for developing interventions aimed at promoting vaccinations. The antenatal period represents a pivotal time when attitudes and beliefs about vaccines first take shape [66] and serves as a strategic "teachable moment" for health promotion and behaviour change [67-69]. Efforts should be intensified to improve the availability of unbiased data on the safety and efficacy of vaccines, including studies from non-industry-sponsored sources [70, 71], and to strengthen vaccine reporting and pharmacovigilance systems [72].

By addressing these barriers through targeted education, improved data transparency, and enhanced healthcare provider engagement, policymakers can foster greater trust in vaccination programmes. Ultimately, these strategies can contribute to higher HPV vaccination

coverage, reduced disease burden, and improved maternal and child health outcomes globally.

Conclusion

This study highlights the critical interplay between socio-demographic and behavioural factors influencing HPV vaccination coverage before pregnancy in women enrolled during pregnancy. The findings underscore the need for targeted public health strategies to address disparities in vaccination coverage and reduce barriers to access. Younger age, marital status, and specific risk perception indices emerged as significant factors associated with HPV vaccination, revealing opportunities for tailored interventions. The unexpected association between smoking and vaccination status suggests areas for further research to understand population-specific dynamics. By enhancing education, promoting equitable access to vaccines, and leveraging the antenatal period as a strategic opportunity for health promotion, these insights can inform policies aimed at improving HPV vaccination coverage and reducing the burden of HPV-related diseases. Future studies specifically designed to investigate HPV vaccination behaviours should incorporate these variables in order to better disentangle structural, behavioural, and socioeconomic determinants of vaccine uptake and to inform more targeted public health interventions.

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Institutional Review Board Statement

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the three Ethics Committees responsible for the involved NPCSS: the Ethics Committee of the University Hospitals of Messina for the NPCSS of Milazzo (18 September 2017, no. 9/2017), the Ethics Committee "Catania 2" for the NPCSS of Augusta-Priolo (11 July 2017, no. 38/2017/CECT2), and the Ethics Committee of Calabria Region for the NPCSS of Crotone (20 July 2017, no. 173).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

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

Conflicts of interest statement

The authors declare that they have no competing interests.

Authors' contributions

FC, CF equally contributed to this work and share the first authorship. GD, SR contributed equally as last authors; FC, CF: Conceptualization; IC, GD, SR: Methodology; FC, GD, SR: Acquisition of data; FC, CF, FB, IC, GD, SR, PC, VL, NA: Writing - original draft preparation; FC, CF, IC, GD, SR, PC, VL, NA: Writing - review and editing; IC: Statistical analysis; GD, SR: Supervision and project administration.

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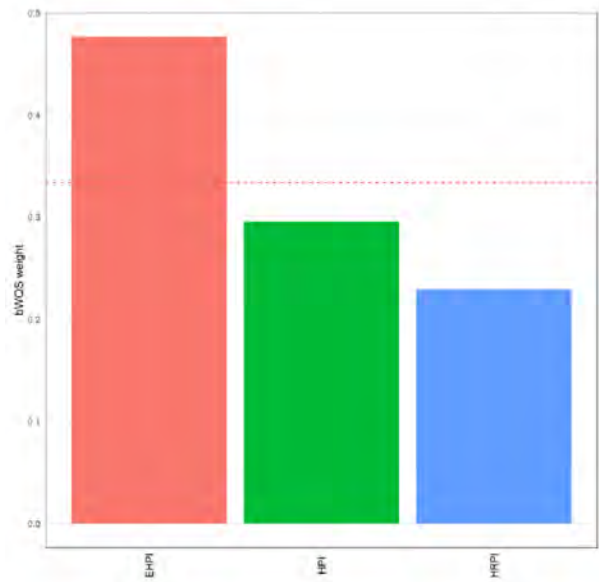
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Supplementary materials

Fig. S1. Correlation plot of the four risk perception indices.



Fig. S2. Weights of the risk perception indices according to the bWQS model.



The dotted red line indicates the threshold above which an index weight is considered relevant.

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HEALTH PROMOTION

Factors Associated with Hypertension and Diabetes Mellitus among University Students and Staff in Indonesia: A Cross-Sectional Study

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Keywords

Hypertension • Diabetes mellitus • Non-communicable diseases • Risk factors • University students
• University Staff • Cross-sectional study

Summary

Introduction. Hypertension and diabetes are among the most prevalent non-communicable diseases (NCDs) and contribute substantially to premature morbidity and mortality worldwide. Early identification of factors associated with these conditions is essential for developing effective prevention strategies. However, evidence regarding factors associated with hypertension and diabetes among university students and staff in Indonesia remains limited. This study aimed to identify factors associated with hypertension and diabetes among university students and staff.

Methods. A cross-sectional study was conducted among 503 students, lecturers, and administrative staff at a private university in Yogyakarta, Indonesia. Data were collected using a structured online questionnaire to obtain information on socio-demographic characteristics, smoking status, physical activity, fruit and vegetable consumption, body mass index (BMI), and self-reported physician-diagnosed hypertension and diabetes. Fisher's exact test was performed for bivariate analysis, followed by multivari-

able logistic regression to identify factors independently associated with hypertension and diabetes.

Results. The prevalence of self-reported hypertension and diabetes was 6.6% and 1.8%, respectively. Participants aged 46–65 years had significantly higher odds of hypertension than those aged 17–45 years (adjusted odds ratio [AOR]=3.23; 95% confidence interval [CI]: 1.11–9.43; $p=0.032$). Fruit and vegetable consumption was also independently associated with hypertension (AOR=2.56; 95% CI: 1.11–5.90; $p=0.027$). For diabetes, age (AOR=35.37; 95% CI: 3.07–407.40; $p=0.004$) and sex (AOR=0.16; 95% CI: 0.03–0.89; $p=0.037$) remained independently associated with the outcome.

Conclusion. Hypertension and diabetes mellitus among university students and staff were independently associated with selected demographic and lifestyle-related factors. Identifying individuals at increased risk may facilitate targeted health promotion, routine screening, and preventive interventions to reduce the burden of NCDs in university populations.

Introduction

Non-communicable diseases (NCDs) are the leading cause of mortality and disability worldwide, accounting for approximately 41 million deaths annually, equivalent to nearly three-quarters of all global deaths. Cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes are responsible for more than 80% of premature NCD-related deaths, particularly in low- and middle-income countries. Beyond their impact on mortality, NCDs contribute substantially to disability, reduced quality of life, increased healthcare expenditure, and socioeconomic burden [1, 2].

Indonesia is currently experiencing an epidemiological transition characterized by an increasing burden of NCDs. According to the National Basic Health Survey (*Riskesdas*), the prevalence of hypertension increased from 25.8% in 2013 to 34.1% in 2018, while diabetes mellitus increased from 6.9% to 8.5%. In the Special Region of Yogyakarta, hypertension and diabetes mellitus remain among the most common chronic

diseases, emphasizing the need for effective prevention strategies targeting modifiable risk factors [3].

The development of hypertension and diabetes is strongly influenced by multiple modifiable behavioral and demographic factors, including unhealthy dietary habits, physical inactivity, tobacco use, overweight and obesity, age, and sex [4, 5]. These factors often coexist and interact throughout the life course, substantially increasing the risk of developing chronic diseases [6, 7]. Previous studies have consistently demonstrated that behavioral risk factors are important predictors of NCD occurrence and represent key targets for preventive interventions [8–10]. Universities comprise heterogeneous populations with diverse demographic characteristics and lifestyle behaviors, including students, lecturers, and administrative staff. These population groups may experience different levels of exposure to behavioral risk factors associated with hypertension and diabetes, making universities an appropriate setting for identifying individuals at increased risk of NCDs. Understanding the distribution of these risk factors

within university populations may facilitate early risk identification, targeted preventive interventions, and routine screening programmes for hypertension and diabetes.

Despite the growing body of evidence on NCD risk factors, evidence regarding hypertension and diabetes mellitus among university populations in Indonesia remains limited. Most previous studies have focused on individual behavioral risk factors or single population groups, providing limited evidence to support comprehensive health promotion planning within higher education institutions. A better understanding of demographic and behavioral factors associated with hypertension and diabetes mellitus among university students and staff may provide valuable evidence for strengthening institutional policies and preventive interventions aimed at reducing NCD risk [11].

This study aimed to identify factors associated with hypertension and diabetes among university students and staff at a private university in Yogyakarta, Indonesia, using a cross-sectional study design. The findings are expected to contribute to the identification of high-risk groups and support evidence-based preventive strategies for reducing the burden of hypertension and diabetes in university populations.

Methods

STUDY DESIGN AND PARTICIPANTS

This cross-sectional study was conducted at a private university in Yogyakarta, Indonesia [12, 13].

The study design was selected to examine the association between demographic and lifestyle-related factors and hypertension and diabetes among university students and staff [14].

Data were collected using a structured online questionnaire. The study population comprised active students, lecturers, and academic staff affiliated with the university.

Participants were recruited using consecutive sampling, whereby all eligible individuals who met the inclusion criteria and voluntarily completed the online questionnaire were consecutively included in the study. A total of 503 respondents participated in the study. For analytical purposes, participants were classified into two groups: students ($n=396$) and lecturers and academic staff ($n=107$).

Eligible participants were students, lecturers, and academic staff aged 17–65 years who voluntarily agreed to participate by providing electronic informed consent and completing the questionnaire. Questionnaires with incomplete responses for the variables included in the analysis were excluded.

STUDY VARIABLES AND DATA COLLECTION

Data were collected using a structured online questionnaire. The independent variables included participant group (students; lecturers and academic

staff), faculty affiliation, sex, age, physical activity (frequency and duration per week), fruit and vegetable consumption (frequency per day), smoking behaviour, smoking duration, number of cigarettes smoked per day, and body mass index (BMI). Age was categorized into 17–45 years and 46–65 years based on the university population structure and to ensure sufficient observations in each category for statistical analysis. Body mass index (BMI) was calculated from self-reported body weight and height using the standard formula of weight in kilograms divided by height in meters squared (kg/m^2). Based on the Asia-Pacific BMI classification, participants were categorized into two groups for analysis: normal BMI ($18.5\text{--}22.9 \text{ kg}/\text{m}^2$) and abnormal BMI ($<18.5 \text{ kg}/\text{m}^2$ or $\geq 23.0 \text{ kg}/\text{m}^2$) [15]. The abnormal BMI category included underweight, overweight, and obese participants. The dependent variables were self-reported physician-diagnosed hypertension and diabetes, based on participants' reports of having previously received a diagnosis from a physician.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize participants' characteristics and are presented as frequencies and percentages. Associations between categorical variables and hypertension or diabetes were initially examined using Fisher's exact test [16, 17]. Variables with a $p\text{-value} < 0.25$ in the bivariate analysis were entered into multivariable binary logistic regression models using the purposeful selection approach recommended by Hosmer, Lemeshow, and Sturdivant [18]. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test, while correlations among independent variables were examined before model interpretation to identify potential multicollinearity. Adjusted odds ratios (AORs) with 95% confidence intervals (95% CIs) were reported, and statistical significance was defined as $p < 0.05$ [18].

ETHICAL APPROVAL

This study was approved by the Research Ethics Committee of Universitas Ahmad Dahlan, Yogyakarta, Indonesia (Approval No. 228.3/FIKES/PL/XI/2021). Electronic informed consent was obtained from all participants before completing the questionnaire. Participation was voluntary, and participant confidentiality and anonymity were maintained throughout the study.

Results

A total of 503 participants were included in the study, comprising 396 (78.7%) students and 107 (21.3%) lecturers and academic staff. Female participants accounted for the majority of the study population (80.3%), and most respondents were aged 17–45 years (94.8%). Regarding lifestyle-related factors, 390 participants (77.5%) reported engaging in physical activity three times or less per week, while 428 (85.1%)

Tab. I. Sociodemographic Characteristics, Lifestyle-Related Factors, and Prevalence of Hypertension and Diabetes Among University Students and Staff (n=503).

Variable	n	%
Participant group		
Student	396	78.7
Lecturer and Academic staff	107	21.3
Sex		
Male	99	19.7
Female	404	80.3
Age (years old)		
17-45	477	94.8
46-65	26	5.2
Physical activity (times/week)		
≤ 3 Times	390	77.5
>3 Times	113	22.5
Fruit and vegetable consumption (times/day)		
≤3 Times	428	85.1
>3 Times	75	14.9
Smoking Status		
Yes	30	6
No	473	94
Body mass index (BMI)		
Abnormal	207	41.2
Normal	296	58.8
Hypertension		
Yes	33	6.6
No	470	93.4
Diabetes Mellitus		
Yes	9	1.8
No	494	98.2

consumed fruits and vegetables three times or less per day. Current smokers represented only 6.0% of the study population, whereas 41.2% of participants had an abnormal body mass index. The prevalence of self-reported hypertension and diabetes mellitus was 6.6% and 1.8%, respectively (Tab. I).

Subsequent bivariate analyses were performed to examine the associations between participants' characteristics, lifestyle-related factors, and the prevalence of hypertension and diabetes mellitus.

Bivariate analysis demonstrated that age, fruit and vegetable consumption, and body mass index (BMI) were significantly associated with self-reported hypertension (Tab. II). Participants aged 46-65 years had a significantly higher prevalence of hypertension than those aged 17-45 years (PR=2.998; 95% CI: 1.027-8.753; $p=0.004$). Participants reporting fruit and vegetable consumption of three times or less per day also had a significantly higher prevalence of hypertension than those consuming them more than three times daily (PR=2.709; 95% CI: 1.233-5.953; $p=0.019$). In addition, body mass index was significantly associated with hypertension ($p=0.030$). No statistically significant associations were observed between hypertension and participant group, sex, physical activity, or smoking status (all $p>0.05$).

STATISTICALLY SIGNIFICANT AT $P<0.05$

Variables with a p -value <0.25 in the bivariate analysis were included in the multivariable logistic regression models. After adjustment for potential confounding variables, age and fruit and vegetable consumption remained independently associated with self-reported hypertension (Tab. III). Participants aged 46-65 years had significantly higher odds of reporting hypertension than those aged 17-45 years (AOR=3.231; 95% CI: 1.107-9.425; $p=0.032$). Likewise, participants reporting fruit and vegetable consumption of three times or less per day had significantly higher odds of hypertension than those consuming fruits and vegetables more than three times per day (AOR=2.563; 95% CI: 1.114-5.900; $p=0.027$). Sex, physical activity, and body mass index were not independently associated with hypertension after adjustment (all $p>0.05$).

For diabetes mellitus, age and sex remained independently associated with the outcome. Participants aged 46-65 years had markedly higher odds of reporting diabetes mellitus than those aged 17-45 years (AOR=35.370; 95% CI: 3.071-407.404; $p=0.004$). Female participants had significantly lower odds of diabetes mellitus than male participants (AOR=0.161; 95% CI: 0.029-0.892; $p=0.037$). Participant group, physical activity, fruit and vegetable consumption, and body mass index were not independently associated with diabetes mellitus after adjustment (all $p>0.05$).

Overall, the multivariable analysis demonstrated that age was the only factor consistently associated with both hypertension and diabetes mellitus, whereas limited fruit and vegetable consumption remained independently associated only with hypertension.

Discussion

This study identified several sociodemographic and lifestyle-related factors associated with self-reported hypertension and diabetes mellitus among university students and staff in Indonesia. In the multivariable analysis, older age and lower fruit and vegetable consumption remained independently associated with hypertension, whereas older age and male sex were independently associated with diabetes mellitus. In contrast, physical activity and body mass index were not independently associated with either outcome after adjustment for potential confounding variables. These findings suggest that non-communicable disease (NCD) risk within university communities is influenced by a combination of demographic characteristics and modifiable lifestyle behaviours, underscoring the importance of strengthening preventive health promotion strategies within higher education settings.

Age emerged as the most consistent factor associated with both self-reported hypertension and diabetes mellitus in this study. After adjustment for potential confounding variables, participants aged 46-65 years had significantly higher odds of reporting hypertension and diabetes mellitus than those aged 17-45 years. This

Tab. II. Bivariate Analysis of Factors Associated with Self-Reported Hypertension Among University Students and Staff (n = 503).

Variable	Hypertension			p-value	Prevalence Ratio (95% CI)
	No	Yes	Total		
Participant group					
Student	373 (74.2%)	23 (4.6%)	396 (78.7%)	0.275	1.672 (0.770-3.630)
Lecturer and academic staff	97 (19.3%)	10 (2.0%)	107 (21.3%)		
Sex					
Male	88 (17.5%)	11 (2.2%)	99 (19.7%)	0.066	0.461 (0.215-0.985)
Female	382 (75.9%)	22 (4.4%)	404 (80.3%)		
Age (years old)					
17-45	450 (89.5%)	27 (5.4%)	477 (94.8%)	0.004	2.998 (1.027-8.753)
46-65	20 (4.0%)	6 (1.2%)	26 (5.2%)		
Physical activity (times/week)					
≤ 3 Times	368 (73.28%)	22 (4.4%)	390 (77.5%)	0.183	1.804 (0.847-3.843)
>3 Times	102 (20.3%)	11 (2.2%)	113 (22.5%)		
Fruit and vegetable consumption (times/day)					
≤3 Times	405 (80.5%)	23 (4.6%)	428 (85.1%)	0.019	2.709 (1.233-5.953)
>3 Times	65 (12.9%)	10 (2.0%)	75 (14.9%)		
Smoking status					
Yes	27 (5.4%)	3 (0.6%)	30 (6.0%)	0.436	1.641 (0.471-5.720)
No	443 (88.1%)	30 (6.0%)	473 (94.0%)		
Body mass index (BMI)					
Abnormal	187 (37.2%)	20 (4.0%)	207 (41.2%)	0.030	0.430 (0.209-0.884)
Normal	283 (56.3%)	13 (2.6%)	296 (58.8%)		

Statistically significant at $p < 0.05$.

finding is consistent with the established epidemiology of non-communicable diseases, which demonstrates that increasing age is an important determinant of hypertension and diabetes because of cumulative exposure to behavioural and metabolic risk factors, progressive vascular changes, reduced insulin sensitivity, and age-related physiological decline [19, 20]. Furthermore, previous epidemiological studies have consistently shown that the prevalence of hypertension and diabetes increases substantially with advancing age [5, 20]. Similarly, Baek et al. (2015) reported that increasing age was strongly associated with hypertension, highlighting the contribution of age-related physiological changes to elevated blood pressure [21].

Although the majority of respondents in the present study were aged 17-45 years, this reflects the demographic composition of the university community rather than a higher age-specific prevalence of hypertension or diabetes within younger adults. Consequently, a greater absolute number of hypertension cases was observed in the younger age group because this group represented nearly the entire study population. Similar considerations have been reported in epidemiological studies, where the distribution of cases is strongly influenced by the age structure of the study population and should therefore be interpreted together with measures of association obtained from multivariable analysis [7, 19]. However, after adjustment for potential confounding variables, older age remained independently associated with both hypertension and diabetes mellitus in the present study. Therefore, these findings should not be interpreted as

indicating that hypertension is more common among younger adults, but rather that the predominance of younger participants influenced the observed distribution of cases. This demographic composition should be considered when interpreting the generalisability of the findings, particularly because the relatively small proportion of participants aged 46-65 years may have reduced the precision of age-specific estimates.

The predominance of younger participants should be considered when interpreting the findings because it may limit the generalisability of the results to university populations with a larger proportion of older adults, which is an important consideration in observational studies [21, 22]. In addition, the relatively small number of respondents aged 46-65 years, particularly among participants with diabetes mellitus, may have contributed to the wide confidence intervals observed in the multivariable model, reflecting limited precision of the estimated associations [18]. Therefore, future studies involving a more balanced age distribution and a larger number of confirmed diabetes cases are warranted to improve the precision and generalisability of the findings.

The present study demonstrated that participants who reported consuming fruits and vegetables three times or less per day had significantly higher odds of self-reported hypertension than those consuming fruits and vegetables more than three times per day. This finding supports the well-established role of adequate fruit and vegetable intake as a protective factor against hypertension and other non-communicable diseases. Previous studies

Tab. III. Multivariable Logistic Regression Analysis of Factors Associated with Self-Reported Hypertension and Diabetes Mellitus Among University Students and Staff.

Variable	B	SE	Wald	p-value	AOR (95% CI)
Hypertension					
Sex	-0.415	0.430	0.932	0.334	0.660 (0.284-1.533)
Age (years old)	1.173	0.546	4.608	0.032	3.231 (1.107-9.425)
Physical activity (times/week)	0.250	0.419	0.355	0.551	1.284 (0.565-2.919)
Fruit and vegetable consumption (times/day)	0.941	0.425	4.897	0.027	2.563 (1.114-5.900)
Body mass index (BMI)	-0.675	0.388	3.019	0.082	0.509 (0.238-1.090)
Diabetes Mellitus					
Sex	-1.825	0.873	4.373	0.037	0.161 (0.029-0.892)
Age (years old)	3.566	1.247	8.178	0.004	35.370 (3.071-407.404)
Physical activity (times/week)	0.434	0.844	0.264	0.607	1.543 (0.295-8.063)
Fruit and vegetable consumption (times/day)	1.004	0.909	1.219	0.269	2.729 (0.459-16.212)
Body mass index (BMI)	0.338	0.848	0.159	0.690	1.402 (0.266-7.395)

AOR: Adjusted Odds Ratio; CI: Confidence Interval. Variables with $p < 0.25$ in the bivariate analysis were included in the multivariable logistic regression model.

have shown that diets rich in fruits and vegetables contribute to blood pressure regulation through multiple biological mechanisms, including increased potassium intake, dietary fibre, antioxidants, and other bioactive compounds that improve endothelial function, reduce oxidative stress, and enhance vascular health [6, 23]. Inadequate fruit and vegetable consumption as one of the major modifiable dietary risk factors for non-communicable diseases, including hypertension, and recommends regular consumption of at least 400 g of fruits and vegetables per day as part of a healthy diet [24]. Although the present study assessed fruit and vegetable consumption using self-reported frequency rather than quantity, the observed association remained significant after adjustment for potential confounding variables. This finding suggests that insufficient consumption of fruits and vegetables may contribute to elevated blood pressure among university populations, even after accounting for demographic and lifestyle-related factors. However, because dietary intake was self-reported and the cross-sectional design precludes establishing temporal relationships, the observed association should be interpreted as an epidemiological association rather than evidence of causality. Future longitudinal studies using more detailed dietary assessment methods are warranted to clarify the dose-response relationship between fruit and vegetable consumption and hypertension among university populations.

The present study also found that sex remained independently associated with self-reported diabetes mellitus after adjustment for potential confounding variables. Female participants had significantly lower odds of reporting diabetes mellitus than male participants. This finding is consistent with previous epidemiological evidence indicating that the distribution of type 2 diabetes differs by sex because of variations in behavioural risk factors, body fat distribution, hormonal regulation, and health-seeking behaviours [25, 26]. Men are generally more likely to be exposed to modifiable risk factors, including tobacco use, unhealthy dietary patterns, and lower utilisation of preventive health

services, which may contribute to a greater burden of diabetes in adulthood [27, 28].

The observed association should be interpreted with caution because the number of participants with self-reported diabetes mellitus in the present study was relatively small, resulting in a wide confidence interval for several estimates in the multivariable model. Moreover, diabetes status was determined through self-reported physician diagnosis rather than biochemical examination, creating the possibility of misclassification due to undiagnosed diabetes or inaccurate reporting. Therefore, future studies incorporating objective clinical measurements, such as fasting blood glucose or glycated haemoglobin (HbA1c), are needed to confirm the observed association between sex and diabetes mellitus among university populations.

The present findings have important implications for public health practice in university settings. From a health promotion perspective, these findings support the implementation of risk-based interventions that combine health education, supportive environments, and behavioural change strategies to reduce modifiable risk factors for non-communicable diseases within university settings. Although university populations are generally perceived as relatively healthy, the identification of age and inadequate fruit and vegetable consumption as factors independently associated with hypertension, together with the association between age and sex and diabetes mellitus, highlights the need for targeted prevention strategies rather than uniform health promotion programmes. Universities provide a strategic environment for implementing evidence-informed interventions that promote healthy dietary behaviours, encourage regular health screening, and facilitate early identification of individuals at increased risk of non-communicable diseases. Such interventions may include periodic blood pressure and blood glucose screening, nutrition education, behavioural counselling, and supportive campus policies that encourage healthy food choices and active lifestyles. These preventive approaches are consistent with the principles of health

promotion and may contribute to reducing the future burden of non-communicable diseases among university communities [6, 29, 30].

STRENGTHS AND LIMITATIONS

This study has several strengths that should be acknowledged. First, it included a relatively large sample of university students, lecturers, and academic staff, providing a comprehensive overview of selected non-communicable disease risk factors within a university community. Second, the use of multivariable logistic regression enabled adjustment for potential confounding variables, thereby providing more robust estimates of the associations between demographic and lifestyle-related factors and self-reported hypertension and diabetes mellitus. These strengths enhance the internal validity of the findings within the study population.

Nevertheless, several limitations should be considered when interpreting the results. First, the cross-sectional design precludes establishing temporal or causal relationships between the identified factors and the study outcomes, and therefore the findings should be interpreted as associations rather than evidence of causation [22, 31]. Second, hypertension and diabetes mellitus were identified based on self-reported physician diagnoses rather than clinical measurements, introducing the possibility of outcome misclassification and underestimation due to undiagnosed cases [22]. Third, most participants were aged 17-45 years, which may limit the generalisability of the findings to university populations with a larger proportion of older adults. Finally, the relatively small number of participants with diabetes mellitus resulted in wide confidence intervals in the multivariable model, indicating limited precision for some estimated associations [18]. Future longitudinal studies incorporating objective clinical assessments and more balanced age distributions are recommended to confirm and extend the present findings. Despite these limitations, the study provides valuable baseline evidence regarding factors associated with hypertension and diabetes mellitus among university students and staff, which may inform future preventive health programmes and longitudinal research in higher education settings.

Conclusion

This study demonstrated that older age and lower fruit and vegetable consumption were independently associated with self-reported hypertension, whereas older age and male sex were independently associated with self-reported diabetes mellitus among university students and staff. These findings highlight the importance of addressing modifiable lifestyle behaviours alongside demographic risk factors in non-communicable disease prevention within university settings. Although causal relationships cannot be inferred because of the cross-sectional design, the findings provide evidence to support targeted health promotion strategies, routine risk screening, and early preventive interventions for

university communities. Future longitudinal studies incorporating objective clinical assessments are recommended to further clarify these associations and strengthen the evidence base for non-communicable disease prevention in higher education institutions.

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Conflict of interest statement

The authors declare that they have no competing interests as defined by the International Committee of Medical Journal Editors (ICMJE). All authors have completed the ICMJE conflict of interest disclosure form, and no conflicts were reported.

Authors' contributions

HT conceived the study, developed the research methodology, and drafted the manuscript. RYF contributed to data analysis and manuscript preparation. R& LH contributed to the critical revision of the manuscript and assisted in manuscript preparation. All authors reviewed, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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Strengthening Arboviral Disease Preparedness through Nursing Education in Italy

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Dear Editor,

Arboviral diseases, including those caused by dengue, chikungunya, Zika, West Nile, Usutu, tick-borne encephalitis, and Toscana viruses, are emerging as a growing public health concern in Italy and across Europe [1]. Climate change, environmental modifications, increasing international mobility, and the expansion of competent vectors, particularly *Aedes albopictus*, are reshaping the epidemiology of vector-borne diseases and facilitating the occurrence of autochthonous transmission events in areas previously considered at low risk. Among the arboviruses of greatest public health relevance in Italy are dengue virus, chikungunya virus, Zika virus, West Nile virus, Usutu virus, tick-borne encephalitis virus, and Toscana virus, all of which are responsible for human disease and require specific surveillance and prevention strategies [1]. Recent outbreaks of dengue and the increasing burden of West Nile virus infection in Italy highlight the need for enhanced preparedness strategies capable of addressing this evolving epidemiological scenario [2, 3]. In response to these emerging challenges, Italy has implemented a National Plan for the Prevention, Surveillance, and Response to Arboviral Diseases, which provides an integrated framework for epidemiological surveillance, laboratory diagnosis, vector control, and coordinated public health interventions [4].

The response to arboviral threats relies not only on surveillance systems and vector-control programmes but also on a healthcare workforce adequately trained to support prevention, early detection, risk communication, and community engagement. In this context, nurses represent a key resource for public health preparedness. As the largest group of healthcare professionals, they contribute substantially to health promotion, community-based interventions, surveillance activities, and the implementation of preventive measures during infectious disease outbreaks.

Despite the increasing relevance of arboviruses in Italy, education on emerging vector-borne diseases remains limited within many undergraduate nursing programmes. This educational gap may reduce future nurses' preparedness to contribute effectively to surveillance systems, support public health responses, and communicate preventive measures to the population. Evidence from nursing education research suggests that knowledge and attitudes toward emerging infectious diseases significantly influence infection-management

behaviours and professional readiness [5].

Strengthening arboviral disease education within undergraduate nursing curricula could therefore represent a valuable investment in health-system resilience. Educational programmes should move beyond the exclusive focus on clinical manifestations and include epidemiological surveillance, vector ecology, environmental determinants of transmission, health communication, digital surveillance tools, and outbreak preparedness. In particular, the growing role of infodemiology and infoveillance in monitoring public awareness and information-seeking behaviours offers additional opportunities for strengthening public health responses to emerging arboviral threats [6].

Furthermore, arboviral disease prevention increasingly requires a One Health approach that recognizes the interconnectedness of human, animal, and environmental health. Integrating these concepts into nursing education may foster interdisciplinary competencies that are essential for addressing contemporary and future public health challenges [7].

The importance of reinforcing preparedness is further supported by the Italian epidemiological situation. According to the integrated national surveillance system coordinated by the Istituto Superiore di Sanità, from the beginning of surveillance in 2002 to 29 October 2025, 773 confirmed cases of West Nile virus infection and 72 associated deaths were reported in Italy, highlighting the persistent and increasing impact of arboviral diseases on public health [8].

As arboviruses continue to expand their geographical distribution and public health impact, nursing education must evolve accordingly. Strengthening competencies in arboviral disease prevention, surveillance, and preparedness among nursing students represents an important step toward building a more resilient healthcare workforce and supporting effective public health responses to emerging vector-borne diseases.

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The authors declare no competing interests.

Authors' contributions

OES, SP, LMA, SF, ASP, CV, GD, AT: Conceptualization; OES, SP: Writing-original draft preparation; OES, SP, LMA, SF, ASP, CV, GD, AT: Writing-review and editing; OES: Supervision. All authors have read and agreed to the published version of the manuscript.

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NURSING

Evaluating critical care nurses' competence in caring for patients undergoing continuous renal replacement therapy: A descriptive study

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Keywords

Acute kidney injury • Continuous renal replacement therapy • Critical care nursing • Nursing competence • Patient safety

Summary

Introduction. Acute kidney injury is common in intensive care units and may require Continuous renal replacement therapy (CRRT). Safe delivery of CRRT depends on nurses' theoretical knowledge and practical competence. This study assessed critical care nurses' competence in CRRT to identify areas requiring educational support.

Methods. A cross-sectional observational study was conducted among 240 nurses working in intensive care units at three Italian hospitals. Competence was assessed through an online survey using the validated Continuous Renal Replacement Therapy Measurement Competency Tool (CRRT-MCT). Descriptive statistics were used to summarise participant characteristics, training and competence levels.

Results. Most participants (76.7%, $n=184$) were classified at the novice level, 17.0% ($n=41$) at the competent level and 4.2%

($n=10$) at the expert level; 2.1% ($n=5$) did not reach the novice threshold. Although 71.3% had received CRRT training, 85.4% of trained participants considered it incomplete and unsatisfactory. The greatest knowledge gaps concerned indications for initiating CRRT and the fundamental principles of renal replacement techniques, whereas knowledge of anticoagulation and vascular access was stronger.

Conclusion. The findings indicate substantial educational needs among intensive care nurses involved in CRRT. Structured programmes combining theory, supervised practice and periodic reassessment should be integrated into continuing professional development. The CRRT-MCT can support both organisational competency mapping and individual self-assessment, enabling training to be targeted to identified knowledge gaps and evaluated over time.

Introduction

Acute kidney injury (AKI) is a severe condition characterised by a rapid deterioration in renal function, usually developing within 48 hours or over several days [1]. Its mortality risk is comparable to that associated with acute lung injury or acute coronary syndromes [1]. AKI affects approximately 1-5% of hospital inpatients and 7-23% of patients admitted to intensive care units (ICUs) [2, 3]. Timely diagnosis and treatment are therefore essential to prevent serious and potentially fatal consequences; reported mortality rates range from 20% to 70% among hospitalised patients [2, 3]. AKI may involve both structural damage and functional impairment and may occur alongside other disorders [4]. It is an important global health problem that requires complex, multidisciplinary management [5].

Approximately one-third of critically ill patients develop AKI, and 5% require renal replacement therapy [6]. Nurses caring for these patients therefore need advanced knowledge and skills. A cohort study conducted following the 2009 National Confidential Enquiry into Patient Outcome and Death identified

several shortcomings in the care of patients with AKI [7], while another report found that only half of patients received adequate care [8]. Continuous renal replacement therapy (CRRT) is frequently used for critically ill patients who require renal support. Continuous veno-venous haemofiltration, based on the principle of haemofiltration, is among the most widely used modalities in ICUs [9]. During the COVID-19 pandemic, 18.3% of infected patients developed renal failure and required renal replacement therapy [10], highlighting the need for specific nursing education on CRRT management [11]. CRRT also requires effective team organisation [12] and an integrated approach supported by appropriately competent nursing staff [5]. Because no specific instrument was available to assess nurses' competence in this field, the Continuous Renal Replacement Therapy Measurement Competency Tool (CRRT-MCT) was developed and validated in 2022 [13]. The present study aimed to assess ICU nurses' competence in CRRT and identify strengths and gaps in the care of critically ill patients receiving this treatment.

Methods

This study investigated critical care nurses' competence in continuous renal replacement techniques.

The CRRT-MCT was developed and validated to measure ICU nurses' competence in the use of CRRT [13]. It comprises 36 items organised into four sections. The first section contains six items on demographic and professional characteristics, including age, sex, professional experience and length of service in the ICU. The second contains nine items on education and training in continuous renal replacement techniques. The third contains six items describing the workplace context. The fourth contains 15 items assessing knowledge of CRRT principles, anticoagulation, prescription and appropriate vascular access.

The responses classify the nurse's knowledge as basic, intermediate or advanced and determine an overall level of competence based on Benner's framework: novice, competent or expert [14].

STUDY DESIGN

This cross-sectional observational study measured nurses' knowledge and competence using the CRRT-MCT.

SAMPLING AND SETTING

Participants were nurses employed in the ICUs of three Italian hospitals. The inclusion criteria were:

- critical care nurses working in an ICU;
- completion of the questionnaire;
- provision of informed consent;
- nurses who did not work in an Italian ICU or did not complete the questionnaire were excluded.

DATA COLLECTION

Data were collected through an online survey administered using Google Forms. Respondents were required to provide informed consent and meet the inclusion criteria before accessing the questionnaire. Data collection continued for three months after validation of the instrument, until the planned sample size was reached.

DATA ANALYSIS

Data were analysed using jamovi version 2.2.2 [15]. Descriptive statistics were used to summarise sample characteristics, workplace context and training. Results are reported as frequencies and percentages, means with standard deviations (SDs), or medians with ranges, as appropriate.

Results

SECTION I: DEMOGRAPHICS AND TRAINING

Among the 240 respondents, 55.0% (n=132) were female, 93.8% (n=225) held a bachelor's degree and 17.9% (n=43) had previous professional experience in

Tab. I. Demographic characteristics of participants (N=240).

Participant characteristics	n (%)	Mean $\pm$ SD (range)
Sex		
Female	132 (55.0)	
Male	108 (45.0)	
Length of service, years		16.2 $\pm$ 11.1 (1-40)
Length of ICU service, years		13.2 $\pm$ 10.2 (1-40)
Previous professional experience in nephrology or dialysis	43 (17.9)	
Highest degree		
Bachelor's degree	225 (93.8)	
Master's degree	15 (6.2)	

nephrology or dialysis (Tab. I). Most participants (71.3%, n=171) had received CRRT training; this was mainly work-based (66.7%, n=114) and combined theory with practice (85.4%, n=146). Among trained participants, 85.4% (n=146) considered the training incomplete and unsatisfactory (Tab. II).

All respondents considered that CRRT training should place greater emphasis on both theoretical and practical content. When first caring for a patient receiving CRRT, 94.2% (n=226) had been supported by a more experienced colleague.

Nevertheless, 65.0% (n=156) reported feeling uncomfortable when caring for a patient receiving CRRT because they were uncertain how to manage potential problems. Only 7.5% (n=18) fully agreed that CRRT should be managed by dialysis nurses, while 32.9% (n=79) partly agreed, citing dialysis nurses' greater experience and competence arising from higher activity volumes. Participants who disagreed (59.6%, n=143) considered dialysis nurses less familiar with managing the critical condition of ICU patients.

SECTION 2: WORKPLACE CONTEXT

Haemodiafiltration, which combines convection and diffusion, was the most frequently performed treatment in respondents' workplaces (89.2%, n=214). Treatment was prescribed mainly by anaesthetists (70.4%, n=169), followed by nephrologists (16.7%, n=40) and

Tab. II. CRRT training undertaken by participants (N=171).

Training characteristics	n (%)
Type of training	
Self-directed	7 (4.1)
Corporate course	50 (29.2)
Work-based	114 (66.7)
Training mode	
Practical	23 (13.5)
Theoretical	2 (1.2)
Theory and practice	146 (85.4)
Perceived quality of training	
Incomplete and unsatisfactory	146 (85.4)
Complete and satisfactory	25 (14.6)

Tab. III. Nurses' competence in CRRT (N=240).

Level of competence	n (%)
Novice	184 (76.7)
Competent	41 (17.0)
Expert	10 (4.2)
Unclassifiable	5 (2.1)

cardiologists (5.4%, n=13). The prescribing physician operated the CRRT machine in 7.5% of cases (n=18), whereas intensive care nurses operated and managed it in 89.6% (n=215). Patients with respiratory conditions (43.8%, n=105) and sepsis (41.7%, n=100) were the most frequent recipients of renal replacement therapy. Among surveyed ICUs, 73.3% (n=176) also performed extracorporeal carbon dioxide removal (ECCO2R).

SECTION 3: LEVEL OF COMPETENCE

Most participants demonstrated novice-level competence in CRRT: 76.7% (n=184) were classified as novice, 17.0% (n=41) as competent and 4.2% (n=10) as expert. A further 2.1% (n=5) did not reach the novice threshold (Tab. III).

QUESTIONS WITH THE HIGHEST NUMBER OF INCORRECT ANSWERS

The questions with the highest proportion of incorrect responses were:

- **Question 15:** "According to the KDIGO criteria, when all parameters determining the start of CRRT treatment are normal, which urinary output value should alarm you?"
 - Incorrect answers: 96.7% (n=232)
 - Question complexity: Medium
- **Question 5:** "Which treatment is described by the following statement: 'Clearance is achieved by diffusion and is effective on small molecules (urea, ions, ...)?"
 - Incorrect answers: 91.7% (n=220)
 - Question complexity: High

These findings suggest important knowledge gaps regarding indications for CRRT initiation and the fundamental principles underlying renal replacement therapies.

QUESTIONS WITH THE HIGHEST NUMBER OF CORRECT ANSWERS

The questions with the highest proportion of correct responses were:

- **Question 9:** "In which category of patients is anticoagulation with citrate most discouraged?"
 - Correct answers: 99.2% (n=238)
- **Question 13:** "In your opinion, which is the best site for venous catheter insertion for CRRT treatment?"
 - Correct answers: 98.8% (n=237)

Question 8: "Which of the following anticoagulation techniques would you choose at the priming stage in a CRRT treatment?"

- Correct answers: 98.3% (n=236)

- **Question 11:** "If heparin is used and the patient develops thrombocytopenia, administration of the anticoagulant..."
 - Correct answers: 97.9% (n=235)

These results indicate a strong level of knowledge regarding anticoagulation management and vascular access for CRRT.

QUESTIONS WITH MORE THAN 50% INCORRECT ANSWERS

Several questions were answered incorrectly by more than half of the participants:

- **Question 15:** "According to KDIGO criteria, when all parameters determining the start of CRRT treatment are in the normal range, which urinary output value should alarm you?"
 - Incorrect answers: 96.7% (n=232)
- **Question 5:** "Indicate which treatment corresponds to the following statement: 'Clearance is achieved by diffusion and is effective on small molecules (urea, ions, ...)'"
 - Incorrect answers: 91.7% (n=220)
- **Question 6:** "Indicate which treatment corresponds to the following statement: 'Clearance is achieved by diffusion and convection with efficacy on larger molecules'."

Incorrect answers: 87.9% (n=211)

- **Question 3:** "Indicate which technique you would choose to treat fluid overload."
 - Incorrect answers: 75.4% (n=181)

These findings highlight substantial deficiencies in nurses' understanding of the fundamental principles and modalities of CRRT.

AREAS OF COMPETENCE

The area in which nurses demonstrated the strongest knowledge was:

- **Principles of anticoagulation:** 96.7% correct answers (n=232)
- Other areas showed lower levels of competency:
- **Prescription and vascular access:** 72.1% correct answers (n=173)
- **Principles of CRRT techniques:** 55.0% correct answers (n=132)

Overall, knowledge related to anticoagulation was considerably stronger than knowledge concerning the fundamental principles of CRRT techniques, which emerged as the area requiring the greatest educational support.

Discussion

CRRT is increasingly prescribed and delivered in intensive care settings and is managed largely by nurses. Nurses must therefore master the theoretical and practical knowledge required to provide competent and safe care.

As the use of CRRT increases, specific nursing education becomes essential. The most concerning finding was

that only 21.2% of participants (n=51) were classified as competent or expert, whereas 76.7% (n=184) were classified as novice. These gaps should be addressed because inadequate competence may compromise patient safety and treatment outcomes.

The CRRT-MCT identified the fundamental principles of CRRT as the area with the greatest knowledge deficit and therefore the main priority for educational intervention.

Educational interventions should focus on the CRRT modalities most frequently used in practice and combine theoretical teaching, practical sessions and supervised workplace learning.

The study also highlights the need for healthcare organisations to assess ICU nurses' competence and provide targeted continuing professional development programmes to strengthen both clinical skills and patient safety [16]. This is particularly important in settings with frequent staff turnover or handovers.

Length of ICU service alone was not sufficient to identify an expert nurse who could supervise colleagues caring for a patient receiving CRRT for the first time, because most participants demonstrated only novice-level knowledge regardless of seniority.

Conclusion

Strengthening nursing competence in CRRT is necessary to promote safe care and prevent adverse outcomes. The CRRT-MCT [13] proved useful for mapping competence among critical care nurses.

It may also support the objective identification of nurses with the expertise required to supervise less experienced colleagues.

The instrument can guide the design of training tailored to a specific group's needs. Reassessment after training may then help evaluate effectiveness and identify any remaining knowledge gaps.

The CRRT-MCT is a valid and useful instrument for measuring nursing competence in CRRT and may also be used by intensive care nurses for self-assessment.

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Ethical considerations

The study procedures complied with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki. The study was

approved by the Territorial Ethics Committee of the Liguria Region (approval no. 13456, 2 October 2023). Participants received written information about the study and provided informed consent before completing the anonymous online questionnaire. Data were downloaded from Google Forms once the target sample size had been reached.

Conflict of interest statement

The authors declared no potential conflict of interest with respect to the research, authorship and/or publication of this article.

Authors' contributions

The individual contributions of authors to the manuscript are as follows: MEM, EC: contributed to the conception and the design of this study. MEM, EC, RW: contributed to data collection, analysis, and interpretation. MEM, MG, GA, RW: drafting, editing and revising critically this manuscript. RW, GC, MZ, LS, AB: supervision of all stages of the work.

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NON COMMUNICABLE DISEASE

Personal Hygiene Behaviors and Socioeconomic Determinants of Child Undernutrition: A National Cross-Sectional Study in Indonesia

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Keywords

Child undernutrition • Stunting • Wasting • Underweight • Sanitation • Socioeconomic factors • Survey-weighted analysis • Indonesia

Summary

Background. Child undernutrition remains a major public health concern in Indonesia. Evidence on the roles of household environmental and socioeconomic factors, based on nationally representative data analyzed using appropriate complex survey methods, remains limited. This study examined the associations between these factors and stunting, wasting, and underweight among Indonesian children under five years.

Methods. A cross-sectional analysis was conducted using data from the 2022 Indonesian Nutrition Status Survey (SSGI), which represents approximately 17.1 million children under 5. Survey-weighted descriptive statistics, Rao-Scott adjusted χ^2 tests, and multivariable logistic regression accounting for the complex sampling design were performed to estimate adjusted odds ratios (AORs) and 95% confidence intervals (CIs).

Results. Regional disparities and parental socioeconomic characteristics were consistently associated with all three forms of

undernutrition. Compared with Eastern Indonesia, children living in Western Indonesia had lower odds of stunting (AOR=0.63, 95% CI: 0.57-0.69), wasting (AOR=0.56, 95% CI: 0.50-0.62), and underweight (AOR=0.58, 95% CI: 0.51-0.66). Low parental education and parental unemployment were independently associated with higher odds of all three outcomes (all $p<0.01$). Unimproved sanitation and inadequate solid waste management were associated with stunting, whereas unimproved sanitation was also associated with wasting.

Conclusion. Child undernutrition in Indonesia is independently associated with regional inequalities, parental socioeconomic disadvantage, and selected household environmental conditions. Multisectoral interventions that target disadvantaged regions, improve parental socioeconomic conditions, and strengthen sanitation infrastructure are needed to reduce child undernutrition.

Introduction

Child undernutrition remains a major challenge for nursing science and practice. It reflects not only inadequate dietary intake but also caregiving behaviors, household environmental conditions, and interactions with health systems within families [1-3]. From a nursing perspective, stunting, wasting, and underweight represent nursing-sensitive outcomes because daily caregiving practices shape them. Nurses assess, guide, and strengthen these practices through family-centered and community-based interventions [4, 5].

Globally, stunting affected approximately 22% of children under five in 2020, representing 149.2 million children [6]. Indonesia continues to face a substantial burden. Although national prevalence declined from 24.4% in 2021 to 21.5% in 2023 [7], the rate remains above the World Health Organization target of below 20% and far from the national target of 14% [8]. These figures

indicate that structural and behavioral determinants continue to limit progress beyond improvements in food access alone.

Household hygiene practices play a critical role in child growth. Caregivers influence exposure to infection through water use, sanitation, waste management, and daily cleanliness [9]. Poor hygiene increases the risk of enteric infections, disrupts nutrient absorption, and contributes to growth faltering [10]. Nurses routinely address these modifiable behaviors during home visits, growth monitoring, and community outreach. Effective nutrition strategies, therefore, must extend beyond food provision and incorporate environmental and behavioral care [11].

Socioeconomic conditions further shape caregiving capacity. Education, employment, and access to health services determine whether families can maintain hygienic environments and respond to their child's health needs [12, 13]. Community and primary care

nurses frequently encounter these structural constraints, which influence the effectiveness of health education and early intervention [14].

Despite extensive research on child undernutrition, few studies integrate hygiene behaviors and socioeconomic conditions within a unified nursing framework at the national level. Most studies examine dietary intake or poverty in isolation. This study addresses that gap by examining how personal hygiene behaviors and socioeconomic factors jointly influence stunting, wasting, and underweight among Indonesian children under five. By framing these determinants as nursing-sensitive, this research strengthens the evidence base for nurse-led, family-centered strategies to reduce child undernutrition.

Methods

STUDY DESIGN AND DATA SOURCE

This study analyzed nationally representative data collected through the 2022 Indonesian Nutrition Status Survey (SSGI). The SSGI is a nationally representative survey conducted by the Ministry of Health of the Republic of Indonesia through the Center for Data and Information Technology, in collaboration with Statistics Indonesia. The survey was designed to provide comprehensive national and subnational estimates of children's nutritional status under 5 years of age.

STUDY POPULATION AND SAMPLING

The study population comprised all children aged 0-59 months included in the SSGI 2022 database. The survey applied a multistage stratified cluster sampling Design based on the 2020 Population Census sampling frame to ensure representativeness across provinces, districts, and urban-rural settings. For the present analysis, children were included if they had complete anthropometric measurements and complete data on household hygiene conditions and socioeconomic characteristics. After data cleaning and eligibility screening, approximately 59,577 children were included in the final analytical sample.

VARIABLES AND MEASUREMENTS

Outcome Variables

Child Nutritional Status

Child nutritional status was the primary outcome variable and was assessed using three standardized anthropometric indicators recommended by the World Health Organization (WHO): stunting, wasting, and underweight.

Stunting was defined as a height-for-age z-score (HAZ) < -2 standard deviations (SD), wasting as a weight-for-height z-score (WHZ) < -2 SD, and underweight as a weight-for-age z-score (WAZ) < -2 SD. Anthropometric z-scores were calculated by the SSGI using WHO growth standards and were obtained directly from the secondary dataset.

Each nutritional outcome was dichotomized into undernourished (< -2 SD) and normal nutritional status (≥ -2 SD) and treated as a nominal variable in the statistical analysis.

Exposure Variables

Personal hygiene behaviours

Personal hygiene behaviors were defined as nursing-sensitive household-level caregiving practices that influence children's exposure to enteric pathogens and subsequent nutritional outcomes. These behaviors primarily reflect routine actions undertaken by mothers or primary caregivers and represent modifiable targets of nurse-led family and community health interventions. Personal hygiene behaviors were measured using four indicators derived from the Clean and Healthy Living Behavior framework incorporated in the Survei Status Gizi Indonesia (SSGI) 2022 questionnaire: (1) household drinking water source, (2) drinking water treatment practices, (3) ownership and use of an improved sanitary latrine, and (4) household solid waste management. All indicators were obtained through structured household interviews and recoded in accordance with national hygiene and sanitation standards.

Household drinking water sources were initially classified into thirteen categories and subsequently dichotomized into good sources (bottled water, refill water, piped water, bore wells, protected dug wells, protected springs, public hydrants, and water terminals) and poor sources (unprotected wells, unprotected springs, rainwater storage, surface water, and informal water vendors). Drinking water treatment practices were coded as good when water was boiled before consumption and as poor when it was untreated. Ownership of an improved sanitary latrine was coded as yes when households had access to and used a private or shared latrine, and as no when no latrine was available or utilized. Solid waste management was classified as adequate when waste was managed through formal collection services, designated disposal sites, recycling, composting, or waste banks, and inadequate when waste was burned, buried, disposed of in rivers, or discarded indiscriminately.

SOCIOECONOMIC FACTORS

Socioeconomic factors were conceptualized as household-level structural determinants that shape caregivers' capacity to meet children's nutritional and healthcare needs and influence the implementation and sustainability of family-centered nursing interventions. Socioeconomic status was assessed using three indicators available in the SSGI 2022 dataset: (1) parental education level (mother and/or father), (2) parental employment status, and (3) ownership of health insurance. Parental education was dichotomized into lower education (no formal education or primary school) and higher education (secondary education or higher). Parental employment status was categorized as unemployed or employed, and health insurance ownership as yes or no.

DATA COLLECTION PROCEDURES

Trained enumerators conducted data collection for SSGI 2022 through household visits. Structured interviews with mothers or primary caregivers were conducted using digital questionnaires administered via tablet applications. Anthropometric measurements were performed using calibrated digital scales and standardized length or height boards, in accordance with WHO measurement protocols. To enhance data accuracy and reliability, measurements were conducted by paired enumerators and entered directly into an electronic data capture system with real-time validation.

STATISTICAL ANALYSIS

Descriptive statistics were generated using weighted frequencies and percentages to account for the complex sampling design of the 2022 Indonesian Nutrition Status Survey (SSGI). The survey employed a multistage stratified cluster sampling design; therefore, all analyses incorporated sampling weights, primary sampling units (PSUs), and stratification variables. Bivariate associations were examined using the Rao-Scott corrected chi-square test. Multivariable associations between personal hygiene behaviours, socioeconomic factors, and child undernutrition (stunting, wasting, and underweight) were estimated using survey-weighted multinomial logistic regression. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were reported. Statistical significance was defined as a two-sided p -value < 0.05 . All analyses accounted for the complex survey design using the Complex Samples module in SPSS version 27.

Results

PARTICIPANT CHARACTERISTICS

Table I presents the weighted characteristics of children under five years and their households based on the complex sampling design of the 2022 Indonesian Nutrition Status Survey (SSGI). The survey represented an estimated 17.1 million children under five years in Indonesia.

Most children had mothers in early adulthood (65.1%; 95% CI: 64.5-65.8), followed by middle adulthood (34.6%; 95% CI: 33.9-35.2), whereas only 0.3% (95% CI: 0.2-0.4) had adolescent mothers. Geographically, three-quarters of the study population resided in Western Indonesia (75.3%; 95% CI: 74.9-75.6), while 16.9% (95% CI: 16.6-17.2) and 7.8% (95% CI: 7.6-8.1) lived in Central and Eastern Indonesia, respectively. Slightly more than half of the participants were from urban areas (54.5%; 95% CI: 53.7-55.3), whereas 45.5% (95% CI: 44.7-46.3) resided in rural settings.

Regarding socioeconomic characteristics, 80.3% (95% CI: 79.7-80.8) of parents had higher educational attainment, while 19.7% (95% CI: 19.2-20.3) had lower educational attainment. Approximately 7 in 10 households (69.9%; 95% CI: 69.2-70.5) had unemployed parents, whereas 30.1% (95% CI: 29.5-30.8) had employed parents.

Tab. I. Weighted characteristics of study participants and household environmental conditions among children under five years in Indonesia, SSGI 2022 (N=59,577).

Variable	Category	Weighted % (95% CI)
Maternal age	Late adolescence (14-19 years)	0.3 (0.2-0.4)
	Early adulthood (20-35 years)	65.1 (64.5-65.8)
	Middle adulthood (36-54 years)	34.6 (33.9-35.2)
Region	Western Indonesia	75.3 (74.9-75.6)
	Central Indonesia	16.9 (16.6-17.2)
	Eastern Indonesia	7.8 (7.6-8.1)
Residence	Urban	54.5 (53.7-55.3)
	Rural	45.5 (44.7-46.3)
Household drinking water source	Poor	10.7 (10.2-11.1)
	Improved	89.3 (88.9-89.8)
Drinking water treatment	Not boiled	39.6 (39.0-40.3)
	Boiled	60.4 (59.7-61.0)
Improved sanitation facility	Unimproved	5.6 (5.4-5.9)
	Improved	94.4 (94.1-94.6)
Household solid waste management	Inadequate	75.8 (75.2-76.4)
	Adequate	24.2 (23.6-24.8)

Values are weighted percentages accounting for the multistage stratified cluster sampling design of the 2022 Indonesian Nutrition Status Survey (SSGI). Percentages were estimated using sampling weights, strata, and primary sampling units (PSUs). Confidence intervals were calculated using Taylor series linearization. Total unweighted sample size=59,577.

Household environmental conditions indicated that nearly all households had improved toilet facilities (99.0%; 95% CI: 98.9-99.0). However, only 24.2% (95% CI: 23.6-24.8) of households reported adequate solid waste management, whereas the majority (75.8%; 95% CI: 75.2-76.4) had inadequate waste management practices.

BIVARIATE ASSOCIATIONS BETWEEN PARTICIPANT CHARACTERISTICS AND CHILD UNDERNUTRITION

Table II presents the weighted bivariate associations between participant characteristics and the three forms of child undernutrition after accounting for the complex survey design. Regional distribution, place of residence, parental education, parental employment, and solid waste management were significantly associated with all three nutritional outcomes (all $p < 0.05$). Children residing in Eastern Indonesia rural areas, households with lower parental education, unemployed parents, and inadequate solid waste management consistently exhibited a higher prevalence of stunting, wasting, and underweight than their respective reference groups.

Environmental sanitation factors demonstrated different patterns across nutritional outcomes. Unimproved drinking water sources, lack of household drinking water treatment, and unimproved toilet facilities were significantly associated with higher prevalences of stunting and wasting (all $p < 0.001$), but these associations were not observed for underweight ($p = 0.237$, $p = 0.522$, and $p = 0.107$, respectively). Similarly, toilet type was

Tab. II. Weighted bivariate associations between participant characteristics and child undernutrition among children under five years in Indonesia, SSGI 2022.

Variable	Category	Stunting Yes (%)	<i>p</i> -value†	Wasting Yes (%)	<i>p</i> -value†	Underweight Yes (%)	<i>p</i> -value†
Maternal age	Late adolescence	22.9	0.220	16.6	0.026	7.9	0.353
	Early adulthood	21.1		15.0		8.6	
	Middle adulthood	22.1		16.3		9.1	
Region	Western Indonesia	20.7	<0.001	14.3	<0.001	8.4	0.000
	Central Indonesia	20.3		16.4		8.0	
	Eastern Indonesia	31.7		24.2		14.0	
Place of residence	Urban	19.6	<0.001	14.3	<0.001	8.1	<0.001
	Rural	23.7		16.7		9.6	
Parental education	Low	26.3	<0.001	18.8	<0.001	10.3	<0.001
	High	20.3		14.6		8.4	
Parental employment	Unemployed	22.7	<0.001	16.6	<0.001	9.4	<0.001
	Employed	18.6		12.8		7.3	
Drinking water source	Unimproved	26.2	<0.001	18.0	<0.001	9.4	0.237
	Improved	20.9		15.1		8.7	
Drinking water treatment	Not boiled	19.5	<0.001	14.4	0.001	8.6	0.522
	Boiled	22.7		16.1		8.9	
Toilet facility	Unimproved	26.4	<0.001	19.3	<0.001	9.9	0.107
	Improved	21.2		15.2		8.7	
Toilet type	Unimproved	22.1	0.676	17.9	0.044	9.1	0.784
	Improved	21.4		15.4		8.8	
Solid waste management	Inadequate	22.7	<0.001	16.7	<0.001	9.1	0.004
	Adequate	17.5		13.6		7.9	
Healthy housing	Inadequate	22.9	0.015	16.1	0.162	9.2	0.352
	Adequate	21.1		15.3		8.7	

associated with wasting ($p=0.044$) but showed no significant association with either stunting ($p=0.676$) or underweight ($p=0.784$).

Maternal age was significantly associated with wasting ($p=0.026$) but not with stunting ($p=0.220$) or underweight ($p=0.353$). In contrast, healthy housing conditions were associated with stunting ($p=0.015$) but showed no significant association with wasting ($p=0.162$) or underweight ($p=0.352$).

Overall, the bivariate analysis indicated that socioeconomic and geographic characteristics were consistently associated with all forms of child undernutrition, whereas the associations of household water, sanitation, and hygiene (WASH) factors varied across nutritional outcomes, with stronger relationships observed for stunting and wasting than for underweight.

MULTIVARIABLE ANALYSIS

After adjusting for all covariates and accounting for the complex survey design, several sociodemographic and environmental factors remained independently associated with child undernutrition (Tab. III).

For stunting, children living in Western Indonesia (AOR=0.63; 95% CI: 0.57-0.69) and Central Indonesia (AOR=0.64; 95% CI: 0.58-0.71) had significantly lower odds of stunting than those residing in Eastern Indonesia (both $p<0.001$). Urban residence was also associated with lower odds of stunting compared with rural residence (AOR=0.92; 95% CI: 0.85-0.99;

$p=0.022$). Conversely, children from households with unimproved drinking water sources (AOR=1.15; 95% CI: 1.05-1.27), unimproved sanitation facilities (AOR=1.17; 95% CI: 1.03-1.31), and inadequate solid waste management (AOR=1.19; 95% CI: 1.09-1.29) had significantly higher odds of stunting. In addition, low parental education (AOR=1.26; 95% CI: 1.16-1.36) and parental unemployment (AOR=1.25; 95% CI: 1.16-1.35) were independently associated with increased odds of stunting (all $p<0.05$). Maternal age, toilet type, and healthy housing were not significantly associated with stunting after adjustment.

For wasting, regional disparities persisted after multivariable adjustment. Compared with children living in Eastern Indonesia, those residing in Western Indonesia (AOR=0.56; 95% CI: 0.50-0.62) and Central Indonesia (AOR=0.68; 95% CI: 0.61-0.75) had significantly lower odds of wasting (both $p<0.001$). Children born to mothers in early adulthood exhibited slightly lower odds of wasting than those born to mothers in middle adulthood (AOR=0.92; 95% CI: 0.85-0.99; $p=0.031$). Unimproved sanitation facilities (AOR=1.15; 95% CI: 1.01-1.32), low parental education (AOR=1.23; 95% CI: 1.12-1.34), and parental unemployment (AOR=1.35; 95% CI: 1.24-1.48) remained significant predictors of wasting, whereas place of residence, drinking water source, drinking water treatment, toilet type, solid waste management, and healthy housing were not independently associated with wasting.

Tab. III. Survey-weighted multivariable logistic regression analysis of factors associated with child undernutrition among children under five years in Indonesia, SSGI 2022.

Variable	Category (comparison)	Stunting AOR (95% CI)	p-value	Wasting AOR (95% CI)	p-value	Underweight AOR (95% CI)	p-value
Maternal age	Late adolescence vs. Middle adulthood	0.92 (0.56-1.52)	0.751	0.88 (0.50-1.53)	0.640	0.78 (0.37-1.63)	0.505
	Early adulthood vs. Middle adulthood	0.96 (0.90-1.03)	0.242	0.92 (0.85-0.99)	0.031	0.95 (0.86-1.04)	0.264
Region	Western vs. Eastern Indonesia	0.63 (0.57-0.69)	<0.001	0.56 (0.50-0.62)	<0.001	0.58 (0.51-0.66)	<0.001
	Central vs. Eastern Indonesia	0.64 (0.58-0.71)	<0.001	0.68 (0.61-0.75)	<0.001	0.55 (0.49-0.63)	<0.001
Place of residence	Urban vs. Rural	0.92 (0.85-0.99)	0.022	0.95 (0.87-1.03)	0.191	0.88 (0.80-0.98)	0.019
Drinking water source	Unimproved vs. Improved	1.15 (1.05-1.27)	0.005	1.06 (0.96-1.18)	0.269	0.95 (0.83-1.08)	0.405
Drinking water treatment	Not boiled vs. Boiled	0.91 (0.85-0.98)	0.008	0.94 (0.87-1.01)	0.100	1.06 (0.96-1.16)	0.246
Sanitation facility	Unimproved vs. Improved	1.17 (1.03-1.31)	0.012	1.15 (1.01-1.32)	0.039	1.02 (0.86-1.21)	0.816
Toilet type	Unimproved vs. Improved	1.00 (0.84-1.19)	0.967	1.12 (0.94-1.33)	0.225	1.00 (0.79-1.27)	0.994
Solid waste management	Inadequate vs. Adequate	1.19 (1.09-1.29)	<0.001	1.07 (0.98-1.18)	0.145	1.04 (0.92-1.17)	0.538
Parental education	Low vs. High	1.26 (1.16-1.36)	<0.001	1.23 (1.12-1.34)	<0.001	1.17 (1.04-1.31)	0.008
Parental employment	Unemployed vs. Employed	1.25 (1.16-1.35)	<0.001	1.35 (1.24-1.48)	<0.001	1.31 (1.17-1.46)	<0.001
Healthy housing	Inadequate vs. Adequate	1.03 (0.95-1.12)	0.493	1.02 (0.93-1.12)	0.663	1.01 (0.89-1.14)	0.928

AOR: adjusted odds ratio; CI: confidence interval. Estimates were obtained using survey-weighted multivariable logistic regression accounting for the complex multistage sampling design of the 2022 Indonesian Nutrition Status Survey (SSGI). Reference categories were: middle adulthood, Eastern Indonesia, rural residence, improved drinking water source, boiled drinking water, improved sanitation improved toilet type, adequate solid waste management, high parental education, employed parents, and adequate healthy housing. Statistical significance was defined as $p < 0.05$.

For the underweight, significant regional differences were also observed. Children living in Western Indonesia (AOR=0.58; 95% CI: 0.51-0.66) and Central Indonesia (AOR=0.55; 95% CI: 0.49-0.63) had significantly lower odds of being underweight than those in Eastern Indonesia (both $p < 0.001$). Urban residence was associated with reduced odds of underweight compared with rural residence (AOR=0.88; 95% CI: 0.80-0.98; $p = 0.019$). Furthermore, low parental education (AOR=1.17; 95% CI: 1.04-1.31) and parental unemployment (AOR=1.31; 95% CI: 1.17-1.46) remained independently associated with underweight. No statistically significant associations were observed for maternal age, drinking water source, drinking water treatment, sanitation facility, toilet type, solid waste management, or healthy housing after multivariable adjustment.

Overall, regional disparities, parental socioeconomic characteristics, and selected environmental conditions emerged as the most consistent determinants of child undernutrition across the three nutritional outcomes, although the magnitude and significance of these associations varied according to the specific anthropometric indicator.

Discussion

This study examined associations between household

environmental conditions, socioeconomic characteristics, and child undernutrition using nationally representative data from the 2022 Indonesian Nutrition Status Survey (SSGI), accounting for the country's complex multistage sampling design. Several important findings emerged. First, regional disparities remained the strongest and most consistent determinants of all three forms of undernutrition. Second, parental socioeconomic disadvantage, particularly low educational attainment and unemployment, independently increased the likelihood of stunting, wasting, and underweight. Third, environmental factors, especially sanitation and solid waste management, showed stronger associations with chronic undernutrition than with acute nutritional deficits, suggesting that different forms of undernutrition may be influenced by distinct causal pathways.

One of the most prominent findings was the substantial regional disparity across Indonesia. Children in Eastern Indonesia consistently had higher odds of stunting, wasting, and underweight than those in Western and Central Indonesia. These findings align with previous national reports and international evidence showing persistent geographic inequalities in child nutrition across low- and middle-income countries [15, 16]. Regional disparities likely reflect unequal access to health services, maternal and child nutrition programs, food security, infrastructure, clean water, sanitation, and socioeconomic opportunities [17-19]. Eastern Indonesia

continues to have lower human development indicators, higher multidimensional poverty, and more limited access to healthcare than Western regions, collectively contributing to poorer child nutritional outcomes [20–22]. The persistence of these regional differences after multivariable adjustment suggests that geographic inequality reflects structural determinants that extend beyond individual household characteristics.

Parental socioeconomic characteristics also emerged as robust predictors of child undernutrition. Children whose parents had lower educational attainment experienced significantly higher odds of stunting, wasting, and underweight. Likewise, parental unemployment remained independently associated with all three nutritional outcomes. These findings reinforce the well-established role of socioeconomic position in shaping child health. Parents with higher educational attainment generally possess greater health literacy, improved infant feeding knowledge, stronger healthcare-seeking behavior, and better hygiene practices [12, 23–25]. Employment further provides economic resources necessary to ensure dietary diversity, healthcare utilization, and adequate living conditions [8]. Together, education and employment influence both material resources and caregiving capacity, thereby affecting children's nutritional status throughout early childhood [26–28].

Environmental determinants demonstrated more heterogeneous relationships across nutritional outcomes. Unimproved sanitation facilities and inadequate solid waste management remained independently associated with stunting, while unimproved sanitation also increased the likelihood of wasting. In contrast, several household water variables lost statistical significance after multivariable adjustment. These findings support the growing evidence that poor sanitation contributes to chronic growth impairment through repeated exposure to enteric pathogens, environmental enteric dysfunction, recurrent diarrheal disease, and chronic intestinal inflammation, all of which reduce nutrient absorption despite adequate food intake [5, 23, 29]. The stronger association observed with stunting than with underweight further supports the hypothesis that prolonged environmental exposures primarily affect long-term linear growth rather than short-term changes in body weight [9, 11, 29, 30].

Interestingly, some variables that showed significant associations in the bivariate analysis became non-significant after adjustment. Maternal age, toilet type, healthy housing, drinking water treatment, and several other environmental indicators no longer independently predicted undernutrition after controlling for socioeconomic and geographic factors. This attenuation suggests that their crude associations were partially explained by confounding, particularly household socioeconomic status and regional context. These findings underscore the importance of multivariable analyses that appropriately adjust for correlated determinants rather than relying solely on unadjusted comparisons.

The present findings underscore the multidimensional

nature of child undernutrition. Although environmental improvements remain important, interventions focused solely on water and sanitation are unlikely to eliminate undernutrition without concurrent efforts to reduce socioeconomic inequalities. Integrated strategies that combine nutrition-specific interventions with nutrition-sensitive programs, including poverty reduction, parental education, job creation, improved sanitation infrastructure, and equitable regional development, are likely to yield greater and more sustainable reductions in child undernutrition. Given the particularly elevated burden observed in Eastern Indonesia, geographically targeted interventions may further enhance program effectiveness.

A major strength of this study is the use of nationally representative SSGI 2022 data, with appropriate survey-weighted analyses that account for stratification, clustering, and sampling weights. This analytical approach addresses an important methodological limitation identified in previous analyses of Indonesian survey data and improves the validity and generalizability of national-level estimates. Nevertheless, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference, and the observed associations should not be interpreted as causal relationships. Second, information on several household characteristics was collected through caregiver reports and may therefore be subject to reporting bias. Third, although multiple socioeconomic and environmental variables were included, residual confounding from unmeasured factors such as dietary intake, infectious diseases, birth weight, maternal nutritional status, breastfeeding practices, and household food security cannot be excluded.

This study shows that child undernutrition in Indonesia results from a combination of geographic disparities, parental socioeconomic challenges, and specific environmental factors. The persistent regional gaps and socioeconomic influences across stunting, wasting, and underweight highlight the need for multisectoral policies that target both structural inequalities and household-level issues. Priorities should include increasing investments in underserved areas, enhancing parental education and economic opportunities, and expanding access to safe sanitation. These actions are essential for speeding up progress toward national nutrition targets and the Sustainable Development Goals.

CONTRIBUTIONS TO NURSING SCIENCE

This study contributes to nursing science in three ways. First, it demonstrates at a national scale that modifiable household hygiene and socioeconomic factors independently predict child undernutrition. Second, it links classical nursing theories with contemporary population-level data. Third, it supports the integration of environmental and social assessment into routine community nursing practice.

By conceptualizing child undernutrition as a nursing-sensitive outcome, the study positions nurses as central actors in preventing growth failure. Nurses can identify environmental risks, strengthen caregiver knowledge, and connect families with social resources.

STRENGTHS AND LIMITATIONS

The study uses nationally representative data from the 2022 Indonesian Nutritional Status Survey, thereby strengthening external validity and enabling population-level inference. The large sample size increases statistical precision. Multivariable modeling reduces confounding by key demographic variables.

However, the cross-sectional design limits causal inference. The analysis identifies associations but cannot establish directionality. Household hygiene variables rely on reported indicators rather than direct observation, which may introduce measurement bias. The dataset also lacks detailed psychosocial measures such as caregiving self-efficacy and health literacy. Future longitudinal and intervention studies should explore these mechanisms.

Conclusion

Using nationally representative survey data analyzed with appropriate survey-weighted methods, this study provides robust evidence that geographic inequality, parental socioeconomic disadvantage, and selected household environmental conditions are independently associated with child undernutrition in Indonesia. The findings indicate that the determinants of stunting, wasting, and underweight are distinct, underscoring the need for nutrition policies tailored to specific forms of undernutrition while also addressing broader structural inequalities. Future interventions should integrate nutrition-specific and nutrition-sensitive strategies, with particular attention to disadvantaged regions and vulnerable households, to achieve equitable improvements in child nutritional status across Indonesia.

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Availability of data and materials

The accompanying author can provide the data supporting the study's conclusions upon reasonable request. Due to ethical or privacy concerns, the data are not accessible to the general public.

Consent for publication

The final manuscript has been read, approved, and published with the approval of all authors.

Ethical approval

This study used anonymized secondary data obtained through formal approval from the Center for Data and Information Technology (PUSDATIN), Ministry of Health of the Republic of Indonesia. Data access was granted upon signing a confidentiality agreement (Document No. FRM/SMKI-PUSDATIN/70/0129/2024). The dataset contained no personal identifiers, and all analyses complied with national data protection regulations and ethical standards for secondary data research.

Conflict of interest statement

The author declares no conflict of interest.

Authors' contributions

YBP and RKH: Conceptualization, Methodology, Software. YBP and WM, HH: Data curation, Writing-Original draft preparation. RKH and NM: Visualization, Investigation. HD: Supervision. IR: Software, Validation. YBP and RKH: Writing- Reviewing and Editing.

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NON COMMUNICABLE DISEASE

Lip and Oral Cavity Cancer Worldwide in 2024: A Comprehensive Ecological Study of Burden, Socio-Demographic Disparities, and Population-Level Risk Factors

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Keywords

Lip cancer • Oral cavity cancer • Ecological study • Global burden • Risk factors • Socio-demographic disparities

Summary

Background. Lip and oral cavity cancer (LOCC) remains a substantial global cancer burden with marked sex and geographical disparities. Updated global estimates integrating cancer burden, behavioral exposures, and socioeconomic context are needed to clarify current patterns and identify population-level priorities for prevention and control.

Methods. We conducted an ecological analysis of GLOBOCAN 2024 LOCC estimates (ICD-10 C00-C06) across 186 countries. Age-standardized incidence (ASIR) and mortality rates (ASMR) were examined by sex, region, and income level. Associations with age-standardized smoking and alcohol Summary Exposure Values and Human Development Index (HDI) indicators were evaluated using multivariable linear regression, with historical analyses based on 1990 and 2010 data.

Results. In 2024, an estimated 452,062 new LOCC cases (ASIR: 4.5 per 100,000) and 194,059 deaths (ASMR: 1.9) occurred glob-

ally, with higher ASIR and ASMR among males than females. In fully adjusted ecological models, smoking prevalence was positively associated with ASIR among females ($\beta=0.349$, $p=0.012$), while alcohol use was positively associated with both ASIR ($\beta=0.275$, $p=0.006$) and ASMR ($\beta=0.206$, $p=0.046$) among males. Historical analyses from 1990 and 2010 showed substantial directional concordance with contemporary associations, indicating persistent but sex-specific ecological patterns across the examined periods.

Conclusion. LOCC continues to impose a substantial and uneven global burden, with distinct sex-specific associations involving tobacco and alcohol exposure. Socioeconomic development showed no independent fully adjusted association with LOCC outcomes. These findings support context-specific prevention, sustained exposure surveillance, and stronger early detection and treatment capacity.

Introduction

Cancer remains a leading global health challenge, with head and neck malignancies comprising a heterogeneous group of tumors that affect the upper aerodigestive tract, including the oral cavity, pharynx, and larynx [1]. Among these, lip and oral cavity cancers (LOCC), defined by ICD-10 codes C00-C06, represent a distinct group of malignancies involving the lip, tongue, gingiva, floor of the mouth, palate, and other sites of the oral cavity [2, 3]. Histologically, LOCCs are predominantly squamous cell carcinomas [4, 5] and can cause substantial morbidity through impairment of essential functions, including speech, mastication, swallowing, and oral competence, as well as through significant psychosocial and aesthetic consequences [6, 7].

The etiology of LOCC is largely attributed to modifiable environmental and behavioral exposures [8]. Tobacco use - whether smoked or smokeless - remains the most significant risk factor globally [9, 10]. Excessive alcohol consumption independently increases risk and acts synergistically with tobacco, amplifying carcinogenic

effects through mechanisms such as mucosal permeability and DNA damage [10-12]. In south and southeast Asia, the habitual chewing of betel quid, containing areca nut and frequently tobacco, is a dominant and culturally ingrained practice contributing significantly to LOCC incidence [13, 14]. Other implicated factors include chronic sun exposure (particularly for lip cancer), high-risk human papillomavirus (HPV) infection, poor oral hygiene, nutritional deficiencies (notably in fruit and vegetable intake), and chronic mechanical irritation [8, 9, 15].

The interplay and prevalence of these exposures vary substantially across regions, producing marked global disparities in LOCC incidence and mortality [1, 2, 16]. Regions such as south-central Asia, Melanesia, and parts of central and eastern Europe have historically reported the highest incidence rates [17]. Shifting epidemiological landscapes - driven by demographic transitions, aging populations, evolving patterns of tobacco and alcohol consumption, and the implementation of cancer control policies - warrant continual surveillance [8, 10, 12, 13].

Despite its burden, LOCC is often underprioritized in global cancer control discourse. Thus, timely and robust epidemiological evaluations are necessary. The Global Cancer Observatory's GLOBOCAN 2024 database, curated by the International Agency for Research on Cancer (IARC), provides a standardized and comprehensive platform for global cancer estimation [1]. The present study utilizes the most recent GLOBOCAN 2024 data to provide an updated and in-depth analysis of LOCC burden across 186 countries. It aims to quantify global incidence and mortality, describe age-standardized rates across continents, World Health Organization (WHO) regions, and national income levels, and explore sex-based disparities. In addition, the study evaluates ecological correlations between LOCC burden and national-level behavioral risk factors - specifically tobacco smoking and alcohol use - and socioeconomic indicators, particularly the Human Development Index (HDI) and its core components (life expectancy, mean years of schooling, and gross national income per capita) [18-22]. Through multivariable linear regression models adjusting for potential confounders, we aim to provide a nuanced understanding of population-level determinants of LOCC incidence and mortality.

Materials and Methods

STUDY DESIGN AND DATA SOURCES

This ecological study assessed the global burden of lip and oral cavity cancer (LOCC) for the year 2024. The ecological design was selected to examine cross-country and regional variation in LOCC incidence and mortality and to evaluate population-level associations between disease burden and selected behavioral and socioeconomic factors [23].

LOCC incidence and mortality estimates for 2024 were obtained from the Global Cancer Observatory (GLOBOCAN), maintained by the International Agency for Research on Cancer (IARC), which provides standardized cancer estimates across countries [24]. In the present study, LOCC was defined according to ICD-10 codes C00-C06, encompassing malignancies of the lip, tongue, gingiva, floor of the mouth, palate, and other sites of the oral cavity. Estimates were available for males, females, and both sexes combined. For countries without population-based cancer registries, national estimates were derived using established modelling approaches incorporating incidence-to-mortality ratios, regional extrapolation, and demographic characteristics [25, 26].

RISK-FACTOR EXPOSURE DATA

Risk-factor exposure data were obtained from the Global Burden of Disease Study 2019 (GBD 2019) and its supplementary results [27]. The present study used the age-standardized Summary Exposure Values (SEVs) for the relevant risk factors. For smoking and alcohol use, point estimates were extracted for 1990, 2010, and 2019, separately for males, females, and both sexes combined. The extracted SEVs represent population-level, risk-

weighted exposure measures rather than conventional survey-based prevalence estimates. SEVs incorporate the distribution of exposure across the population and the corresponding relative risk associated with different exposure levels and are expressed on a 0-100 scale, with higher values indicating greater exposure relative to the theoretical minimum-risk level. Therefore, the smoking and alcohol variables used in the regression analyses were interpreted as SEVs rather than direct percentages of individuals reporting current smoking or alcohol use. Only reported point estimates were used in the analyses. Uncertainty intervals, percentage changes, or values derived from alternative sources were not substituted for the reported estimates. When a valid point estimate was unavailable for a specific country, sex, or year, the corresponding observation was treated as missing and was not imputed.

For the primary analyses, smoking and alcohol-use SEVs for 2019 were used. Additional historical analyses were performed using the corresponding 1990 and 2010 exposure estimates to evaluate the temporal robustness of the observed ecological associations.

HDI AND ITS COMPONENTS

Socioeconomic development was assessed using the HDI and its three core components: life expectancy at birth, mean years of schooling, and gross national income (GNI) per capita. HDI data were obtained from the United Nations Development Programme (UNDP) Human Development Reports and associated standardized time-series data [28].

For the primary analyses presented in this report, 2023 HDI values and the corresponding component indicators were used. For the additional historical analyses, HDI and its components were extracted for 1990 and 2010. This approach allowed the relationship between long-term socioeconomic development and LOCC burden to be examined across different periods.

GNI per capita was expressed in purchasing power parity-adjusted international dollars and entered into the regression models in units of 1,000 international dollars. HDI summarizes national achievement across health, education, and income dimensions, and the use of harmonized time-series data allowed consistent comparisons across the study years.

OUTCOME MEASURES

The primary outcomes were the age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) for LOCC, expressed per 100,000 person-years and standardized using the Segi world standard population. Crude rates and absolute numbers of incident cases and deaths were also considered. Sex-specific ASIRs and ASMRs were used to calculate male-to-female ratios, and the proportional contribution of each WHO region to the global LOCC burden was estimated.

GEOGRAPHIC AND ECONOMIC CLASSIFICATION

Analyses were conducted at global, continental (Africa, Asia, Europe, Latin America and the Caribbean,

Northern America, and Oceania), and WHO regional levels (AFRO, PAHO, SEARO, EURO, EMRO, and WPRO). Countries were also classified according to the 2024 World Bank income classification as high-income, upper-middle-income, lower-middle-income, or low-income countries.

STATISTICAL ANALYSIS

Descriptive analyses included absolute numbers, crude rates, ASIRs, ASMRs, and sex-specific ratios. Inferential analyses used multivariable linear regression to evaluate ecological associations between country-level smoking and alcohol-use exposure, HDI and its components, and LOCC outcomes (ASIR and ASMR). Regression models were estimated separately for males, females, and both sexes combined.

For analyses of smoking and alcohol use, four sequential models were specified. Model 1 was unadjusted. Model 2 adjusted for the other behavioral exposure (alcohol when smoking was the primary exposure and smoking when alcohol was the primary exposure). Model 3 adjusted for HDI. Model 4 was fully adjusted for the behavioral exposure and HDI.

For analyses of HDI and its components, Model 1 was unadjusted, Model 2 adjusted for smoking exposure, Model 3 adjusted for alcohol-use exposure, and Model 4 adjusted for both smoking and alcohol-use exposures. Regression outputs included unstandardized coefficients (B), standard errors (SE), standardized coefficients (β), and two-sided *p*-values. Statistical significance was defined as *p* < 0.05. Multicollinearity was assessed using variance inflation factors (VIF), and model assumptions, including linearity and homoscedasticity, were evaluated using residual plots.

To assess temporal robustness, additional ecological regression analyses were conducted using smoking and alcohol-use SEVs from 1990 and 2010 and HDI and its components from the corresponding years, while retaining the 2024 LOCC ASIR and ASMR as outcomes. These analyses were performed separately by sex and followed the same four-model framework. Complete-case observations were used for each model, and no missing exposure or socioeconomic values were imputed. Analyses were performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA).

Results

GLOBAL BURDEN OF LIP AND ORAL CAVITY CANCER

In 2024, an estimated 452,062 new LOCC cases occurred globally, with an ASIR of 4.5 per 100,000. Males accounted for 70.6% of all incident cases (*n*=319,240), compared to 29.4% among females (*n*=132,822). The ASIR was 6.7 in males and 2.4 in females, yielding a male-to-female ratio of 2.79 (Tab. I).

Global LOCC mortality totaled 194,059 deaths, with 70.7% (*n*=137,169) in males and 29.3% (*n*=56,890) in females. The overall ASMR was 1.9 per 100,000, with

sex-specific rates of 2.8 (males) and 0.99 (females). The male-to-female mortality ratio was 2.83 (Tab. II).

GEOGRAPHICAL VARIATION BY CONTINENT AND WHO REGION

Marked regional disparities were observed. Among WHO regions, SEARO reported the highest LOCC burden, with ASIR of 10.4 and ASMR of 4.6, contributing the largest share of global incident cases and deaths. Other regions showed moderate burdens: EURO (ASIR 3.8; ASMR 1.4), EMRO (ASIR 2.6; ASMR 1.6), PAHO (ASIR 3.4; ASMR 0.87), and WPRO (ASIR 1.9; ASMR 0.84). AFRO reported the lowest ASIR (1.6) and ASMR (1.0).

By continent, Oceania had the highest ASIR (7.1), followed by Asia (5.3), Northern America (4.6), and Europe (4.1). In contrast, Africa (1.6) and Latin America and the Caribbean (2.4) had lower ASIRs. However, despite relatively higher incidence in Europe and North America, mortality was often lower than in Asia, reflecting regional differences in detection and treatment (Tabs. I, II).

BURDEN BY INCOME LEVEL

LOCC incidence and mortality demonstrated clear variation across national income levels, with the greatest burden observed in lower-middle-income countries, where the ASIR reached 7.7 and the ASMR was 3.6, largely reflecting the substantial contribution of South Asian populations. In contrast, high-income countries exhibited comparatively lower age-standardized rates (ASIR 3.9; ASMR 0.93), although their crude rates remained elevated, likely due to demographic aging.

A consistent male predominance was evident across all income strata, with lower-middle-income countries again showing the highest sex-specific burden, as indicated by a male ASIR of 11.7 and an ASMR of 5.4 (Tabs. I, II).

COUNTRY-SPECIFIC LOCC BURDEN

The highest number of new LOCC cases were observed in India (205,878), China (39,438), and the USA (29,547). The highest ASIRs were found in Papua New Guinea (20 per 100,000), India (13.4 per 100,000), and Bangladesh (9.4 per 100,000) (Tab. S1).

In terms of mortality, India (86,307), China (20,699), and Bangladesh (9,210) recorded the highest number of LOCC deaths. The highest ASMR were found in Papua New Guinea (12.6 per 100,000), followed by Maldives (6.7 per 100,000), and Bangladesh (5.9 per 100,000) (Tab. S1).

CORRELATION WITH SMOKING PREVALENCE

Regression analyses identified positive ecological correlations between national smoking prevalence and LOCC incidence and mortality, although the strength and statistical significance varied across sex and outcome. In the total population, smoking prevalence was positively correlated with ASIR (β =0.149, *p*=0.163) and ASMR (β =0.123, *p*=0.264) in the fully adjusted model, although

Tab. I. The ASIR of LOCC in different regions of the World in 2024.

Population Numbers		All			Males			Females		
		ASIR	Crude Rate	Numbers	ASIR	Crude Rate	Numbers	ASIR	Crude Rate	Numbers
World		452062	4.5	5.6	319240	6.7	7.8	132822	2.4	3.3
WHO regions	WHO Africa region (AFRO)	11968	1.6	0.94	7141	2.1	1.1	4827	1.2	0.76
	WHO Americas region (PAHO)	53309	3.4	5.1	35237	4.8	6.8	18072	2	3.4
	WHO East Mediterranean region (EMRO)	16767	2.6	2	10295	3.2	2.4	6472	2	1.6
	WHO Europe region (EURO)	66641	3.8	7.1	44718	5.7	9.8	21923	2.1	4.5
	WHO South-East Asia region (SEARO)	238217	10.4	11.3	180162	15.8	16.7	58055	5	5.6
	WHO Western Pacific region (WPRO)	65160	1.9	3.4	41687	2.6	4.3	23473	1.3	2.5
Continents	Africa	15364	1.6	1	9196	2.1	1.2	6168	1.2	0.81
	Latin America and the Caribbean	20187	2.4	3	13055	3.4	4	7132	1.5	2.1
	Northern America	33175	4.6	8.6	22218	6.4	11.5	10957	2.8	5.7
	Europe	62402	4.1	8.4	42065	6.3	11.7	20337	2.2	5.3
	Oceania	4721	7.1	10.2	3092	9.6	13.4	1629	4.7	7.1
	Asia	316356	5.3	6.6	229714	7.8	9.5	86642	2.7	3.7
Income levels	High income	96121	3.9	8	62079	5.4	10.3	34042	2.5	5.7
	Upper middle income	84347	2.1	3.3	55799	2.9	4.4	28548	1.3	2.2
	Lower middle income	263978	7.7	7.4	196921	11.7	10.9	67057	3.9	3.8
	Low income	6896	1.5	0.89	3986	1.9	1	2910	1.2	0.75

neither association remained statistically significant. Among males, smoking prevalence remained positively correlated with ASIR ($\beta=0.107$, $p=0.222$) and ASMR ($\beta=0.139$, $p=0.128$), but these associations were also not statistically significant after full adjustment. In contrast, among females, smoking prevalence remained significantly correlated with ASIR ($\beta=0.349$, $p=0.012$), whereas the association with ASMR was positive but not statistically significant ($\beta=0.148$, $p=0.278$). Overall, adjustment attenuated the smoking-LOCC associations, particularly for males and the total population (Tab. III).

CORRELATION WITH ALCOHOL USE PREVALENCE

Alcohol use prevalence also demonstrated a positive ecological correlation with LOCC burden, particularly among males. In the total population, alcohol use was positively correlated with both ASIR ($\beta=0.146$, $p=0.163$) and ASMR ($\beta=0.071$, $p=0.506$) in the fully adjusted model, although neither association was statistically significant. Among males, these correlations remained significant after adjustment for smoking and HDI, for both ASIR ($\beta=0.275$, $p=0.006$) and ASMR ($\beta=0.206$, $p=0.046$). In females, however, the associations were negative and non-significant for both ASIR ($\beta=-0.188$, $p=0.139$) and ASMR ($\beta=-0.179$, $p=0.153$), indicating a weaker association in this population group (Tab. IV).

Correlation with HDI and Socioeconomic Indicators
The correlation between national HDI and LOCC burden was more complex. HDI showed positive associations

with ASIR in unadjusted analyses among males ($\beta=0.239$, $p=0.002$) and in the total population ($\beta=0.195$, $p=0.013$), but these associations were attenuated after adjustment and were no longer statistically significant in the fully adjusted model (male: $\beta=0.007$, $p=0.949$; female: $\beta=-0.056$, $p=0.651$; total: $\beta=0.005$, $p=0.963$). Similarly, HDI was not significantly correlated with ASMR after full adjustment among males ($\beta=-0.198$, $p=0.075$), females ($\beta=-0.226$, $p=0.066$), or the total population ($\beta=-0.198$, $p=0.085$). Analyses of HDI components showed that life expectancy at birth and mean years of schooling were positively correlated with ASIR in unadjusted models, particularly among males, but these associations diminished after adjustment. For mortality, inverse associations were more evident for mean years of schooling and GNI per capita in the fully adjusted models, particularly among females for mean years of schooling ($\beta=-0.304$, $p=0.009$) and among males for GNI per capita ($\beta=-0.192$, $p=0.031$). However, associations with the HDI components were generally inconsistent across sex and outcomes (Tabs. V, VI).

TEMPORAL ROBUSTNESS OF ECOLOGICAL ASSOCIATIONS USING HISTORICAL EXPOSURE AND DEVELOPMENT INDICATORS

Additional analyses using historical exposure and socioeconomic data showed broadly consistent ecological patterns with those observed in Tables III-VI. For 1990, smoking remained positively associated

Tab. II. The ASMR of LOCC in Different Regions of the World in 2024.

Population Numbers		All			Males			Females		
		ASMR	Crude Rate	Numbers	ASMR	Crude Rate	Numbers	ASMR	Crude Rate	Numbers
World		194059	1.9	2.4	137169	2.8	3.4	56890	0.99	1.4
WHO regions	WHO Africa region (AFRO)	7341	1	0.58	4406	1.3	0.7	2935	0.78	0.46
	WHO Americas region (PAHO)	14762	0.87	1.4	9960	1.3	1.9	4802	0.48	0.91
	WHO East Mediterranean region (EMRO)	9729	1.6	1.2	6222	2	1.5	3507	1.1	0.87
	WHO Europe region (EURO)	24825	1.4	2.6	17313	2.2	3.8	7512	0.63	1.6
	WHO South-East Asia region (SEARO)	106251	4.6	5	78465	7	7.3	27786	2.4	2.7
	WHO Western Pacific region (WPRO)	31151	0.84	1.6	20803	1.2	2.2	10348	0.47	1.1
Continents	Africa	9159	1	0.6	5537	1.3	0.73	3622	0.75	0.48
	Latin America and the Caribbean	8718	1	1.3	6051	1.6	1.9	2667	0.52	0.79
	Northern America	6070	0.72	1.6	3929	1	2	2141	0.44	1.1
	Europe	23263	1.5	3.1	16339	2.4	4.5	6924	0.66	1.8
	Oceania	1506	2.2	3.3	978	3	4.2	528	1.5	2.3
	Asia	145392	2.4	3.1	104373	3.5	4.3	41019	1.2	1.8
Income levels	High income	26716	0.93	2.2	16833	1.4	2.8	9883	0.53	1.6
	Upper middle income	41014	0.95	1.6	28576	1.4	2.2	12438	0.5	0.98
	Lower middle income	121683	3.6	3.4	88945	5.4	4.9	32738	1.9	1.9
	Low income	4323	1	0.56	2607	1.3	0.68	1716	0.75	0.44

with LOCC incidence after full adjustment among males ($\beta=0.215$, $p=0.043$), females ($\beta=0.490$, $p=0.003$), and the total population ($\beta=0.333$, $p=0.009$), whereas associations with mortality were positive but not statistically significant. In 2010, the positive association of smoking with incidence persisted, particularly among females ($\beta=0.444$, $p=0.001$) and the total population ($\beta=0.270$, $p=0.020$), while significant positive associations with mortality were observed among males ($\beta=0.214$, $p=0.026$) and the total population ($\beta=0.237$, $p=0.045$).

Alcohol showed a similar pattern across time, with the strongest associations observed among males. In 2010, alcohol use was positively associated with both incidence ($\beta=0.306$, $p=0.002$) and mortality ($\beta=0.231$, $p=0.025$) in males after adjustment, whereas associations among females and the total population were not statistically significant. The 1990 analyses showed weaker associations, particularly after adjustment.

Associations between HDI and its components and incidence were generally attenuated after adjustment in both 1990 and 2010. In contrast, inverse associations between HDI and mortality were more evident, particularly in 2010, when fully adjusted HDI was negatively associated with mortality among males ($\beta=-0.308$, $p=0.007$), females ($\beta=-0.341$, $p=0.007$), and the total population ($\beta=-0.336$, $p=0.005$).

Overall, the historical analyses were broadly concordant with the patterns observed in Tables 3-6. Based on

the direction of the standardized β coefficients in the fully adjusted models, 60 of 72 comparisons (83.3%) were directionally concordant between the 1990/2010 analyses and the corresponding analyses presented in Tables III-VI. The greatest consistency was observed for the patterns involving smoking, alcohol use, and HDI in relation to mortality. This percentage represents a descriptive measure of directional agreement and does not imply identical effect sizes or statistical significance.

Discussion

This study provides a comprehensive ecological assessment of the global burden of LOCC in 2024 and examines population-level associations with behavioral and socioeconomic indicators. We identified 452,062 new LOCC cases and 194,059 deaths worldwide, with a pronounced male predominance in both incidence and mortality. The highest burden was observed in the WHO SEARO, where the ASIR and ASMR reached 10.4 and 4.6 per 100,000, respectively. These findings are consistent with the substantial global and regional burden of oral cancer reported in previous studies and with the established contribution of tobacco, alcohol, and other regionally prevalent exposures to LOCC risk [2, 15-7, 29-36].

The marked male predominance observed in the present study is consistent with established epidemiological

Tab. III. Examining the Correlation Between smoking prevalence and Incidence and Mortality Rates of LOCC.

Smoking prevalence Unstandardized Coefficients (SE)		Incidence			Mortality		
		Standardized Coefficients	<i>p-value</i>	Unstandardized Coefficients (SE)	Standardized Coefficients	<i>p-value</i>	Unstandardized Coefficients (SE)
Males	Model 1	0.100 (0.033)	0.223	0.003	0.030 (0.020)	0.115	0.124
	Model 2	0.048 (0.034)	0.108	0.162	0.019 (0.021)	0.072	0.375
	Model 3	0.058 (0.041)	0.125	0.162	0.042 (0.025)	0.153	0.098
	Model 4	0.050 (0.041)	0.107	0.222	0.038 (0.025)	0.139	0.128
Females	Model 1	0.063 (0.022)	0.219	0.004	-0.020 (0.013)	-0.121	0.114
	Model 2	0.089 (0.033)	0.298	0.008	0.001 (0.019)	0.007	0.947
	Model 3	0.079 (0.032)	0.264	0.014	0.013 (0.019)	0.071	0.5
	Model 4	0.107 (0.042)	0.349	0.012	0.027 (0.025)	0.148	0.278
Total	Model 1	0.103 (0.030)	0.251	≤0.001	0.007 (0.018)	0.027	0.717
	Model 2	0.063 (0.037)	0.153	0.088	0.006 (0.023)	0.025	0.789
	Model 3	0.083 (0.044)	0.193	0.061	0.037 (0.027)	0.144	0.17
	Model 4	0.064 (0.046)	0.149	0.163	0.031 (0.028)	0.123	0.264

Model 1: crude or unadjusted model. Model 2: Adjusted for alcohol use prevalence. Model 3: Adjusted for HDI. Model 4: Adjusted for HDI, and alcohol use prevalence.

Tab. IV. Examining the Correlation Between Alcohol use prevalence and Incidence and Mortality Rates of LOCC.

Alcohol use prevalence Unstandardized Coefficients (SE)		Incidence			Mortality		
		Standardized Coefficients	<i>p-value</i>	Unstandardized Coefficients (SE)	Standardized Coefficients	<i>p-value</i>	Unstandardized Coefficients (SE)
Males	Model 1	0.153(0.032)	0.338	0.001	0.037(0.020)	0.139	0.063
	Model 2	0.134(0.035)	0.296	0.001	0.029(0.021)	0.111	0.171
	Model 3	0.130(0.045)	0.284	0.004	0.059(0.028)	0.218	0.035
	Model 4	0.126(0.045)	0.275	0.006	0.056(0.028)	0.206	0.046
Females	Model 1	0.029(0.033)	0.072	0.371	-0.046(0.019)	-0.190	0.017
	Model 2	-0.060(0.046)	-0.146	0.188	-0.052(0.027)	-0.216	0.053
	Model 3	-0.003(0.047)	-0.007	0.948	-0.022(0.027)	-0.085	0.425
	Model 4	-0.081(0.054)	-0.188	0.139	-0.046(0.032)	-0.179	0.153
Total	Model 1	0.108(0.031)	0.256	0.001	0.005(0.019)	0.019	0.803
	Model 2	0.070(0.038)	0.167	0.063	0.001(0.023)	0.004	0.965
	Model 3	0.082(0.043)	0.188	0.061	0.027(0.026)	0.106	0.300
	Model 4	0.063(0.045)	0.146	0.163	0.018(0.028)	0.071	0.506

Model 1: crude or unadjusted model. Model 2: Adjusted for smoking prevalence. Model 3: Adjusted for HDI. Model 4: Adjusted for HDI, and smoking prevalence.

patterns and is likely related, at least in part, to sex differences in exposure to major behavioral risk factors. Tobacco smoking and alcohol consumption have historically been more prevalent among men in many populations, while the long latency of carcinogenesis means that contemporary cancer burden may reflect exposures accumulated over earlier decades [2, 9, 29, 30]. The historical analyses performed in this study provide additional support for this interpretation, as several associations between earlier smoking or alcohol exposure and current LOCC outcomes remained evident, although their magnitude and statistical significance varied by sex and outcome.

Our ecological regression analyses indicate that the relationship between smoking exposure and LOCC burden is sex- and outcome-specific. In the fully adjusted current models, smoking exposure remained positively associated with LOCC incidence among females ($\beta=0.349$, $p=0.012$), whereas the corresponding

associations were not statistically significant among males or in the total population. For mortality, positive but non-significant associations were observed in all three groups. Notably, the historical analyses showed a similar positive association between smoking exposure and incidence among females in both 1990 and 2010, while the total population also showed a positive association in these historical models. Smoking exposure in 2010 was additionally associated with mortality among males and the total population. The persistence of positive associations across historical periods, particularly for female incidence, suggests temporal consistency in the direction of the ecological relationship, although the variation in statistical significance indicates that the strength of the association is not uniform across time or population groups. These findings are broadly compatible with the established relationship between tobacco exposure and oral cancer reported in epidemiological studies [31, 37-41].

Tab. V. Examining the Correlation Between HDI and its components and Incidence Rates of LOCC.

HDI and components		Male			Female			Total		
		Standardized Coefficients	Unstandardized Coefficients (se)	<i>p</i> -value	Standardized Coefficients	Unstandardized Coefficients (se)	<i>p</i> -value	Standardized Coefficients	Unstandardized Coefficients (se)	<i>p</i> -value
HDI	Model 1	5.240 (1.689)	0.239	0.002	0.772 (0.757)	0.081	0.310	2.898 (1.155)	0.195	0.013
	Model 2	3.841 (1.957)	0.175	0.051	-0.953 (1.018)	-0.099	0.351	1.019 (1.518)	0.069	0.503
	Model 3	1.225 (2.160)	0.056	0.571	0.766 (1.061)	0.079	0.471	1.128 (1.480)	0.076	0.447
	Model 4	0.150 (2.328)	0.007	0.949	-0.543 (1.197)	-0.056	0.651	0.076 (1.656)	0.005	0.963
Life expectancy at birth	Model 1	0.104 (0.037)	0.217	0.006	0.023 (0.016)	0.108	0.171	0.063 (0.025)	0.195	0.013
	Model 2	0.071 (0.042)	0.148	0.096	-0.006 (0.021)	-0.028	0.787	0.025 (0.032)	0.077	0.432
	Model 3	0.035 (0.042)	0.074	0.401	0.027 (0.021)	0.128	0.198	0.034 (0.029)	0.104	0.241
	Model 4	0.016 (0.045)	0.034	0.714	0.003 (0.024)	0.016	0.886	0.016 (0.032)	0.049	0.629
Mean years of schooling	Model 1	0.225 (0.080)	0.217	0.006	0.004 (0.036)	0.010	0.903	0.105 (0.055)	0.149	0.059
	Model 2	0.150 (0.094)	0.145	0.113	-0.085 (0.046)	-0.189	0.067	-0.007 (0.071)	-0.009	0.926
	Model 3	0.005 (0.105)	0.005	0.960	-0.024 (0.049)	-0.052	0.633	-0.008 (0.072)	-0.012	0.909
	Model 4	-0.061 (0.114)	-0.059	0.596	-0.074 (0.054)	-0.162	0.168	-0.071 (0.079)	-0.102	0.371
GNI per capita	Model 1	0.021 (0.011)	0.151	0.057	0.006 (0.005)	0.103	0.194	0.014 (0.008)	0.146	0.065
	Model 2	0.014 (0.011)	0.099	0.222	-0.002 (0.006)	-0.030	0.760	0.004 (0.008)	0.046	0.594
	Model 3	0.001 (0.012)	0.004	0.964	0.006 (0.007)	0.094	0.375	0.004 (0.009)	0.039	0.658
	Model 4	-0.002 (0.012)	-0.011	0.900	-0.001 (0.007)	-0.019	0.865	0.001 (0.009)	0.005	0.952

GNI per capita based on every 1000 \$. Model 1: crude or un adjusted model. Model 2: Adjusted for smoking prevalence. Model 3: Adjusted for alcohol use prevalence. Model 4: Adjusted for alcohol use prevalence, and smoking prevalence.

Alcohol exposure demonstrated a different pattern, with the clearest associations observed among males. In the current fully adjusted analysis, alcohol exposure was positively associated with both LOCC incidence ($\beta=0.275$, $p=0.006$) and mortality ($\beta=0.206$, $p=0.046$) among males, while associations in females and the total population were not statistically significant. The 2010 historical analysis reproduced this male-specific pattern, with significant positive associations with both incidence ($\beta=0.306$, $p=0.002$) and mortality ($\beta=0.231$, $p=0.025$). Associations were weaker in the 1990 analysis and were attenuated after adjustment. The consistency of the male-specific association across the current and 2010 analyses is compatible with evidence that tobacco and alcohol jointly contribute to oral carcinogenesis and that their effects may interact biologically [10, 42-8]. However, because the present analysis is ecological and the GBD exposure measures are Summary Exposure Values rather than direct survey percentages, these findings should be

interpreted as population-level exposure associations rather than individual-level causal effects.

The socioeconomic findings were more heterogeneous. In the current analyses, HDI was positively associated with LOCC incidence in some unadjusted models, particularly among males and the total population, but these associations were largely attenuated after adjustment and were not statistically significant in the fully adjusted models. HDI was likewise not significantly associated with mortality after full adjustment. Analyses of individual HDI components showed that positive associations with incidence for life expectancy and mean years of schooling were mainly observed in unadjusted models and diminished after adjustment, whereas several inverse associations with mortality were observed for mean years of schooling and GNI per capita.

The historical analyses provide an important additional perspective on the socioeconomic findings. For both 1990 and 2010, associations between HDI and its

Tab. VI. Examining the Correlation Between HDI and its components and Mortality Rates of LOCC.

HDI and components		Male			Female			Total		
		Standard-ized Coef-ficients	Unstan-dardized Coeffi-cients (se)	<i>p-value</i>	Standard-ized Coef-ficients	Unstan-dardized Coeffi-cients (se)	<i>p-value</i>	Standard-ized Coef-ficients	Unstan-dardized Coeffi-cients (se)	<i>p-value</i>
HDI	Model 1	0.078 (1.024)	0.006	0.939	-1.287 (0.435)	-0.229	0.004	-0.643 (0.698)	-0.073	0.358
	Model 2	-0.927 (1.184)	-0.072	0.435	-1.606 (0.593)	-0.285	0.008	-1.477 (0.922)	-0.167	0.111
	Model 3	-1.734 (1.325)	-0.134	0.193	-0.990 (0.612)	-0.172	0.108	-1.237 (0.902)	-0.140	0.172
	Model 4	-2.556 (1.425)	-0.198	0.075	-1.297 (0.701)	-0.226	0.066	-1.752 (1.011)	-0.198	0.085
Life expectancy at birth	Model 1	-0.002 (0.022)	-0.008	0.921	-0.024 (0.010)	-0.199	0.012	-0.013 (0.015)	-0.067	0.398
	Model 2	-0.024 (0.025)	-0.085	0.349	-0.026 (0.012)	-0.211	0.041	-0.028 (0.019)	-0.144	0.155
	Model 3	-0.028 (0.026)	-0.100	0.272	-0.014 (0.012)	-0.114	0.242	-0.019 (0.018)	-0.100	0.273
	Model 4	-0.043 (0.028)	-0.153	0.121	-0.019 (0.014)	-0.149	0.194	-0.029 (0.020)	-0.149	0.150
Mean years of schooling	Model 1	0.005 (0.048)	0.008	0.916	-0.073 (0.020)	-0.276	≤0.001	-0.039 (0.033)	-0.094	0.237
	Model 2	-0.044 (0.056)	-0.073	0.433	-0.090 (0.027)	-0.340	≤0.001	-0.084 (0.043)	-0.201	0.054
	Model 3	-0.088 (0.064)	-0.145	0.173	-0.072 (0.028)	-0.266	0.011	-0.078 (0.044)	-0.186	0.077
	Model 4	-0.133 (0.070)	-0.218	0.059	-0.082 (0.031)	-0.304	0.009	-0.104 (0.048)	-0.251	0.032
GNI per capita	Model 1	-0.007 (0.007)	-0.080	0.312	-0.007 (0.003)	-0.199	0.011	-0.007 (0.004)	-0.117	0.140
	Model 2	-0.010 (0.007)	-0.122	0.138	-0.008 (0.004)	-0.216	0.027	-0.010 (0.005)	-0.168	0.059
	Model 3	-0.015 (0.007)	-0.179	0.043	-0.006 (0.004)	-0.147	0.156	-0.009 (0.005)	-0.165	0.069
	Model 4	-0.016 (0.007)	-0.192	0.031	-0.007 (0.004)	-0.192	0.091	-0.011 (0.005)	-0.184	0.050

GNI per capita based on every 1000 \$. Model 1: crude or unadjusted model. Model 2: Adjusted for smoking prevalence. Model 3: Adjusted for alcohol use prevalence. Model 4: Adjusted for alcohol use prevalence, and smoking prevalence.

components and incidence were generally attenuated after adjustment. In contrast, inverse associations between HDI and mortality were more consistent, particularly in 2010, when fully adjusted HDI was negatively associated with mortality among males ($\beta=-0.308$, $p=0.007$), females ($\beta=-0.341$, $p=0.007$), and the total population ($\beta=-0.336$, $p=0.005$). Similar inverse associations were also observed using 1990 HDI values. These findings are compatible with previous ecological studies showing that socioeconomic development may be associated differently with cancer incidence and mortality, potentially reflecting differences in cancer detection, stage at diagnosis, treatment availability, and health-system capacity [20, 49-53]. Nevertheless, these mechanisms remain interpretive rather than directly tested in the present study.

Taken together, the comparison of contemporary and historical analyses suggests that the principal ecological patterns are reasonably stable but not identical across

time. Smoking showed the most consistent positive relationship with incidence, particularly among females, whereas alcohol showed the clearest and most persistent association with both incidence and mortality among males. In contrast, socioeconomic indicators showed greater temporal and outcome-specific heterogeneity. Based on the direction of the standardized β coefficients in the fully adjusted models, 60 of 72 comparisons (83.3%) between the historical analyses and the corresponding current analyses were directionally concordant. This descriptive level of agreement indicates substantial consistency in the direction of associations, but it should not be interpreted as evidence of identical effect sizes or statistical significance.

The present findings should also be interpreted in light of the nature of the exposure data. GBD 2019 summarizes exposure using age-standardized SEVs, which are risk-weighted measures designed to facilitate comparisons across risks, locations, and time rather than direct

survey-based prevalence estimates [27]. Accordingly, the observed ecological associations reflect cross-national variation in modeled exposure burden and cannot be directly translated into individual-level risk estimates. This distinction is particularly relevant when interpreting the relatively strong sex-specific associations observed for smoking and alcohol.

The geographical findings further reinforce the heterogeneous epidemiology of LOCC. The particularly high burden in SEARO is consistent with the substantial contribution of smokeless tobacco and betel quid use in south and southeast Asia [13, 15, 37, 38, 54-6]. Conversely, comparatively lower incidence and mortality in some regions may partly reflect differences in cancer registration, diagnosis, access to care, and completeness of mortality ascertainment rather than genuinely lower underlying disease burden [49, 57-61]. The divergence between incidence and mortality across regions therefore likely reflects a combination of exposure patterns and differences in health-system performance.

Overall, these findings support a multifactorial and sex-specific interpretation of the global LOCC burden. The consistency of selected associations across historical periods suggests that long-term patterns of tobacco and alcohol exposure may contribute to contemporary national differences in LOCC burden, while the heterogeneous associations with HDI and its components indicate that socioeconomic development cannot be interpreted as a uniform predictor of either incidence or mortality. The findings therefore strengthen the rationale for continued tobacco and alcohol control, while also emphasizing the importance of early detection, cancer registration, treatment access, and broader health-system capacity in shaping population-level LOCC outcomes [11, 50-3].

As an ecological analysis, this study cannot establish causality or determine whether the observed national-level associations apply to individuals. In addition, LOCC has a long and variable latency period, and historical exposure patterns may therefore be more relevant to current disease burden than contemporaneous measurements alone. The use of exposure data from 1990, 2010, and 2019 provides a useful temporal perspective, but residual confounding by factors such as betel quid use, HPV infection, diet, occupational exposures, and differences in cancer detection and registration remains possible [13, 54, 62, 63]. Future longitudinal and individual-level studies integrating these determinants are needed to clarify the temporal and causal pathways underlying the observed associations.

STRENGTHS AND LIMITATIONS

A major strength of this study is its use of the most recent GLOBOCAN 2024 estimates to provide a standardized assessment of the global burden of lip and oral cavity cancer across countries, geographic regions, and sexes. The analysis combines contemporary cancer burden estimates with harmonized population-level exposure and socioeconomic indicators from the GBD study and the UNDP. In addition to evaluating contemporary associations using 2019 smoking and

alcohol exposure estimates and 2023 socioeconomic indicators, the study incorporates historical exposure and development measures from 1990 and 2010, providing an additional temporal perspective. Sex-stratified analyses and multivariable regression models further allowed examination of whether observed ecological associations differed between males, females, and the total population. The use of standardized regression coefficients, complete-case analyses, and model diagnostics including variance inflation assessment and residual examination also strengthened the analytical framework.

Several limitations should nevertheless be considered. First, the ecological design precludes individual-level inference and causal interpretation. Associations observed between country-level exposures and cancer rates may not reflect corresponding relationships at the individual level and may be influenced by within-country heterogeneity. Second, the exposure variables derived from GBD 2019 are age-standardized SEVs, which represent risk-weighted exposure distributions rather than conventional survey-based prevalence estimates. Consequently, they should not be interpreted as direct measures of the proportion of individuals exposed at a specified level. Third, temporal alignment remains an important limitation. The primary analyses relate 2019 smoking and alcohol exposure estimates and 2023 socioeconomic indicators to 2024 cancer outcomes, whereas cancer development may reflect cumulative exposures over substantially longer periods. The historical analyses using 1990 and 2010 indicators provide supportive temporal context but do not constitute longitudinal individual-level analyses or establish exposure-to-disease time sequences. Fourth, incomplete availability of some exposure and socioeconomic variables reduced the analytic sample size in selected models, and complete-case analysis may introduce selection bias when missingness is not random. Finally, residual confounding is possible because important determinants of LOCC, including smokeless tobacco and betel quid/areca nut exposure, HPV infection, dietary factors, occupational exposures, and differences in diagnostic and treatment access, could not be comprehensively incorporated into the regression models [62, 63]. These limitations warrant cautious interpretation of the observed ecological associations.

PUBLIC HEALTH IMPLICATIONS

The findings have several implications for global LOCC prevention and control. The marked geographical heterogeneity, together with the particularly high burden observed in the SEARO, supports the need for context-specific prevention strategies that address locally predominant exposures, including smokeless tobacco and betel quid/areca nut use. At the global level, continued tobacco and alcohol control, including prevention of initiation, reduction of exposure, cessation support, and effective regulatory and educational measures, remains essential given the established role of these exposures

in oral carcinogenesis and the ecological associations observed in the present study [55, 56, 64].

The sex-specific regression findings further indicate that prevention and surveillance should not necessarily be based on a uniform population-wide exposure profile. In the fully adjusted models, smoking exposure was positively associated with LOCC incidence among females, whereas alcohol exposure was positively associated with both incidence and mortality among males. These findings do not establish causality, but they provide population-level evidence that may help identify settings in which sex-specific exposure patterns and cancer burden warrant closer surveillance. The historical analyses, which showed substantial directional concordance with the contemporary models, further support the value of sustained monitoring of tobacco and alcohol exposure patterns over time.

The absence of statistically significant fully adjusted associations between HDI and LOCC incidence or mortality also has practical implications. Although selected HDI components, particularly mean years of schooling and GNI per capita, showed inverse associations with mortality in some sex groups, these ecological findings should not be interpreted as evidence of direct causal effects of socioeconomic development. Rather, they suggest that socioeconomic conditions, health-system capacity, diagnostic pathways, and treatment access may operate through complex and context-dependent mechanisms. Accordingly, improving early detection, diagnostic capacity, treatment availability, and continuity of cancer care remain important, particularly in settings where the burden of mortality is high and health-system resources are constrained [65, 66]. Prevention efforts should therefore be accompanied by strengthening oral health services and access to timely cancer diagnosis and treatment.

FUTURE RESEARCH

Future studies should validate these ecological findings through individual-level and longitudinal designs, particularly using appropriately lagged exposure measures to account for the long latency and cumulative nature of LOCC. Further research should also incorporate underrepresented determinants such as smokeless tobacco and betel quid/areca nut use, HPV infection, dietary and occupational factors, and indicators of diagnostic and treatment access.

The sex-specific patterns observed in this study, together with differences across historical and contemporary analyses, warrant further investigation of differences in exposure intensity, duration, co-exposure, and social context. Future studies should also assess whether improvements in early detection, treatment access, and health-system capacity modify the relationship between socioeconomic conditions and LOCC mortality.

Conclusion

Lip and oral cavity cancer remains a substantial global

health burden, with marked sex-based and geographical disparities and particularly high rates in the south-east Asia region. In fully adjusted ecological analyses, smoking exposure was positively associated with LOCC incidence among females, whereas alcohol exposure was positively associated with incidence and mortality among males. HDI was not significantly associated with LOCC incidence or mortality after full adjustment, although selected socioeconomic components showed inverse associations with mortality in some groups. Historical analyses from 1990 and 2010 showed substantial directional concordance with the contemporary findings, while also demonstrating variation in the magnitude and statistical significance of associations.

Overall, the findings support a multifactorial and sex-specific pattern of LOCC burden. Because of the ecological study design, the observed relationships should not be interpreted as causal effects. Sustained tobacco and alcohol control, attention to regionally relevant risk factors, and strengthening of early detection, diagnostic capacity, and access to effective treatment remain important priorities for global LOCC control.

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Not applicable.

Ethics approval

Only publicly available, aggregated data were used. No identifiable personal information was accessed. The Shahrekord University of Medical Sciences Ethics Committee (IR.SKUMS.REC.1402.124) granted ethical approval for this study.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Ethical considerations

Only publicly available, aggregated data were used. No identifiable personal information was accessed. The Shahrekord University of Medical Sciences Ethics Committee (IR.SKUMS.REC.1402.124) granted ethical approval for this study.

Availability of data and materials

All the data generated or analysed during this study are included in this published article (and its supplementary

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

STD, AMH: Drafted the manuscript, participated in the data curation, formal analysis, and supervision. UYC, AMH: Assisted in writing - original draft, methodology, and project administration. All the authors provided final approval.

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Supplementary material

Tab. S1. The ASIR and ASMR of lip and oral cavity cancer in the countries of the world in 2024.

Population	ASIR	ASIR in males	ASIR in females	ASMR	ASMR in males	ASMR in females
Afghanistan	2.9	3.7	2.3	1.8	2.4	1.2
Albania	2.2	3.3	1.2	0.73	1.2	0.30
Algeria	0.90	1.1	0.66	0.44	0.56	0.33
Angola	3.1	5.3	1.3	2.1	3.5	0.86
Azerbaijan	0.65	1.1	0.32	0.21	0.37	0.08
Argentina	2.2	2.9	1.5	0.87	1.3	0.45
Australia	5.8	8.3	3.5	0.91	1.3	0.55
Austria	3.2	4.8	1.7	1.1	1.7	0.56
Bahamas	1.0	2.2	0.00	0.72	1.6	0.00
Bahrain	2.0	3.0	0.75	1.1	2.1	0.00
Bangladesh	9.4	11.9	6.9	5.9	7.7	4.1
Armenia	1.3	1.9	0.84	0.48	0.88	0.20
Barbados	1.4	2.6	0.28	1.0	2.1	0.20
Belgium	4.0	5.7	2.5	0.79	1.2	0.39
Bhutan	3.1	3.8	2.4	1.9	2.1	1.7
Bolivia (Plurinational State of)	0.89	1.4	0.47	0.31	0.50	0.16
Bosnia Herzegovina	2.1	3.3	1.1	0.79	1.5	0.23
Botswana	4.3	7.5	1.5	2.6	4.4	0.93
Brazil	3.9	6.1	1.9	1.6	2.7	0.64
Belize	0.00	0.00	0.00	0.00	0.00	0.00
Solomon Islands	2.7	4.4	0.96	1.2	2.0	0.32
Brunei Darussalam	0.72	0.60	0.80	0.38	0.32	0.42
Bulgaria	2.9	4.7	1.4	1.5	2.5	0.51
Myanmar	6.1	9.8	2.9	3.9	6.5	1.5
Burundi	1.5	2.0	1.1	1.1	1.4	0.72
Belarus	5.7	11.3	1.4	3.3	6.4	0.83
Cambodia	3.3	4.3	2.4	2.1	3.0	1.4
Cameroon	1.4	1.8	1.1	1.0	1.3	0.81
Canada	4.5	5.9	3.2	0.82	1.2	0.49
Cape Verde	2.8	4.4	1.6	2.2	3.2	1.6
Central African Republic	1.4	2.5	0.59	0.87	1.6	0.39
Sri Lanka	7.5	12.6	3.3	4.8	8.3	1.9
Chad	2.4	2.2	2.5	1.6	1.5	1.6
Chile	0.69	0.86	0.52	0.40	0.56	0.25
China	1.6	2.1	1.0	0.74	1.1	0.39
Colombia	1.6	1.6	1.6	0.62	0.70	0.56
Comoros	0.88	1.3	0.39	0.73	1.0	0.39
Congo, Republic of	1.0	1.8	0.33	0.62	1.1	0.18
Congo, Democratic Republic of	1.6	2.3	1.0	1.1	1.6	0.66
Costa Rica	1.5	1.8	1.3	0.57	0.79	0.36
Croatia	3.6	5.9	1.6	1.8	3.1	0.66
Cuba	3.3	4.9	1.9	1.8	3.0	0.71
Cyprus	2.5	3.4	1.7	0.69	1.1	0.31
Czechia	4.2	6.2	2.2	1.8	2.7	0.88
Benin	1.3	2.0	0.79	0.82	1.1	0.56
Denmark	4.2	5.7	2.8	1.0	1.4	0.65
Dominican Republic	1.3	1.6	1.1	0.71	1.0	0.42
Ecuador	0.90	0.80	0.98	0.50	0.51	0.48
El Salvador	1.3	1.2	1.3	0.67	0.69	0.67
Equatorial Guinea	1.4	1.9	0.91	0.98	1.3	0.68
Ethiopia	1.1	1.2	0.91	0.73	0.89	0.60
Eritrea	1.7	2.5	1.1	1.1	1.7	0.65
Estonia	4.3	7.3	1.8	1.9	3.7	0.43



Fiji	2.8	5.3	0.66	0.76	1.5	0.22
Finland	3.5	4.6	2.3	0.86	1.2	0.52
France (metropolitan)	4.8	6.8	2.9	1.0	1.5	0.53
French Guyana	0.97	2.0	0.00	0.62	1.3	0.00
French Polynesia	3.8	5.3	2.1	0.86	0.94	0.66
Djibouti	1.4	2.0	0.93	0.80	1.0	0.59
Gabon	1.2	1.7	0.72	0.90	1.2	0.57
Georgia	2.5	4.5	1.1	1.1	2.1	0.36
The Republic of the Gambia	0.28	0.00	0.51	0.21	0.00	0.38
Gaza Strip and West Bank	1.9	2.9	1.1	1.0	1.8	0.44
Germany	3.5	4.6	2.3	1.1	1.6	0.58
Ghana	1.2	2.2	0.35	0.77	1.4	0.26
Greece	3.0	4.1	2.1	0.73	1.1	0.41
France, Guadeloupe	2.5	4.5	0.88	1.0	2.3	0.00
Guam	1.6	3.2	0.00	0.00	0.00	0.00
Guatemala	0.78	0.76	0.80	0.44	0.46	0.43
Guinea	0.00	0.00	0.00	0.00	0.00	0.00
Guyana	1.7	1.4	2.0	0.74	0.86	0.65
Haiti	0.96	0.70	1.2	0.28	0.19	0.34
Honduras	0.94	1.4	0.58	0.58	0.83	0.36
Hungary	5.8	9.7	2.4	2.6	4.4	1.0
Iceland	3.9	5.2	2.5	0.40	0.54	0.25
India	13.4	20.6	6.1	5.7	8.5	2.8
Indonesia	1.5	1.8	1.3	0.92	1.2	0.68
Iran, Islamic Republic of	1.5	1.6	1.4	0.91	1.0	0.79
Iraq	0.91	1.1	0.80	0.56	0.68	0.46
Ireland	3.3	4.9	1.8	0.85	1.3	0.45
Israel	2.1	2.8	1.5	0.46	0.53	0.39
Italy	3.3	4.3	2.3	0.89	1.3	0.56
Côte d'Ivoire	0.98	1.1	0.85	0.73	0.83	0.62
Jamaica	0.95	0.77	1.1	0.40	0.46	0.37
Japan	3.6	4.7	2.5	0.71	0.95	0.47
Kazakhstan	1.7	2.4	1.1	1.0	1.5	0.61
Jordan	0.64	0.92	0.44	0.22	0.38	0.10
Kenya	2.9	2.8	2.9	1.8	1.9	1.7
Korea, Democratic People's Republic of	0.82	1.1	0.56	0.50	0.72	0.31
Korea, Republic of	1.8	2.4	1.2	0.50	0.73	0.30
Kuwait	1.4	1.7	1.1	0.73	1.1	0.34
Kyrgyzstan	2.0	2.9	1.4	1.3	1.9	0.73
Lao People's Democratic Republic	3.4	2.9	3.6	2.1	2.0	2.1
Lebanon	1.4	2.0	0.90	0.59	0.91	0.32
Lesotho	1.3	1.9	0.82	0.88	1.3	0.63
Latvia	3.9	7.2	1.5	2.5	4.6	0.97
Liberia	1.1	0.94	1.2	0.62	0.47	0.75
Libya	1.2	1.3	1.1	0.63	0.70	0.58
Lithuania	4.4	7.5	1.8	2.5	4.5	0.79
Luxembourg	1.6	2.2	1.0	0.50	0.82	0.20
Madagascar	1.4	1.6	1.1	1.0	1.3	0.77
Malawi	1.1	1.7	0.57	0.70	1.2	0.32
Malaysia	2.0	2.2	1.9	1.3	1.5	1.1
Maldives	9.4	12.2	5.5	6.7	8.5	4.4
Mali	2.3	1.7	2.8	1.6	1.3	1.9
Malta	2.8	3.2	2.5	0.79	1.3	0.34
France, Martinique	2.0	3.3	0.93	0.31	0.70	0.00
Mauritania	1.4	1.6	1.2	0.90	0.88	0.91
Mauritius	2.8	3.6	2.0	1.4	1.9	0.84
Mexico	1.0	1.0	1.1	0.49	0.62	0.37
Mongolia	1.6	2.3	1.1	0.56	0.93	0.31



Republic of Moldova	4.6	9.5	1.1	2.3	5.0	0.43
Montenegro	4.2	4.4	3.9	1.2	1.5	0.91
Morocco	1.1	1.3	0.99	0.69	0.82	0.56
Mozambique	1.3	1.7	0.94	0.93	1.3	0.64
Oman	2.2	2.7	1.3	0.96	1.4	0.42
Namibia	6.8	10.5	4.3	4.7	6.9	3.2
Nepal	5.1	7.0	3.5	3.2	4.6	2.0
The Netherlands	3.7	4.5	2.9	0.66	0.76	0.55
Curaçao	3.0	4.9	1.5	1.3	3.2	0.00
New Caledonia	3.9	5.8	2.2	0.66	1.4	0.00
Vanuatu	2.8	4.5	1.1	0.00	0.00	0.00
New Zealand	4.3	6.0	2.6	0.82	1.1	0.61
Nicaragua	1.0	1.3	0.86	0.55	0.75	0.40
Niger	2.5	3.3	2.0	1.7	2.1	1.3
Nigeria	1.6	2.0	1.2	1.1	1.3	0.87
Norway	3.9	5.1	2.8	0.65	0.84	0.48
Pakistan	5.5	7.0	4.0	3.4	4.5	2.3
Panama	1.4	1.5	1.3	0.56	0.82	0.33
Papua New Guinea	20.0	25.1	14.8	12.6	16.8	8.3
Paraguay	1.9	3.2	0.78	1.1	2.1	0.26
Peru	2.6	2.6	2.6	0.66	0.65	0.68
Philippines	1.7	2.0	1.3	1.1	1.4	0.80
Poland	4.0	6.1	2.0	2.4	3.9	1.0
Portugal	5.4	9.2	2.0	1.8	2.8	0.84
Guinea-Bissau	0.55	0.00	0.95	0.45	0.00	0.77
Timor-Leste	1.3	1.6	1.0	1.2	1.4	1.0
Puerto Rico	4.0	6.8	1.7	2.5	4.6	0.70
Qatar	2.4	2.4	1.8	1.2	1.5	0.47
France, La Réunion	4.4	7.0	2.1	1.1	1.9	0.48
Romania	5.8	10.5	1.7	2.6	4.9	0.55
Russian Federation	4.4	7.9	1.9	2.0	3.6	0.78
Rwanda	1.3	1.8	0.88	0.83	1.2	0.58
Saint Lucia	0.84	1.7	0.00	0.42	0.86	0.00
Sao Tome and Principe	0.00	0.00	0.00	0.00	0.00	0.00
Saudi Arabia	1.7	1.9	1.4	0.80	0.92	0.60
Senegal	0.85	0.58	1.1	0.56	0.43	0.69
Serbia	4.3	5.8	3.0	1.7	2.5	0.92
Sierra Leone	1.4	1.6	1.3	0.86	0.91	0.82
Singapore	1.8	2.3	1.4	0.52	0.67	0.38
Slovakia	5.4	9.4	2.0	2.8	5.1	0.84
Viet Nam	2.7	4.3	1.4	1.8	2.9	0.77
Slovenia	3.5	5.2	2.0	0.68	1.0	0.36
Somalia	2.0	2.0	1.9	1.4	1.4	1.4
South Africa	2.0	3.1	1.2	1.0	1.6	0.60
Zimbabwe	1.5	2.3	1.0	1.0	1.5	0.70
Spain	3.9	5.5	2.5	0.99	1.4	0.59
South Sudan	1.9	2.4	1.4	1.3	1.7	0.95
Sudan	2.6	3.8	1.4	1.6	2.5	0.77
Suriname	2.6	3.5	1.5	1.1	1.8	0.45
Eswatini	1.0	1.6	0.66	0.95	1.6	0.50
Sweden	3.6	4.4	2.9	0.76	1.0	0.53
Switzerland	4.2	5.5	2.9	0.98	1.3	0.63
Syrian Arab Republic	1.0	1.2	0.79	0.61	0.81	0.44
Tajikistan	1.9	2.3	1.6	1.1	1.5	0.78
Thailand	3.7	4.6	2.8	2.1	2.6	1.6
Togo	2.2	2.2	2.1	1.5	1.4	1.5
Trinidad and Tobago	1.3	1.6	0.99	0.72	1.0	0.56
United Arab Emirates	2.7	3.1	2.1	1.4	1.8	0.84



Tunisia	1.5	1.9	1.0	0.70	0.94	0.48
Türkiye	1.9	2.5	1.2	0.41	0.52	0.30
Turkmenistan	2.7	3.9	2.1	1.4	2.2	0.97
Uganda	1.8	2.5	1.3	1.3	1.9	0.87
Ukraine	4.4	8.4	1.2	2.5	4.9	0.57
North Macedonia	2.5	3.3	1.8	0.91	1.3	0.59
Egypt	1.7	2.1	1.3	0.83	1.0	0.65
United Kingdom	4.5	6.2	3.0	1.1	1.6	0.64
Tanzania, United Republic of	1.4	1.6	1.2	0.94	1.1	0.82
United States of America	4.6	6.5	2.7	0.70	0.99	0.43
Burkina Faso	2.7	1.5	3.5	1.8	1.1	2.2
Uruguay	3.0	5.0	1.2	1.3	2.1	0.56
Uzbekistan	2.0	2.6	1.5	1.1	1.6	0.74
Venezuela	1.7	2.4	1.2	0.79	1.1	0.52
Samoa	1.0	2.0	0.00	0.56	1.1	0.00
Yemen	0.90	1.0	0.80	0.55	0.67	0.45
Zambia	1.3	1.9	0.87	0.84	1.3	0.50

Tab. S2. Examining the Correlation Between smoking prevalence and Incidence and Mortality Rates of LOCC in 1990.

Smoking prevalence		Incidence			Mortality		
Sex	Model	Unstandardized Coefficients (SE)	Standardized Coefficients	<i>p-value</i>	Unstandardized Coefficients (SE)	Standardized Coefficients	<i>p-value</i>
Males	Model 1	0.110 (0.028)	0.289	≤0.001	0.028 (0.017)	0.125	0.096
	Model 2	0.084 (0.030)	0.221	0.005	0.030 (0.018)	0.134	0.104
	Model 3	0.088 (0.045)	0.208	0.052	0.049 (0.026)	0.199	0.065
	Model 4	0.091 (0.044)	0.215	0.043	0.050 (0.026)	0.202	0.060
Females	Model 1	0.057 (0.017)	0.246	0.001	-0.016 (0.010)	-0.116	0.131
	Model 2	0.092 (0.028)	0.388	0.001	0.011 (0.016)	0.082	0.491
	Model 3	0.099 (0.030)	0.391	0.001	0.026 (0.017)	0.182	0.125
	Model 4	0.127 (0.042)	0.49	0.003	0.042 (0.024)	0.28	0.080
Total	Model 1	0.104 (0.024)	0.307	≤0.001	0.006 (0.015)	0.03	0.687
	Model 2	0.099 (0.031)	0.291	0.002	0.022 (0.019)	0.108	0.258
	Model 3	0.136 (0.046)	0.36	0.004	0.054 (0.027)	0.245	0.048
	Model 4	0.126 (0.048)	0.333	0.009	0.054 (0.028)	0.244	0.057

Model 1: crude or unadjusted model. Model 2: adjusted for 1990 alcohol use prevalence. Model 3: adjusted for 1990 HDI. Model 4: adjusted for 1990 HDI and 1990 alcohol use prevalence. HDI: 1990 value. Outcome: LOCC incidence and mortality rates (2024).

Tab. S3. Examining the Correlation Between Alcohol use prevalence and Incidence and Mortality Rates of LOCC in 1990.

Alcohol use prevalence		Incidence			Mortality		
Sex	Model	Unstandardized Coefficients (SE)	Standardized Coefficients	<i>p-value</i>	Unstandardized Coefficients (SE)	Standardized Coefficients	<i>p-value</i>
Males	Model 1	0.131 (0.037)	0.257	≤0.001	0.010 (0.022)	0.033	0.663
	Model 2	0.085 (0.040)	0.167	0.033	-0.006 (0.024)	-0.022	0.792
	Model 3	0.108 (0.061)	0.202	0.080	0.033 (0.036)	0.105	0.367
	Model 4	0.112 (0.060)	0.210	0.065	0.035 (0.036)	0.112	0.329
Females	Model 1	0.031 (0.034)	0.073	0.361	-0.054 (0.020)	-0.216	0.007
	Model 2	-0.097 (0.051)	-0.223	0.060	-0.075 (0.030)	-0.294	0.014
	Model 3	0.024 (0.061)	0.052	0.698	-0.014 (0.033)	-0.053	0.680
	Model 4	-0.101 (0.073)	-0.220	0.168	-0.056 (0.041)	-0.211	0.176
Total	Model 1	0.095 (0.034)	0.205	0.006	-0.016 (0.020)	-0.059	0.432
	Model 2	0.012 (0.042)	0.025	0.782	-0.034 (0.026)	-0.126	0.188
	Model 3	0.086 (0.057)	0.176	0.133	0.018 (0.033)	0.062	0.595
	Model 4	0.045 (0.058)	0.092	0.436	0.000 (0.034)	0.000	0.997

Model 1: crude or unadjusted model. Model 2: adjusted for 1990 smoking prevalence. Model 3: adjusted for 1990 HDI. Model 4: adjusted for 1990 HDI and 1990 smoking prevalence. HDI: 1990 value. Outcome: LOCC incidence and mortality rates (2024).

Tab. S4. Examining the Correlation Between smoking prevalence and Incidence and Mortality Rates of LOCC in 2010.

Smoking prevalence		Incidence			Mortality		
Sex	Model	Unstandardized Coefficients (SE)	Standardized Coefficients	p-value	Unstandardized Coefficients (SE)	Standardized Coefficients	p-value
Males	Model 1	0.111 (0.031)	0.260	≤0.001	0.033 (0.019)	0.129	0.084
	Model 2	0.058 (0.034)	0.135	0.087	0.022 (0.021)	0.088	0.293
	Model 3	0.090 (0.042)	0.204	0.032	0.061 (0.025)	0.234	0.016
	Model 4	0.078 (0.041)	0.177	0.057	0.056 (0.025)	0.214	0.026
Females	Model 1	0.066 (0.020)	0.244	0.001	-0.017 (0.012)	-0.108	0.158
	Model 2	0.094 (0.030)	0.338	0.002	0.004 (0.018)	0.024	0.826
	Model 3	0.105 (0.030)	0.375	≤0.001	0.028 (0.018)	0.170	0.117
	Model 4	0.128 (0.039)	0.444	0.001	0.039 (0.023)	0.228	0.091
Total	Model 1	0.111 (0.028)	0.284	≤0.001	0.009 (0.017)	0.037	0.620
	Model 2	0.078 (0.036)	0.200	0.031	0.010 (0.022)	0.044	0.645
	Model 3	0.130 (0.044)	0.323	0.004	0.064 (0.027)	0.265	0.018
	Model 4	0.109 (0.046)	0.270	0.020	0.057 (0.028)	0.237	0.045

Model 1: crude or unadjusted model. Model 2: Adjusted for 2010 alcohol use prevalence. Model 3: Adjusted for 2010 HDI. Model 4: Adjusted for 2010 HDI, and 2010 alcohol use prevalence. HDI: 2010 value. Outcome: LOCC incidence and mortality rates (2024).

Tab. S5. Examining the Correlation Between Alcohol use prevalence and Incidence and Mortality Rates of LOCC in 2010.

Alcohol use prevalence		Incidence			Mortality		
Sex	Model	Unstandardized Coefficients (SE)	Sta	p-value	Unstandardized Coefficients (SE)	Standardized Coefficients	p-value
Males	Model 1	0.156 (0.032)	0.342	≤0.001	0.036 (0.020)	0.133	0.076
	Model 2	0.129 (0.036)	0.282	≤0.001	0.025 (0.022)	0.094	0.259
	Model 3	0.150 (0.046)	0.324	0.001	0.069 (0.028)	0.252	0.015
	Model 4	0.142 (0.046)	0.306	0.002	0.063 (0.028)	0.231	0.025
Females	Model 1	0.029 (0.032)	0.071	0.377	-0.045 (0.019)	-0.188	0.018
	Model 2	-0.069 (0.044)	-0.17	0.119	-0.053 (0.026)	-0.223	0.044
	Model 3	0.011 (0.046)	0.027	0.808	-0.009 (0.026)	-0.037	0.727
	Model 4	-0.072 (0.051)	-0.168	0.166	-0.038 (0.030)	-0.152	0.206
Total	Model 1	0.109 (0.031)	0.259	≤0.001	0.004 (0.019)	0.016	0.829
	Model 2	0.057 (0.039)	0.134	0.145	-0.003 (0.024)	-0.012	0.905
	Model 3	0.099 (0.043)	0.229	0.024	0.038 (0.026)	0.148	0.148
	Model 4	0.066 (0.045)	0.151	0.148	0.021 (0.027)	0.08	0.453

Model 1: crude or unadjusted model. Model 2: adjusted for 2010 smoking prevalence. Model 3: adjusted for 2010 HDI. Model 4: adjusted for 2010 HDI and 2010 smoking prevalence. HDI: 2010 value. Outcome: LOCC incidence and mortality rates (2024).

Tab. S6. Examining the Correlation Between HDI and its components and Incidence Rates of LOCC in 1990.

HDI and components	Model	Male			Female			Total		
		Standardized Coefficients	Unstandardized Coefficients (se)	p-value	Standardized Coefficients	Unstandardized Coefficients (se)	p-value	Standardized Coefficients	Unstandardized Coefficients (se)	p-value
HDI	Model 1	2.934 (1.915)	0.136	0.128	-0.156 (0.850)	-0.016	0.855	1.320 (1.312)	0.090	0.316
	Model 2	0.403 (2.292)	0.019	0.861	-2.705 (1.143)	-0.283	0.020	-2.404 (1.790)	-0.163	0.182
	Model 3	0.138 (2.472)	0.006	0.956	-0.624 (1.285)	-0.065	0.628	-0.367 (1.718)	-0.025	0.831
	Model 4	-2.588 (2.781)	-0.120	0.354	-2.157 (1.362)	-0.224	0.116	-3.014 (1.956)	-0.205	0.126
Life expectancy at birth	Model 1	0.068 (0.026)	0.207	0.009	0.010 (0.011)	0.066	0.404	0.037 (0.017)	0.168	0.034
	Model 2	0.012 (0.033)	0.037	0.716	-0.017 (0.015)	-0.117	0.261	-0.021 (0.025)	-0.094	0.398
	Model 3	0.038 (0.030)	0.117	0.207	0.011 (0.015)	0.075	0.456	0.023 (0.020)	0.104	0.260
	Model 4	-0.013 (0.036)	-0.041	0.712	-0.010 (0.017)	-0.072	0.534	-0.021 (0.025)	-0.095	0.398

Mean years of schooling	Model 1	0.220 (0.103)	0.182	0.034	0.008 (0.046)	0.014	0.869	0.105 (0.071)	0.128	0.140
	Model 2	0.092 (0.119)	0.077	0.438	-0.098 (0.060)	-0.184	0.104	-0.065 (0.090)	-0.079	0.471
	Model 3	0.090 (0.134)	0.074	0.506	-0.021 (0.066)	-0.039	0.750	0.025 (0.094)	0.030	0.792
	Model 4	-0.035 (0.146)	-0.029	0.809	-0.061 (0.070)	-0.112	0.388	-0.087 (0.101)	-0.106	0.392
GNI per capita	Model 1	0.013 (0.016)	0.069	0.400	0.004 (0.007)	0.043	0.596	0.009 (0.011)	0.070	0.391
	Model 2	-0.005 (0.016)	-0.025	0.759	-0.006 (0.008)	-0.072	0.435	-0.009 (0.011)	-0.068	0.435
	Model 3	-0.003 (0.017)	-0.015	0.859	0.003 (0.010)	0.033	0.752	0.001 (0.012)	0.005	0.958
	Model 4	-0.013 (0.017)	-0.068	0.429	-0.004 (0.010)	-0.047	0.659	-0.009 (0.012)	-0.069	0.443

Model 1: crude/unadjusted. Model 2: adjusted for 1990 smoking prevalence. Model 3: adjusted for 1990 alcohol use prevalence. Model 4: adjusted for 1990 alcohol use prevalence and 1990 smoking prevalence. HDI and its components were measured in 1990. GNI per capita was entered per 1,000 USD. Outcome: LOCC incidence and mortality rates (2024).

Tab. S7. Examining the Correlation Between HDI and its components and Mortality Rates of LOCC in 1990.

HDI and components	Model	Male			Female			Total		
		Standardized Coefficients	Unstandardized Coefficients (se)	p-value	Standardized Coefficients	Unstandardized Coefficients (se)	p-value	Standardized Coefficients	Unstandardized Coefficients (se)	p-value
HDI	Model 1	-1.400 (1.125)	-0.111	0.216	-1.680 (0.462)	-0.310	≤0.001	-1.566 (0.760)	-0.181	0.041
	Model 2	-2.815 (1.348)	-0.222	0.039	-2.355 (0.641)	-0.432	≤0.001	-3.051 (1.055)	-0.353	0.005
	Model 3	-2.248 (1.465)	-0.178	0.127	-1.513 (0.705)	-0.274	0.034	-1.914 (1.002)	-0.222	0.059
	Model 4	-3.751 (1.652)	-0.296	0.025	-2.008 (0.769)	-0.362	0.010	-3.052 (1.156)	-0.353	0.009
Life expectancy at birth	Model 1	-0.002 (0.015)	-0.010	0.895	-0.020 (0.007)	-0.231	0.003	-0.011 (0.010)	-0.085	0.282
	Model 2	-0.035 (0.020)	-0.179	0.085	-0.022 (0.009)	-0.258	0.014	-0.033 (0.015)	-0.249	0.031
	Model 3	-0.005 (0.018)	-0.027	0.780	-0.012 (0.008)	-0.135	0.169	-0.009 (0.012)	-0.068	0.466
	Model 4	-0.036 (0.022)	-0.187	0.102	-0.017 (0.010)	-0.197	0.087	-0.030 (0.015)	-0.229	0.049
Mean years of schooling	Model 1	-0.029 (0.061)	-0.042	0.629	-0.078 (0.025)	-0.259	0.002	-0.058 (0.041)	-0.121	0.160
	Model 2	-0.090 (0.071)	-0.129	0.204	-0.095 (0.034)	-0.315	0.006	-0.112 (0.054)	-0.235	0.038
	Model 3	-0.052 (0.080)	-0.074	0.518	-0.067 (0.036)	-0.218	0.068	-0.062 (0.055)	-0.130	0.263
	Model 4	-0.112 (0.088)	-0.159	0.204	-0.076 (0.040)	-0.244	0.060	-0.102 (0.060)	-0.214	0.093
GNI per capita	Model 1	-0.012 (0.009)	-0.105	0.197	-0.010 (0.004)	-0.195	0.015	-0.010 (0.006)	-0.131	0.108
	Model 2	-0.019 (0.010)	-0.167	0.049	-0.009 (0.005)	-0.187	0.046	-0.014 (0.007)	-0.184	0.043
	Model 3	-0.014 (0.010)	-0.126	0.152	-0.006 (0.006)	-0.105	0.307	-0.009 (0.007)	-0.120	0.178
	Model 4	-0.019 (0.010)	-0.167	0.061	-0.007 (0.006)	-0.137	0.200	-0.013 (0.007)	-0.163	0.078

Model 1: crude or unadjusted model. Model 2: Adjusted for 1990 smoking prevalence. Model 3: Adjusted for 1990 alcohol use prevalence. Model 4: Adjusted for 1990 alcohol use prevalence, and smoking prevalence. HDI and its components were measured in 1990. GNI per capita was entered per 1,000 USD. Outcome: LOCC incidence and mortality rates (2024).

Tab. S8. Examining the Correlation Between HDI and its components and Incidence Rates of LOCC in 2010.

HDI and components	Model	Male			Female			Total		
		Standardized Coefficients	Unstandardized Coefficients (se)	p-value	Standardized Coefficients	Unstandardized Coefficients (se)	p-value	Standardized Coefficients	Unstandardized Coefficients (se)	p-value
HDI	Model 1	4.358 (1.662)	0.204	0.010	0.361 (0.742)	0.039	0.627	2.253 (1.136)	0.156	0.049
	Model 2	1.844 (2.013)	0.086	0.361	-2.082 (1.012)	-0.223	0.041	-1.067 (1.579)	-0.074	0.500
	Model 3	-0.096 (2.112)	-0.005	0.964	0.177 (1.036)	0.019	0.865	0.170 (1.445)	0.012	0.907
	Model 4	-2.034 (2.325)	-0.095	0.383	-1.708 (1.191)	-0.181	0.154	-1.902 (1.674)	-0.132	0.258
Life expectancy at birth	Model 1	0.070 (0.030)	0.185	0.019	0.015 (0.013)	0.087	0.270	0.043 (0.020)	0.167	0.035
	Model 2	0.024 (0.035)	0.062	0.505	-0.013 (0.017)	-0.076	0.453	-0.005 (0.026)	-0.021	0.840
	Model 3	0.016 (0.033)	0.042	0.619	0.018 (0.016)	0.105	0.273	0.020 (0.022)	0.076	0.377
	Model 4	-0.010 (0.036)	-0.026	0.782	-0.007 (0.019)	-0.039	0.731	-0.007 (0.026)	-0.027	0.789
Mean years of schooling	Model 1	0.213 (0.079)	0.210	0.008	-0.000 (0.035)	-0.000	0.995	0.095 (0.054)	0.138	0.082
	Model 2	0.098 (0.095)	0.096	0.306	-0.104 (0.046)	-0.235	0.023	-0.061 (0.072)	-0.088	0.403
	Model 3	-0.033 (0.108)	-0.033	0.760	-0.032 (0.049)	-0.072	0.512	-0.034 (0.074)	-0.050	0.645
	Model 4	-0.134 (0.118)	-0.132	0.260	-0.089 (0.053)	-0.198	0.098	-0.127 (0.081)	-0.185	0.120
GNI per capita	Model 1	0.016 (0.012)	0.102	0.196	0.005 (0.005)	0.069	0.384	0.011 (0.008)	0.102	0.196
	Model 2	0.005 (0.013)	0.031	0.701	-0.005 (0.006)	-0.078	0.401	-0.003 (0.009)	-0.024	0.783
	Model 3	-0.004 (0.013)	-0.026	0.751	0.005 (0.008)	0.061	0.555	0.001 (0.009)	0.006	0.942
	Model 4	-0.007 (0.013)	-0.047	0.566	-0.006 (0.008)	-0.078	0.485	-0.005 (0.009)	-0.043	0.619

Model 1: crude or unadjusted model. Model 2: adjusted for 2010 smoking prevalence. Model 3: adjusted for 2010 alcohol use prevalence. Model 4: adjusted for 2010 alcohol use prevalence and 2010 smoking prevalence.

HDI and its components were measured in 2010. GNI per capita was entered per 1,000 USD. Outcome: LOCC incidence and mortality rates (2024).

Tab. S9. Examining the Correlation Between HDI and its components and Mortality Rates of LOCC in 2010.

HDI and components	Model	Male			Female			Total		
		Standardized Coefficients	Unstandardized Coefficients (se)	<i>p-value</i>	Standardized Coefficients	Unstandardized Coefficients (se)	<i>p-value</i>	Standardized Coefficients	Unstandardized Coefficients (se)	<i>p-value</i>
HDI	Model 1	-0.447 (1.000)	-0.036	0.655	-1.480 (0.419)	-0.270	≤0.001	-1.009 (0.679)	-0.117	0.140
	Model 2	-2.146 (1.206)	-0.171	0.077	-2.159 (0.588)	-0.395	≤0.001	-2.627 (0.952)	-0.306	0.006
	Model 3	-2.492 (1.288)	-0.198	0.055	-1.350 (0.591)	-0.242	0.024	-1.809 (0.872)	-0.210	0.040
	Model 4	-3.869 (1.412)	-0.308	0.007	-1.901 (0.696)	-0.341	0.007	-2.889 (1.015)	-0.336	0.005
Life expectancy at birth	Model 1	-0.007 (0.018)	-0.032	0.689	-0.021 (0.008)	-0.210	0.007	-0.013 (0.012)	-0.087	0.274
	Model 2	-0.035 (0.021)	-0.155	0.101	-0.023 (0.010)	-0.234	0.022	-0.032 (0.016)	-0.206	0.049
	Model 3	-0.026 (0.020)	-0.116	0.193	-0.013 (0.009)	-0.130	0.165	-0.018 (0.014)	-0.116	0.191
	Model 4	-0.045 (0.022)	-0.200	0.043	-0.018 (0.011)	-0.182	0.108	-0.032 (0.016)	-0.206	0.051
Mean years of schooling	Model 1	-0.003 (0.048)	-0.005	0.953	-0.074 (0.020)	-0.286	≤0.001	-0.045 (0.032)	-0.109	0.169
	Model 2	-0.073 (0.057)	-0.122	0.205	-0.098 (0.027)	-0.376	≤0.001	-0.109 (0.044)	-0.266	0.014
	Model 3	-0.110 (0.066)	-0.184	0.098	-0.079 (0.028)	-0.298	0.005	-0.094 (0.045)	-0.231	0.036
	Model 4	-0.173 (0.072)	-0.289	0.018	-0.091 (0.031)	-0.342	0.004	-0.133 (0.050)	-0.326	0.008
GNI per capita	Model 1	-0.010 (0.007)	-0.103	0.192	-0.008 (0.003)	-0.205	0.009	-0.008 (0.005)	-0.133	0.093
	Model 2	-0.014 (0.008)	-0.156	0.057	-0.009 (0.004)	-0.224	0.018	-0.012 (0.006)	-0.192	0.029
	Model 3	-0.017 (0.008)	-0.178	0.036	-0.007 (0.005)	-0.152	0.131	-0.011 (0.005)	-0.167	0.055
	Model 4	-0.018 (0.008)	-0.197	0.022	-0.009 (0.005)	-0.206	0.065	-0.012 (0.006)	-0.195	0.030

Model 1: crude or unadjusted model. Model 2: adjusted for 2010 smoking prevalence (sex-specific). Model 3: adjusted for 2010 alcohol use prevalence (sex-specific). Model 4: adjusted for 2010 alcohol use prevalence and smoking prevalence (sex-specific). HDI and its components were measured in 2010. GNI per capita was entered per 1,000 USD.



Occupational disease compensation claims in Italy: an epidemiological analysis of national insurance data with predictive insights

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Keywords

Occupational diseases • Epidemiological surveillance • Impairment severity • Neural networks • Predictive modelling

Summary

Introduction. Occupational diseases remain an underreported public health problem. In Italy, national insurance claims provide a useful view of recognized occupational diseases, although they do not measure the full burden of disease in the workforce. Few studies have combined descriptive analysis of insurance claims with predictive modelling to assess factors associated with recognized impairment.

Methods. We conducted a retrospective observational analysis of 310,189 occupational disease claims from the Italian National Institute for Insurance against Accidents at Work (INAIL) open data, covering the period 2020 to 2024. Multivariable linear regression was used to estimate associations between demographic, clinical, and occupational factors and the degree of impairment. Neural-network models with embedding layers were developed to classify claims with recognized impairment (>0%) and to predict impairment severity.

Results. Musculoskeletal disorders represented the largest share

of claims, whereas neoplasms and asbestos-related diseases were associated with the highest impairment. Diagnostic category and causal agent were the strongest predictors of severity among claims. The classification model achieved 98.15% accuracy and 99.99% sensitivity for recognized impairment. The regression model attained a mean absolute error of 2.31% and $R^2=0.71$, outperforming the linear regression baseline $R^2=0.55$.

Conclusion. Combining descriptive epidemiology with machine learning yields actionable insights for prioritizing high-risk claims and supporting administrative decision-making in occupational health surveillance. These findings represent a proof of concept given inherent administrative data limitations, including underreporting, lack of workforce denominators, and potential data bias. Future developments should incorporate explainable artificial intelligence techniques to bridge the gap between predictive performance and clinical interpretability.

Introduction

Occupational diseases represent a massive component of the global work-related disease burden, with recent estimates attributing approximately 2.58 million deaths to work-related illnesses in 2019 [1, 2]. These pathologies are linked to a wide range of risk factors, including exposure to carcinogens, ergonomic stressors, noise, and long working hours, the latter being a leading risk factor for ischemic heart disease and stroke. Beyond the human cost, the economic impact is profound: the total loss resulting from work-related disability and death is estimated at 6% of the global GDP [3].

Despite these alarming figures, the true scale of the problem remains largely hidden due to the “iceberg phenomenon”, where official records often represent only the visible portion of the total burden. Global systematic reviews and conceptual models indicate that underreporting rates are exceptionally high, ranging between 50% and 95%, driven by “conceptual filters” such as job insecurity, limited worker knowledge of legal benefits, and diagnostic difficulties [4, 5].

In the European context, the European Agency for Safety and Health at Work (EU-OSHA) defines occupational

diseases as those for which a causal link is established between workplace exposure and the pathology [6]. Current European strategies emphasize the need for sustainable work and improved conditions to address the evolving nature of risk in a changing labor market [7].

To address the need for comparative data, the European Occupational Diseases Statistics (EODS) provide experimental statistics based on cases recognized by national authorities [8]. However, interpreting regional data remains complicated by significant heterogeneity in national insurance systems and recognition rules, which often penalize countries with structured and inclusive reporting systems. Across the countries, musculoskeletal disorders, cancers, and respiratory diseases remain primary concerns, with annual incidence rates varying widely from 1.71 to 1,387 per 100,000 employees depending on the reporting mechanism used [5].

In Italy, occupational diseases are recorded through the national insurance system managed by the Italian National Institute for Insurance against Accidents at Work (INAIL). The system collects administrative and medico-legal information on occupational disease claims, including diagnoses, causal agents, economic sectors, and compensation outcomes. Over

the past decade, INAIL data have documented an increase in reported occupational disease claims, with musculoskeletal disorders accounting for the largest share [9]. Studies of Italian reporting pathways also show that missed recognition and delayed reporting remain important problems [10]. For this reason, INAIL claims data are best interpreted as data on registered and assessed claims, not as a direct estimate of occupational disease incidence in the whole workforce [11].

Beyond claim counts, impairment severity is an important dimension for occupational health surveillance. In the Italian system, the degree of impairment reflects permanent damage to a worker's psychophysical integrity and directly influences compensation and long-term support [12].

Understanding which factors are associated with higher impairment levels can support medico-legal evaluation, prevention planning, and resource allocation.

Previous Italian studies have mainly described occupational disease trends or specific disease groups [13, 14]. These analyses are valuable, but severity among compensated or assessed claims may depend on several factors at once, including demographic characteristics, diagnostic categories, causal agents, and occupational sectors. Traditional regression methods are useful for interpretation, but they may not capture non-linear relations among these variables.

Machine learning has been applied in occupational safety and health to predict injury, identify risk patterns, and support prevention research [15, 16]. Explainable and neural-network approaches have also been explored for musculoskeletal disorders and occupational disease prediction [17, 18]. In compensation systems, however, predictive models require careful interpretation because administrative variables may reflect recognition rules as well as clinical severity.

The present study addresses these gaps by combining descriptive epidemiology and predictive modelling in INAIL occupational disease claims from 2020 to 2024. We first describe the distribution of claims by demographic characteristics, economic sector, diagnostic category, and causal agent. We then identify factors associated with impairment severity through multivariable linear regression. Finally, we test whether embedding-based neural-network models can classify claims with recognized impairment and predict impairment severity as a proof of concept for administrative support.

Throughout the analysis, the unit of observation is the insurance claim. The findings therefore describe the profile and severity of claims handled within the INAIL system rather than the risk of developing an occupational disease in the Italian workforce.

Methods

STUDY DESIGN AND DATA SOURCE

This study is a retrospective observational analysis based on administrative data provided by INAIL, the public institution responsible for compulsory insurance

against occupational injuries and diseases in Italy. We used open-access data on occupational disease claims registered between January 1, 2020 and December 31, 2024. The INAIL occupational disease archive records claims submitted for medico-legal assessment and compensation. For each claim, the database may include worker demographics, country of birth, economic sector, ICD-10 diagnostic classification, suspected or recognized causal agent, asbestos-related status, scheduled disease status, compensated days, and the final degree of recognized impairment.

Because the database is built for insurance and compensation purposes, it does not include the total number of workers at risk in each sector and it does not capture unreported or unrecognized occupational diseases. It is therefore suitable for describing registered claims and their outcomes, but not for estimating disease incidence or relative risk in the general workforce.

The use of anonymized and publicly available data exempted the study from ethical approval requirements.

STUDY POPULATION

The initial dataset included 321,744 occupational disease claims recorded during the study period. Records with missing information on the degree of impairment were excluded, as this variable was the primary outcome of interest. After data preprocessing and cleaning, the final analytical sample consisted of 310,189 claims.

Each record corresponded to a single occupational disease claim and included information on the worker, the disease diagnosis, and the administrative outcome of the claim.

VARIABLES

The primary outcome was the degree of impairment, expressed as a percentage ranging from 0 to 100, representing the permanent damage to the worker's psychophysical integrity as recognized by INAIL [12]. This measure is used in the Italian compensation system to determine eligibility for benefits and the level of compensation. For analytical purposes, impairment was treated as a continuous variable in regression analyses. Independent variables were selected based on their epidemiological relevance and availability in the dataset and were grouped into four main domains:

1. Demographic and administrative characteristics, including sex, country of birth (Italy vs. abroad), classification as a scheduled (tabulated) occupational disease [19, 20], asbestos-related disease status, number of compensated days off work, and time to impairment definition ("days to definition" expressed as the number of days between claim submission and final impairment assessment).
2. Diagnostic categories, defined according to the International Classification of Diseases, 10th Revision (ICD-10).
3. Causal agents, categorized into macro-groups representing different types of occupational exposures, including chemical, physical, biological, ergonomic, psychological, and environmental factors.

4. Economic sector, classified into agriculture and fishing, industry, services, craftsmanship, public administration, and cases with unspecified sector.

Categorical variables were encoded using binary indicators for regression analyses.

Data preprocessing included consistency checks, exclusion of records with missing outcome data, and aggregation of diagnostic and causal variables into meaningful macro-categories to reduce dimensionality and improve interpretability. Continuous variables were examined for distributional properties, and descriptive statistics were used to identify outliers and data anomalies.

STATISTICAL ANALYSIS

Descriptive statistics were used to characterize the study population. Continuous variables were summarized using means, medians, standard deviations, and ranges, while categorical variables were described using absolute and relative frequencies. To identify determinants of impairment severity, a multivariable linear regression model was applied with degree of impairment as the dependent variable. Independent variables included demographic characteristics, diagnostic categories, causal agents, and economic sectors. Model performance was assessed using the coefficient of determination (R^2), and statistical significance was evaluated using p-values and 95% confidence intervals. This approach allowed estimation of the independent contribution of each predictor to impairment severity while controlling for potential confounding. All statistical analyses were conducted using Jamovi and Python, employing standard data science libraries including pandas, numpy, and scikit-learn. Alternative modeling strategies were considered; however, linear regression was preferred for clarity and comparability with previous epidemiological studies.

PREDICTIVE MODELING

As a secondary analysis, two predictive models were developed using neural networks with embedding layers: a classification model to distinguish occupational disease claims with recognized impairment ($>0\%$) from those without (0%), and a regression model to predict the specific degree of impairment among recognized cases. This dual formulation was chosen to support both case prioritization and severity estimation in occupational health surveillance.

Given the high cardinality of key categorical variables, particularly ICD-10 diagnostic codes and causal agents, a neural network architecture with embedding layers was implemented. This approach was selected to overcome the limitations of traditional encoding strategies, such as one-hot encoding, which would have substantially increased dimensionality and model complexity. Embedding layers allow each category to be represented as a dense, low-dimensional vector, enabling the model to capture latent similarities among categories and complex non-linear relationships.

High-cardinality categorical variables (ICD-10 codes and

causal agents) were encoded using label encoding and processed through embedding layers, while demographic and administrative variables were included as binary features. The feature set selected for model training specifically included: asbestos-related status, scheduled (tabulated) disease classification, sex, country of birth (Italy vs. abroad), ICD-10 diagnostic codes, causal agents, and economic sectors (unspecified, agriculture and fishing, industry, services, craftsmanship, and public administration). This variable subset was chosen to avoid data leakage, intentionally excluding features that are determined concurrently with or after the assessment of impairment, such as compensated days or the duration of the administrative process. Duplicate records were also removed prior to model training to prevent information leakage between training and validation datasets and to improve generalizability.

After preprocessing, approximately 250,000 observations were retained. For the regression task, training was restricted to cases with impairment $>0\%$. Both models used stratified sampling (90% training, 10% validation). Training was performed for 200 epochs using the Adam optimizer ($\eta=1\times10^{-3}$). The classification model used a weighted CrossEntropyLoss to account for class imbalance, while the regression model employed the Huber Loss to robustly handle outliers in impairment scores. Classification performance was evaluated using accuracy, precision, recall, and F1-score, while regression performance was assessed using R^2 , Mean Absolute Error (MAE), and Root Mean Squared Error (RMSE).

Results

After data cleaning and exclusion of records with missing information on impairment, the final analytical sample consisted of 310,189 occupational disease claims registered between 2020 and 2024. Men accounted for 73.4% of claims and women for 26.6%. Most claimants were born in Italy (92.0%), while 8.0% were born abroad. More than half of claims had an unspecified economic sector. Among claims with a defined sector, industry accounted for approximately 15%, followed by craftsmanship (14%), services (11%), and agriculture and fishing (10%); public administration represented less than 1%.

Musculoskeletal disorders were the largest ICD-10 diagnostic group among claims. Other frequent groups included diseases of the ear and mastoid process, disorders of the nervous system, and diseases of the respiratory system. Neoplasms and hematological diseases were less frequent but were associated with greater impairment. The distribution of causal agents was dominated by ergonomic and physiological factors, followed by claims in which the causal agent was still undetermined. Material agents, industrial products, and physical agents were also common.

Chemical and biological agents accounted for smaller shares of claims but were relevant in specific occupational contexts. Asbestos-related diseases

Tab. I. Distribution of compensated days and recognized impairment severity among occupational disease claims.

Variable	Mean	Median	SD	Min	Max
Compensated days (>0)	70.1	55	52.6	1	342
Impairment severity (%)	2.2	0	5.9	0	100

Tab. II. Multivariable linear regression analysis of factors associated with recognized impairment severity among occupational disease claims. Dependent variable: degree of impairment (%); $R^2 = 0.551$; $n = 310,189$.

Variable	β	SE	95% CI	<i>p</i>
Demographic and administrative variables				
Days to definition (per day)	0.001	<0.001	0.001 to 0.002	<0.001
Asbestos-related disease (yes vs no)	13.053	0.167	12.726 to 13.379	<0.001
Sex (male vs female)	0.208	0.021	0.166 to 0.250	<0.001
Country of birth (Italy vs abroad)	-0.115	0.033	-0.179 to -0.050	<0.001
Scheduled disease (yes vs no)	-0.266	0.024	-0.313 to -0.219	<0.001
Diagnostic category (ICD-10; reference: absent)				
Infectious and parasitic diseases	2.823	1.373	0.132 to 5.513	0.040
Neoplasms	16.401	0.986	14.469 to 18.333	<0.001
Blood diseases	5.112	1.169	2.821 to 7.403	<0.001
Endocrine diseases	4.808	1.218	2.420 to 7.195	<0.001
Mental disorders	5.087	0.995	3.138 to 7.036	<0.001
Nervous system diseases	4.291	0.986	2.359 to 6.223	<0.001
Eye diseases	4.360	1.051	2.300 to 6.421	<0.001
Ear diseases	5.111	0.986	3.179 to 7.044	<0.001
Circulatory system diseases	4.991	1.001	3.029 to 6.952	<0.001
Respiratory system diseases	-5.852	0.987	-7.787 to -3.917	<0.001
Digestive system diseases	4.758	1.021	2.758 to 6.758	<0.001
Skin diseases	-0.520	0.993	-2.467 to 1.426	0.600
Musculoskeletal system diseases	5.280	0.985	3.349 to 7.211	<0.001
Genitourinary system diseases	5.086	0.985	3.155 to 7.017	<0.001
Symptoms / signs	4.372	5.061	-5.548 to 14.292	0.388
Causal agent (reference: absent)				
Organic chemical agents	4.734	1.001	2.771 to 6.697	<0.001
Inorganic chemical agents	10.503	1.046	8.454 to 12.552	<0.001
Biological agents	10.947	0.999	8.990 to 12.905	<0.001
Industrial materials and products	11.097	0.976	9.183 to 13.010	<0.001
Physical agents	-1.122	0.964	-3.012 to 0.767	0.244
Physiological factors	-1.693	0.964	-3.581 to 0.196	0.079
Psychological factors	-0.330	1.044	-2.377 to 1.717	0.752
Agent yet to be determined	-4.691	0.976	-6.603 to -2.778	<0.001
Not determined	-3.380	0.182	-3.737 to -3.023	<0.001
Economic sector (reference: unspecified)				
Agriculture and fishing	-1.546	0.088	-1.718 to -1.374	<0.001
Industry	-1.405	0.087	-1.575 to -1.235	<0.001
Services	-1.101	0.088	-1.274 to -0.928	<0.001
Craftsmanship	-1.379	0.087	-1.549 to -1.208	<0.001

β : unstandardized regression coefficient (percentage-point change in impairment severity).

represented approximately 2% of the total sample (5,913 claims). Overall, 27.1% of claims were classified as scheduled occupational diseases, while 72.9% were non-scheduled.

Summary statistics for the continuous outcome and compensation variables are shown in Table I. Compensated days were right-skewed, with a mean of 70.1 days among claims with at least one compensated absence. Impairment severity had a mean of 2.2% and a

median of 0%, confirming that most registered claims did not result in permanent recognized impairment. Values nevertheless ranged up to 100%, indicating a small group of highly severe claims.

Results of the multivariable linear regression analysis are reported in Table II. The model explained 55.1% of the variability in impairment severity. Among diagnostic categories, neoplasms showed the strongest association with impairment severity, with an average increase of

Tab. III. Global performance metrics of the predictive model (validation set).

Dataset	Accuracy	Precision	Recall	F1-Score
Validation	98.15%	98.21%	98.15%	98.15%

Class-specific performance metrics are reported in Table IV. The model showed particularly high recall for cases with recognized impairment, while maintaining excellent precision for cases without impairment.

16.4 percentage points compared with claims outside that category ($p < 0.001$). Positive associations were also observed for hematological, endocrine, neurological, ear, circulatory, musculoskeletal, genitourinary, and mental disorder categories. Among causal agents, asbestos-related status was associated with an increase of 13.1 percentage points. Inorganic chemical agents, biological agents, and industrial materials/products were each associated with increases greater than 10 percentage points. Male sex showed a small positive association, while being born in Italy and having a scheduled disease classification showed small negative associations. Economic sector indicators had modest negative coefficients after adjustment for diagnostic and causal factors, supporting the interpretation that claim severity was driven mainly by diagnosis and exposure category rather than sector alone.

Diagnostic category, causal agent, and economic sector variables are binary (1 = present/yes; reference = absent/no). Economic sector reference category: unspecified sector. CI: confidence interval.

The moderate explanatory power of the linear regression model suggested that non-linear methods could capture additional structure in the claim data. In the secondary predictive analysis, a neural network-based classification model was developed to distinguish claims with recognized impairment (> 0%) from those without impairment (0%). After removal of duplicate records, approximately 250,000 observations

were used, with 90% allocated to training and 10% to validation using stratified sampling.

The distribution analysis showed a relatively balanced dataset, with 114,385 claims without recognized impairment (44.52%) and 142,546 claims with recognized impairment (55.48%). To account for this mild class imbalance and to optimize performance across both outcome categories, a weighted loss function was adopted during training (weighted CrossEntropyLoss), assigning a weight of 1.12 to the minority class and 0.90 to the majority class.

Model training was conducted over 200 epochs using the Adam optimizer with a learning rate of 1×10^{-3} . The training process exhibited stable convergence without significant overfitting, monitored via validation metrics to ensure generalizability.

Overall model performance on the validation set was high (Tab. III), with accuracy exceeding 98% and similarly elevated values for precision, recall, and F1-score.

The confusion matrix (Fig. 1) confirms the model's strong ability to correctly identify cases resulting in recognized impairment, with a sensitivity of 99.99% and a very low number of false negatives. This characteristic is particularly relevant from both clinical and administrative perspectives, as it minimizes the risk of underestimating cases requiring compensation.

When compared with the multivariable linear regression

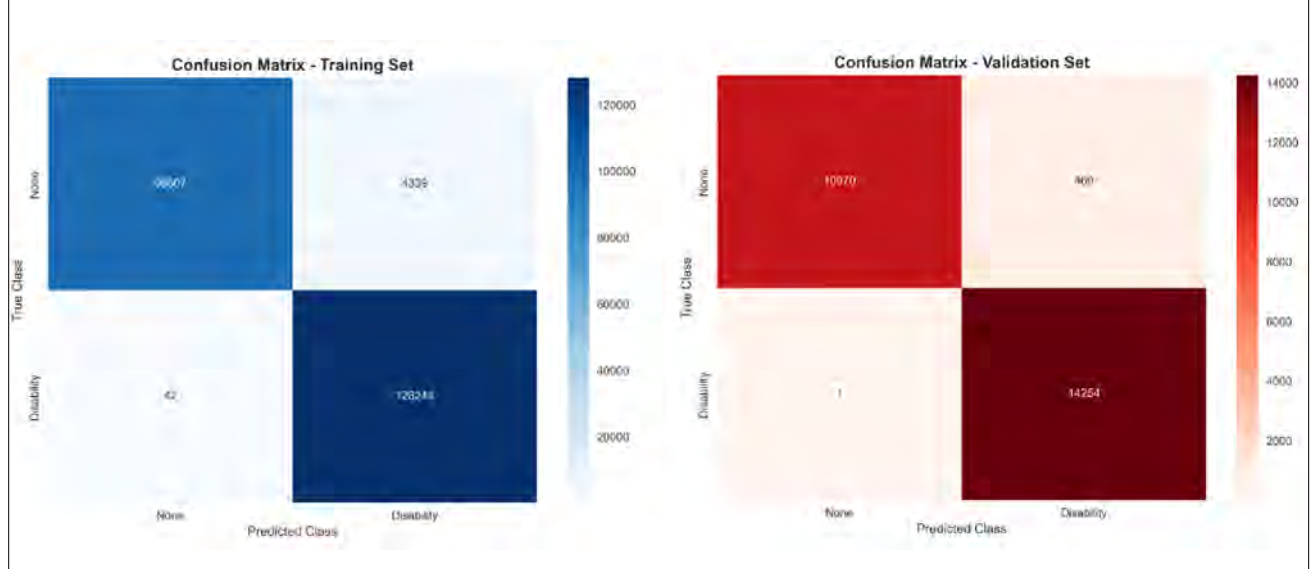
Fig. 1. Confusion matrices of the predictive model for training set (left) and validation set (right).

Fig. 2. Precision, recall, and F1-score for impairment classification on the validation set.**Tab. IV.** Class-specific performance of the predictive model (validation set).

Class	Precision	Recall	F1-Score
No impairment	99.98%	95.87%	97.88%
Recognized impairment	96.79%	99.99%	98.36%

Tab. V. Performance metrics of the regression model (validation set).

Metric	Value
MSE	30.37
RMSE	5.51%
MAE	2.31%
R ² 0.71	

model described previously, the neural network with embedding layers demonstrated a superior capacity to capture complex, non-linear relationships among predictors. The model's classification performance is summarized in Figure 2. The embedding-based approach proved especially effective in handling high-cardinality categorical variables, overcoming limitations associated with traditional encoding techniques. Although the binary classification model does not predict the exact degree of impairment, it provides a more robust and operationally meaningful decision-support output, with direct implications for case management and occupational health surveillance.

The regression model, trained on cases with recognized impairment to predict the specific degree of severity, demonstrated strong predictive capability. On the validation set, the regression model similarly achieved robust performance (Tab. V), with a Coefficient of Determination (R^2) of 0.71. This represents a substantial improvement over the linear regression model ($R^2=0.55$) presented in Table II, highlighting the neural network's ability to capture non-linear interactions between risk factors. The Mean Absolute Error (MAE) of 2.31% indicates that, on average, the model's prediction deviates from the actual impairment degree by less than 2.31 percentage points.

Discussion

This study describes occupational disease compensation claims registered by INAIL in Italy between 2020 and 2024. By combining descriptive analysis, multivariable regression, and predictive modelling, it identifies which claim characteristics were most strongly associated with recognized impairment. The findings should be read as patterns within the insurance claims system, not as estimates of disease risk in the workforce.

Consistent with previous national and international studies [9, 14], musculoskeletal disorders represented the largest proportion of occupational disease claims. This predominance reflects the persistent exposure of workers to ergonomic risk factors such as repetitive movements, manual handling of loads, and prolonged awkward postures. Despite their high frequency, musculoskeletal disorders were generally associated with lower levels of impairment compared with other diagnostic groups, suggesting that their overall impact on permanent disability is substantial mainly due to volume rather than individual severity.

In contrast, neoplasms and asbestos-related diseases, although accounting for a smaller proportion of claims, were associated with markedly higher impairment

levels. The strong association observed between asbestos exposure and impairment severity confirms the long-term health consequences of past occupational exposures and underscores the continued relevance of asbestos-related surveillance, even decades after regulatory bans. Similarly, the elevated impairment associated with chemical and biological agents highlights the need for targeted preventive measures in high-risk occupational settings, including healthcare and industrial environments.

THE PARADOX OF FREQUENCY AND SEVERITY

A striking finding of this analysis is the inverse relationship between claim frequency and clinical severity. Musculoskeletal disorders (MSDs) dominate the volume of claims (>65%) yet show low average impairment. This phenomenon can be partially explained by the “Healthy Worker Survivor Effect”: workers with severe MSDs may leave the workforce early or transition to disability pensions (INPS) rather than filing continuous INAIL claims for permanent impairment. Conversely, the high severity of neoplasms (coefficient +16.4%) reflects the aggressive nature of occupational cancers (e.g., mesothelioma, sinonasal carcinoma), which often present at advanced stages due to long latency periods and lack of early symptoms. The high impairment scores in this group are unfortunately often a proxy for poor prognosis and reduced life expectancy, necessitating expedited compensation pathways.

IMPLICATIONS FOR SOCIAL DIALOGUE AND LEGISLATION

The integration of predictive insights into the “social dialogue” is crucial for modernizing occupational health governance in Italy. The granular risk profiling provided by this study can inform negotiations between trade unions and employer associations, facilitating the development of targeted prevention measures in collective bargaining agreements. This approach aligns with the principles of legislative Decree 81/2008 [21], which emphasizes participatory risk assessment. By identifying high-severity drivers, such as specific material agents in the industrial sector, stakeholders can move beyond generic safety protocols to implement evidence-based interventions. Furthermore, the ability to predict impairment probability can assist outcomes-based policy planning, allowing regional health authorities and INAIL to allocate resources where the burden of permanent disability is highest.

PREDICTIVE MODELING AS A SUPPORT TOOL

As a secondary objective, this study explored the feasibility of predictive modeling to support occupational disease surveillance. The very high predictive performance observed is likely influenced not only by clinical severity patterns, but also by structured medico-legal and administrative rules embedded in the INAIL compensation process. In this context, the model may partially learn consistent decision-making patterns related to impairment recognition, rather than

purely clinical features. For this reason, the predictive analysis should be interpreted as a proof of concept for administrative support rather than as a diagnostic or clinical prediction tool. Specifically, the model could serve as a “triage engine” to flag high-probability impairment claims for expert review, thereby optimizing resource allocation in the compensation process.

The integration of traditional epidemiological methods with predictive modeling represents a promising approach for occupational safety and health research. While regression models offer interpretability and causal insight, machine learning techniques, specifically neural networks with embedding layers, capture complex, non-linear relationships that are difficult to model using conventional approaches. This is evidenced by the superior performance of the neural network regression model ($R^2=0.72$) compared to the linear baseline ($R^2=0.55$), suggesting that the determinants of impairment interact in non-additive ways. Their combined use may enhance both understanding and practical application, provided that transparency and validation requirements are adequately addressed.

LIMITATIONS

The main limitation is the claim-based design. The database does not provide workforce denominators by sector and region, so incidence rates and relative risks could not be calculated. The results describe registered and assessed claims, not the risk of disease in the Italian workforce.

Underreporting and delayed recognition of occupational diseases may also affect the composition of the dataset. The data were collected for compensation rather than research. Diagnoses, exposures, and economic sectors may therefore be incomplete or misclassified, and more than half of records lacked a specific economic sector. The outcome, degree of impairment, is a medico-legal measure rather than a pure clinical severity scale, and the distribution was zero-inflated because many claims had 0% recognized impairment. Finally, although duplicates were removed and leakage-prone variables were excluded from predictive modelling, external validation on independent data is needed before any operational use.

Conclusion

This study demonstrates the value of integrating national insurance administrative data with advanced analytical techniques to enhance occupational health surveillance in Italy. The findings confirm that while musculoskeletal disorders dominate the volume of claims, the highest burden of permanent impairment remains linked to neoplasms and asbestos-related diseases, highlighting the need for continued vigilance and targeted prevention for high-risk exposures.

The successful implementation of a neural network-based model to predict recognized impairment represents a significant step towards more proactive and data-driven

decision-making in occupational medicine. Despite limitations inherent in administrative datasets, such as underreporting and lack of detailed clinical variables, this integrated approach provides a robust framework for identifying high-risk cases and optimizing resource allocation within compensation systems.

Future developments should focus on incorporating explainable AI techniques to bridge the gap between predictive performance and clinical interpretability, ultimately supporting practitioners and policymakers in developing more effective strategies for worker protection.

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Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

MP conceived the study, performed the literature review, interpreted the results, and drafted the manuscript. AP designed and implemented the data analysis pipeline, developed the predictive models, and contributed to manuscript writing. Both authors read and approved the final manuscript.

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Governing Hospital Bed Allocation in Iran: A Stakeholder Network Analysis

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Keywords

Hospital bed allocation • Stakeholder network analysis • Health governance • Equity • Iran

Summary

Hospital beds are usually treated as little more than a headcount – a number meant to signal how ready a health system is to absorb demand. But their real functional value depends on how well they are linked to workforce, governance, and the other building blocks of the system. In Iran, national-level equity indicators look reassuring on their own (Gini coefficient ≈ 0.24), yet they conceal sharp sub-national disparities, with city-level inequality reaching as high as 0.68–0.70 in Shiraz. What has been missing from this literature is any account of who actually makes bed-allocation decisions, and how the relationships among these actors shape the outcomes so often described in aggregate terms.

This study combined 34 semi-structured interviews with policy-makers, university leaders, and hospital managers with Social Network Analysis (SNA) to map the stakeholder network governing hospital bed allocation in Iran. The resulting network comprised 17 actors connected through 81 directed ties (density=0.298). Medical Universities showed the highest betweenness centrality (0.289), positioning them as the network's principal structural

brokers, while the Ministry of Health held the highest weighted out-degree (27), reflecting its concentrated directive influence. Political-social ties dominated the network, accounting for 43.2% of all edges, while regulatory and oversight ties were comparatively scarce (9.9%). A series of robustness checks – including sensitivity analysis across evidence thresholds and a random edge-deletion perturbation analysis with 500 iterations – confirmed that both of these central findings held up under scrutiny. Taken together, the results suggest that Iran's coexistence of national equity and local inequity is not merely a statistical artifact of how the data happen to be aggregated, but reflects a genuine structural problem in governance: Medical Universities, the actors best positioned to observe local need, lack authority commensurate with that position, while independent regulatory oversight remains minimal. Addressing bed-allocation inequity, then, is likely to require structural reform of decision-making authority and oversight mechanisms – not simply expanding capacity.

Introduction

Hospital beds are often treated as a simple headcount – a number that signals how ready a health system is to absorb demand. But that framing misses something important. Resource generation functions like bed capacity only translate into actual service delivery when they are linked to workforce, governance, and the other building blocks of the system [1]. Strip away those supporting layers, and a bed count becomes a fairly hollow metric.

This becomes clear once you look at how differently countries handle it. A survey of decision-makers and academics across eighteen high-income countries found that resource allocation is still largely driven by historical patterns and ad hoc decisions rather than any consistent, evidence-based logic [2] – which goes a long way toward explaining why bed supply varies so much even among comparably wealthy systems. And more beds does not automatically translate into better performance: in a ten-country European comparison, once financing arrangements and physician remuneration systems were accounted for, expanding the number of beds had little

independent effect on occupancy rates or length of stay [3] – the health system's underlying institutional design mattered more than sheer capacity.

The same tension shows up when countries move in the other direction. Efficiency-driven reforms – trimming length of stay, shifting care toward outpatient and community settings – have often paid off on paper, but they have also exposed a real fragility. A county-level analysis in China illustrates this well: even as the national bed-to-population ratio grew by roughly 50% between 2000 and 2019, regional disparities in allocation not only persisted but continued to widen [4]. Supply and equity, in other words, do not automatically move together.

What ties these threads together is that allocation decisions are rarely just technical exercises. A study of priority-setting in two Kenyan hospitals described hospitals as complex adaptive systems in which outcomes depend as much on organizational “software” – relationships, norms, informal negotiation – as on formal rules or “hardware” like budgets and beds [5]. A recent scoping review of universal health system reforms across high- and upper-middle-income countries reinforces this: reform trajectories consistently reflect

the roles, relationships, and power dynamics among the actors involved, not a single centralized plan working itself out [6].

A related point comes from recent reflections on where health policy and systems research needs to go next: achieving health equity requires paying closer attention to how power is distributed among the actors who shape decisions – not just to the decisions themselves [7]. Some actors inevitably end up occupying more influential positions than others, acting as intermediaries or gatekeepers in how resources and decisions actually flow [8].

Yet despite this shift in the literature toward governance and relational thinking, most empirical work on hospital bed allocation still leans on aggregate indicators. A systematic review of governance frameworks found that most existing tools were designed to assess a single level of the system – national, regional, or facility – even though real decision-making authority is typically split across all of them, with formal and informal actors operating simultaneously at each level [9]. This gap is not merely theoretical; it shows up clearly once you look at how the literature on hospital bed equity in Iran itself has developed.

Iran offers a particularly instructive case, precisely because the evidence on outcomes is now fairly rich, while the evidence on the actors producing those outcomes is almost nonexistent. At the national level, the bed-to-population ratio has been found to vary so widely across provinces that its dispersion coefficient stood at 36% in 2015, with projections suggesting this would only fall to 19% by 2025 even under planned expansion [10]. Around the same period, a comparison of inequality across different health resources nationally found that hospital beds were in fact the most unequally distributed of all major resources – a Gini coefficient of 0.58, compared to 0.47 for physicians and 0.39 for paramedics [11]. More localized work tells a similar story: a regional analysis of Lorestan Province documented a moderate level of inequality (Gini=0.27) using the Gini coefficient and Lorenz curve, with certain cities such as Khorramabad and Aligudarz showing considerably worse imbalances than others [12]. Most recently, a systematic review and meta-analysis pooling thirty studies conducted between 2000 and 2025 found a national Gini coefficient of 0.24 – suggesting relative equity at the country level – while provincial figures ranged from 0.229 in South Khorasan to over 0.50 in Sistan and Baluchestan and Bushehr, and city-level inequality reached as high as 0.68-0.70 in Shiraz [13]. Taken together, these four studies tell a genuinely puzzling story: national-level equity appears reasonable, yet it conceals sharp and persistent sub-national disparities that none of these aggregate measures can, by design, explain. A parallel strand of Iranian research has approached the problem from the indicator side rather than the outcome side. One study identified 75 criteria affecting hospital bed allocation through a scoping review, narrowed these to 28 through an expert Delphi process, and used network analysis to determine which

factors most strongly drove distributional decisions – concluding that bed distribution in the region studied remained highly unequal and that a comprehensive monitoring and evaluation system was still lacking [14]. A follow-up study built a system dynamics model to predict future bed shortages and test policy scenarios, showing that government intervention aimed at simultaneously expanding beds and home-care services could meaningfully close projected gaps [15].

What none of these six Iran-focused studies do – and this is precisely the gap this study addresses – is examine who is actually making these allocation decisions, how they relate to one another, and whether the structure of those relationships helps explain why national equity and local inequity can coexist so persistently. Hospital bed allocation in Iran involves a genuinely complex mix of actors – policymakers, financial authorities, service providers, and socio-political stakeholders – but no study to date has systematically mapped how these actors interact or examined their relative influence through a network-based governance lens. This study addresses that gap directly: it analyzes the stakeholder network governing hospital bed allocation in Iran, with particular attention to how the structure of this network shapes equity and efficiency in the distribution of inpatient capacity.

Methods

This study examined the network of stakeholders involved in hospital bed allocation in Iran, combining a qualitative inquiry with Social Network Analysis (SNA). Rather than treating stakeholders as isolated actors, we modeled them as nodes within a directed network, with the ties between them representing the flow of authority, resources, and oversight. This dual design allowed us to move beyond a simple inventory of “who is involved” toward a structural account of how decisions about bed allocation actually move – and stall – across national, provincial, organizational, and sociopolitical levels.

STUDY SETTING

The research was situated within the governance system that shapes hospital bed allocation in Iran, spanning policy formulation, financing, regulation, service delivery, implementation, and oversight. The relevant institutional landscape included national ministries and agencies, the Plan and Budget Organization, medical universities, public and private hospitals, insurance bodies, the Social Security Organization, members of parliament, provincial health authorities, private-sector representatives, civil society organizations, and service users.

PARTICIPANTS AND SAMPLING

The aim of this phase was to identify the actors involved in hospital construction and bed-distribution policy, and to characterize the relationships among them. Rather than seeking self-reports from every actor in the system,

participants were purposively selected for their first-hand knowledge of how these decisions are actually made – that is, individuals whose institutional position gave them visibility into the actors, dependencies, and decision pathways governing hospital bed allocation, health financing, regulation, or broader health system governance. Eligibility required at least five years of relevant professional experience and direct engagement in decision-making, implementation, monitoring, or advisory functions related to healthcare resource allocation.

Because influence in this system is not always formally visible – much of the real decision-making occurs outside official titles – purposive sampling was supplemented with snowball sampling, allowing participants to point us toward further actors and relationships that shaped allocation outcomes without necessarily holding prominent formal positions themselves [16].

Recruitment and data collection continued until interviews and documents stopped surfacing anything new about the system: no new actor categories, no new recurring relationships, and no meaningfully different interaction patterns. In other words, sampling continued until the picture of the network itself, as reconstructed from participants' accounts, appeared to stabilize. Saturation was effectively reached at the 32nd participant, and the final two interviews (participants 33 and 34) were conducted mainly to confirm that saturation and to rule out the emergence of any new actor or pattern [17]. The characteristics of the participants are summarized in Table I.

DATA COLLECTION

Data were drawn from two sources: semi-structured interviews and document review. The document set included laws, regulations, national development plans, administrative and organizational reports, and academic literature relevant to the planning, financing, expansion, distribution, and monitoring of hospital beds in Iran.

The interview guide was built around five core lines of inquiry: who the key stakeholders are, what role each actor plays, whether and in which direction relationships exist between actors, what these relationships are based on, and where coordination problems or decision-making bottlenecks tend to arise. Interviews were conducted face-to-face or by telephone depending on participant availability, and all were audio-recorded with consent and transcribed verbatim before analysis.

STAKEHOLDER IDENTIFICATION AND NETWORK CONSTRUCTION

Stakeholder identification proceeded iteratively rather than as a single fixed step. An initial list of actors was compiled from documentary sources, earlier phases of the broader research program, and the first round of interviews, and this list was revised continuously as new data emerged. Actors who carried different titles but performed the same institutional function were merged into a single node; conversely, units with clearly distinct formal responsibilities – even within the same

organization – were retained as separate nodes.

The final network comprised the following 17 nodes: the Ministry of Health (MoH); Universities of Medical Sciences, including their affiliated public hospitals; the Plan and Budget Organization (PBO); the Currency Board; Basic Health Insurance Organizations; Provincial Governments and Local Authorities; Influential Politicians, including Members of Parliament and Government Officials; the State Organization for the Construction of Governmental and Public Buildings and Installations, a subsidiary of the Ministry of Roads and Urban Development; the Private Health Sector, including Private Hospitals and Healthcare Centers; the Social Security Organization (SSO), including its affiliated hospitals; Patients and the Public; Patient Support Groups and Non-Governmental Organizations (NGOs); Media; Military Health Facilities, including their affiliated hospitals; Medical Equipment Suppliers; Health Philanthropists; and Other Governmental and Public Bodies, including hospitals affiliated with other public institutions.

We used two structured recording forms to organize the raw data. The first captured each stakeholder's name, level of governance (national, provincial, or organizational), and functional role. The second recorded, for every identified relationship, the source actor, the target actor, the type of relationship, the direction of influence, the evidence supporting it, and two separately assigned scores – tie intensity and evidential corroboration (see Tie Weighting, below).

A tie was entered into the network only when the evidence pointed to a concrete, policy-relevant connection between two actors specifically in relation to hospital bed allocation – for instance, an actor issuing a binding directive, releasing or withholding budget, exercising formal regulatory review, or coordinating implementation with another actor. General institutional proximity or informal familiarity, without a demonstrable link to an allocation-relevant action, was not sufficient to establish a tie. Relationships were coded into four categories: financial and resource-provision, regulatory and policy-making, political-social pressure, and operational and service-delivery. Each tie was directed from the actor exercising influence toward the actor receiving or being affected by it.

DATA ANALYSIS

Interview transcripts and documents were analyzed using directed content analysis in MAXQDA 2020. Stakeholder names, institutional roles, and inter-organizational relationships were extracted and coded against the predefined categories described above, then converted into a node-edge matrix suitable for network analysis.

The resulting network was analyzed as a directed weighted multigraph in Gephi (version 0.10). Because some actor pairs were connected through more than one relationship type, parallel edges were retained to preserve distinct relational pathways between actors. Each edge represented a specific relationship type

and carried its own intensity weight. Three measures anchored the analysis: network density, to characterize overall connectedness; betweenness centrality, to identify intermediary actors and potential decision-making bottlenecks; and weighted out-degree centrality, to assess the extent of outward influence exercised by each stakeholder within the allocation process.

TIE WEIGHTING

Because the substantive strength of a relationship and the strength of the evidence supporting it are conceptually distinct, each tie was scored along two independent dimensions: tie intensity and evidential corroboration.

Tie intensity reflects the strength of the relationship itself, based on the content of the interaction described in interviews and documents, independent of how many sources reported it. A weak tie (score=1) reflected an informal, advisory, or non-binding interaction, or one occurring on an irregular, ad hoc basis, with the target actor retaining full discretion over whether to act on it. A moderate tie (score=2) reflected interaction through an established, recurring institutional channel – such as periodic reporting or standing coordination mechanisms – in which the initiating actor's influence required negotiation or the counterpart's cooperation rather than unilateral authority. A strong tie (score=3) reflected the exercise of direct, binding, and largely unilateral authority with a demonstrable effect on a specific bed-allocation outcome, such as approving or withholding budget, issuing a binding regulatory directive, or a documented act of political intervention that altered an allocation decision. This intensity score was used as the final edge weight in network construction and in all centrality calculations reported below.

Evidential corroboration reflects how well a tie was supported across independent data sources, following established triangulation logic in qualitative research whereby independent corroboration is treated as evidence of a claim's validity rather than as a graded measure of its substantive strength (Denzin, 1978; Patton, 1999). It was scored using the same three-point structure applied in earlier coding: a score of 1 was assigned when a relationship appeared in a single interview or document without corroboration elsewhere; a score of 2 was assigned when the same relationship was independently confirmed across more than one source; and a score of 3 was reserved for relationships confirmed by multiple sources that also demonstrated direct relevance to a bed-allocation decision. This corroboration score did not contribute to network weighting; it was retained solely to define the progressively stricter evidentiary thresholds used in the sensitivity analysis reported below.

Two coders independently assigned both scores for every tie. Inter-coder agreement was assessed based on the initial independent ratings. Discrepancies were subsequently discussed and resolved through consensus before generating the final network dataset.

SENSITIVITY AND ROBUSTNESS ANALYSIS

Any network built this way carries some unavoidable

uncertainty – both the intensity and corroboration scores assigned to a tie reflect a judgment call, and thirty-four informants, however carefully chosen, are still a finite window onto a much larger system. We wanted to know how much that uncertainty mattered for our two main findings, so we tested it three ways. First, holding each tie's intensity score fixed, we rebuilt the network at progressively stricter evidential-corroboration cutoffs – keeping all ties regardless of corroboration, then only those independently confirmed by more than one source, then only the strongest, doubly-confirmed ties – and watched whether the same actors stayed on top. Second, we assessed robustness to random data loss through an edge-deletion perturbation analysis: across 500 iterations, we randomly removed 10% of the network's ties, recalculated centrality on the remaining edges, and tracked how much each actor's rank shifted relative to the full network, summarizing this with the mean rank, its spread, and a Spearman correlation against the original full-network ranking. Third, because betweenness centrality depends on a somewhat arbitrary choice – how each tie's intensity score gets converted into path “distance” – we recomputed it under three different conversions (inverse weighting, *i.e.*, distance=1/intensity; linear rank-inversion, *i.e.*, distance=4 – intensity; and unweighted topological distance, ignoring intensity entirely) to see which conclusions held up regardless of that choice and which didn't.

TRUSTWORTHINESS

Credibility and dependability were addressed through triangulation across interviews and documents, and through fixing the rules for stakeholder identification, relationship classification, tie direction, and weighting before the final round of analysis – rather than adjusting them retrospectively to fit emerging patterns.

Two researchers independently coded the data to minimize individual bias in the classification process. Inter-coder agreement was assessed across three dimensions of the coding process. Agreement on whether a tie existed between two actors – assessed across all candidate relationships screened by both coders, including those ultimately not retained – was evaluated using unweighted Cohen's kappa ($k=0.81$). Among the 81 retained ties, agreement on the assigned tie-intensity score was assessed using linearly weighted Cohen's kappa ($k_w=0.76$), and agreement on the assigned evidential-corroboration score was likewise assessed using linearly weighted Cohen's kappa ($k_w=0.79$). According to the standard interpretation guidelines proposed by Landis and Koch, agreement was almost perfect for tie identification and substantial for both tie-intensity and evidential-corroboration ratings [18]. Where disagreements arose, they were resolved through discussion between the two coders until consensus was reached. Prior to final analysis, the complete dataset was thoroughly screened for duplicate nodes, inconsistent naming conventions, contradictory tie directions, and missing attribute data.

Tab. I. Characteristics of participants in the qualitative interviews.

Participant Group	N	Position	Role(s)
Ministry of Health staff	6	Senior officials and health-sector experts	Policymaking, planning, and macro-level management of the health system
Presidents of medical universities	2	University president	Leadership and decision-making at the university/provincial health system level
Vice presidents of medical universities	4	Vice presidents for treatment, and for management and resource development	Prioritization, management, and distribution of treatment resources at the provincial level
Senior managers and experts at medical universities	8	Responsible managers and experts	Implementation of programs related to the distribution of treatment resources and bed capacity
Managers of public and private hospitals	6	Deputy director and hospital director	Management of operations, resources, beds, and hospital services
Faculty members and researchers	4	Faculty member / researcher	Research, analysis, and evaluation on health system issues and equity in bed distribution
Former members of parliament	2	Member of the Health, Treatment, Education and Research Commission	Legislation, oversight, and influence over the agenda and priorities of healthcare investment
Provincial officials of the Social Security Organization	2	Deputy for treatment, Social Security Organization	Oversight and management of treatment services provided by the Social Security Organization at the provincial level
Total	34		

Results

PARTICIPANTS AND SAMPLING

Data were obtained from 34 key informants with in-depth knowledge of the actors, dependencies, and decision pathways governing hospital bed allocation in Iran, drawn from the Ministry of Health, medical university leadership and management, hospital administration, academic and research institutions, parliament, and the Social Security Organization (Tab. I). Informants were selected for their first-hand insight into how bed-allocation decisions and stakeholder interactions actually unfold, rather than to reach a predetermined sample size. Saturation was effectively reached at the 32nd informant, with the final two interviews (informants 33 and 34) conducted to confirm saturation and rule out the emergence of any new actor category or interaction pattern.

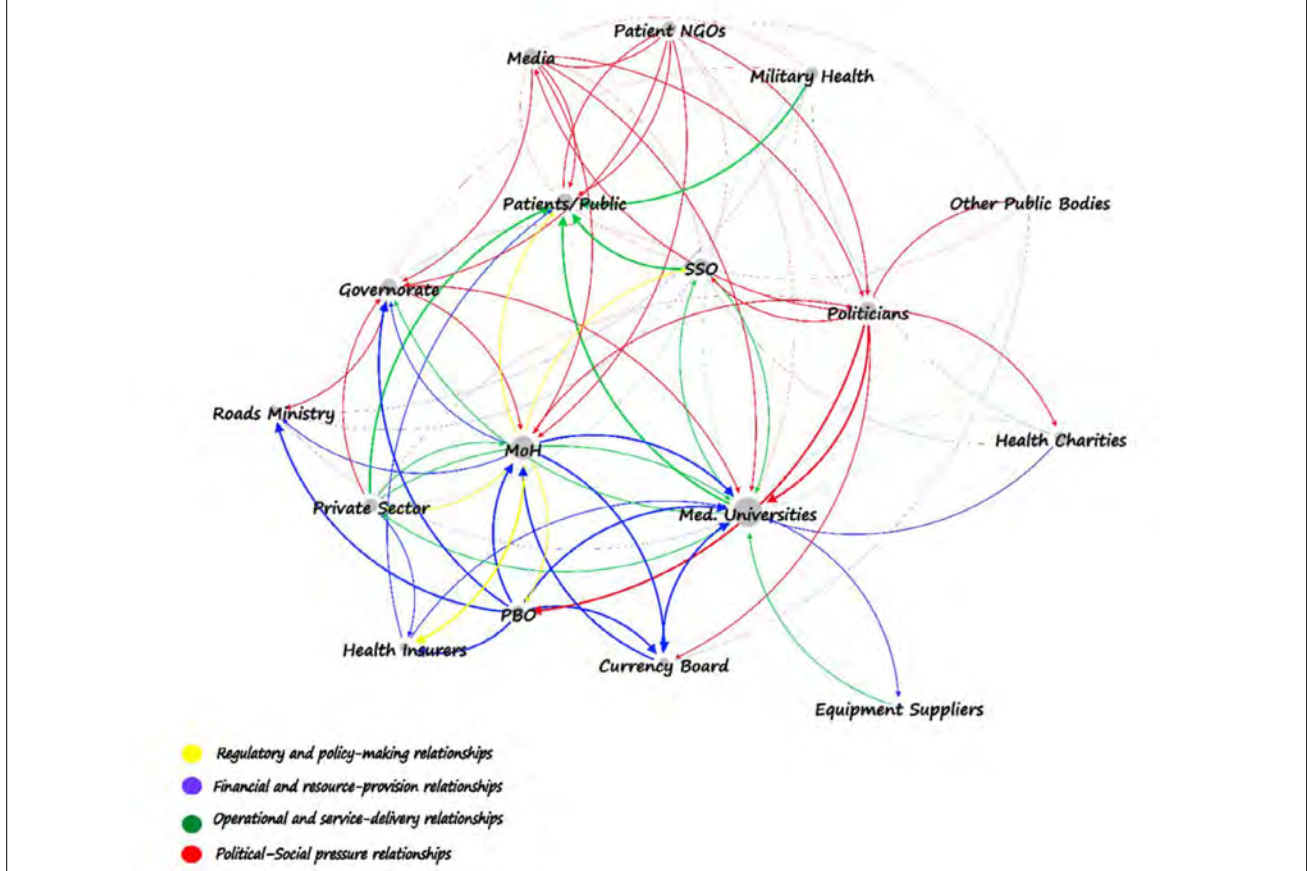
STAKEHOLDER NETWORK STRUCTURE

Drawing on the interview and document data, a stakeholder relationship network was constructed comprising 17 actors involved in hospital bed allocation governance, connected through 81 directed ties (network density=0.298), indicating a moderately dense system in which a substantial share of theoretically possible relationships are actually realized. These 81 ties corresponded to 79 unique directed actor dyads, with two actor pairs connected through more than one relationship type (*i.e.*, parallel ties representing distinct relational pathways). Collapsing these parallel channels into single directed dyads yields a simple directed density of 0.290. Because tie intensity scores affect only the coded strength of an observed relationship and not whether it was observed, this figure is unaffected by the intensity-based reweighting described in Tie Weighting.

Node size is proportional to each actor's weighted outdegree – the sum of intensity-weighted ties it directs toward other actors – reflecting the magnitude of its direct outward influence rather than its brokerage position (reported separately as betweenness centrality in Fig. 2). Edge color denotes relationship type: yellow – regulatory and policy-making relationships; blue – financial and resource-provision relationships; green – operational and service-delivery relationships; red – political-social pressure relationships. Edge thickness is proportional to tie intensity, based on the intensity-weighted relational data derived from interview and document analysis (see Tie Weighting).

As shown in Figure 1, Medical Universities and the Ministry of Health (MoH) occupy the most visually central positions in the network, connected through dense, high-intensity ties – particularly financial/resource and political-social pressure relationships – to actors such as the Plan and Budget Organization (PBO), the Currency Board, Health Insurers, and Politicians. Peripheral actors such as Patient Groups, the Military, Philanthropists, and Other Government Bodies are connected mainly through thinner, lower-intensity ties, suggesting a more marginal or indirect role in day-to-day allocation decisions.

To characterize this structure more precisely, three sets of network metrics were calculated for the 17 actors and 81 ties: brokerage position (betweenness centrality), directive influence (weighted outdegree), and the distribution of relationship types across all ties. These metrics are widely used in recent applications of social network analysis to stakeholder governance in the Iranian health system, where betweenness centrality identifies actors who broker information and resource flows between otherwise unconnected parties, and weighted outdegree captures the direct influence an actor exerts on others.

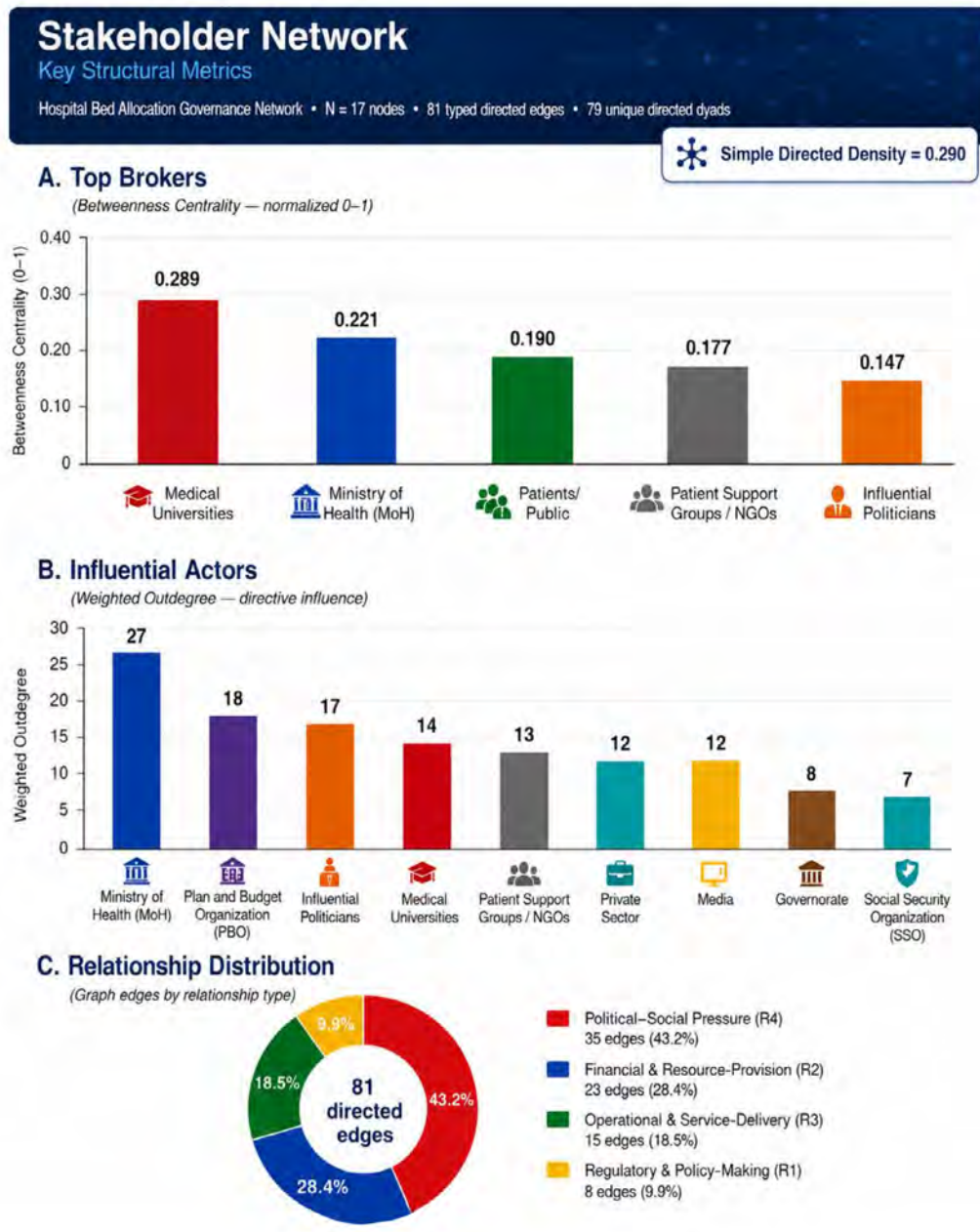
Fig. 1. Stakeholder Relationship Network in Hospital Bed Allocation Governance.

Panel A of Figure 2 shows the five actors with the highest betweenness centrality – the degree to which an actor sits along the shortest paths connecting other stakeholders, and thus acts as a broker within the network. Medical Universities recorded the highest betweenness centrality (0.289), followed by MoH (0.221), Patients/Public (0.190), Patient Support Groups/NGOs (0.177), and Influential Politicians (0.147); Media, by contrast, recorded a negligible betweenness score (0.003) despite its moderate outdegree, indicating that its outward ties rarely place it on the shortest path between other actors. This indicates that Medical Universities function as the principal intermediaries in the system: a large share of resource and information flows between other stakeholders passes through them rather than occurring via direct ties. Notably, Patients/Public and Patient Support Groups/NGOs together emerged as meaningful brokers despite their comparatively peripheral position in the visual layout of Figure 1, pointing to an indirect but structurally important role in connecting otherwise disconnected parts of the network.

Panel B shows weighted outdegree, which captures each actor's directive influence through its outgoing ties. Here a somewhat different pattern emerged: MoH showed by far the highest directive influence (weighted outdegree=27), consistent with its regulatory mandate, followed by the Plan and Budget Organization (18) and Influential Politicians (17), and then Medical Universities

(14), Patient Support Groups/NGOs (13), the Private Sector and Media (12 each), the Governorate (8), and the Social Security Organization (7); the remaining actors recorded weighted outdegrees of 6 or below (Fig. 2, Panel B), with the State Organization for the Construction of Governmental and Public Buildings and Installations recording no outgoing ties at all, consistent with its purely executive role in hospital construction rather than allocation governance. This divergence – Medical Universities leading on brokerage, MoH leading on directive influence – suggests a functional division of labor within the network: MoH acts as the primary source of top-down directives and financial allocation, while Medical Universities serve as the operational intermediary that channels and redistributes these directives toward hospitals and provincial-level actors, consistent with the dense cluster of ties converging on “Med. Universities” in Figure 1.

Panel C presents the distribution of the 81 edges across four relationship categories: regulatory and policy-making (R1), financial and resource-provision (R2), operational and service-delivery (R3), and political-social pressure (R4). Political-social pressure ties (R4) were the most frequent category, accounting for 43.2% of all edges (35 of 81), followed by financial and resource-provision ties (R2, 28.4%), operational and service-delivery ties (R3, 18.5%), and regulatory/policy-making ties (R1, only 9.9%). This pattern is visually corroborated in Figure 1,

Fig. 2. Structural Metrics of the Stakeholder Network.

where red (political-social pressure) and blue (financial) edges dominate the densest portions of the network – particularly around MoH, Politicians, PBO, and Medical Universities – while yellow (regulatory) ties are comparatively sparse and concentrated among a small subset of actors (*e.g.*, MoH, SSO, Health Insurers). The relative scarcity of formal regulatory ties compared to the prevalence of political-social pressure and financial relationships suggests that resource-allocation decisions in this system may be shaped as much, or more, by informal political influence and financial dependency as by formal regulatory mechanisms – a pattern consistent with recent stakeholder-network findings in other large-scale infrastructure and public-governance contexts, where information asymmetry and coordination power

have been shown to concentrate around a small number of high-centrality actors regardless of formal regulatory hierarchy [19].

Before drawing conclusions from these two positions, we checked how much they could be trusted. Medical Universities' lead in betweenness centrality held up at a moderate evidentiary threshold – ties corroborated by at least two independent sources – where it remained the top broker even as network density fell substantially. It did not hold, however, at the most extreme threshold, an 11-tie network retaining only the most strongly corroborated ties, where the Plan and Budget Organization moved to the top position on both measures; given how sparse this residual network is, we treat this reversal as a stress test of an unusually thin evidentiary base rather

than as a competing finding about the network's true structure. MoH's dominance in weighted out-degree was, if anything, even more solid: across 500 iterations of the edge-deletion perturbation analysis, its rank barely moved (mean Spearman $p=0.975$ for out-degree, 0.936 for betweenness), and it remained the top-ranked actor on out-degree in 98.8% of iterations. One comparison did turn out to be more fragile than it looks in the raw numbers – MoH edges out Patients/Public on betweenness in the main network, and this ordering held in only 68.4% of perturbation iterations, reversing under two of the three distance conversions tested, so we would not lean too hard on that particular gap. A few peripheral actors – the Currency Board, the Governorate, Health Charities, Medical Equipment Suppliers, Military Health Facilities, Other Governmental and Public Bodies and Patient Support Groups/NGOs – dropped out of the network altogether once we restricted ourselves to the most strongly corroborated ties, which tells us their marginal position rests more on evidence from a limited number of sources evidence than on a well-confirmed pattern.

Taken together, these findings indicate a governance structure in which formal regulatory authority (concentrated in MoH) and operational brokerage (concentrated in Medical Universities) are structurally separated but tightly interdependent, while civil-society and oversight actors – such as Media and Patient Support Groups/NGOs – occupy a limited but non-trivial position within an otherwise state- and institution-dominated allocation network.

Discussion

The puzzle we set out with in the introduction was a simple one to state and a hard one to explain: why does hospital bed allocation in Iran look reasonably equitable at the national level while remaining so uneven underneath it, at the level of provinces and cities? The six Iran-focused studies reviewed there could describe that pattern in impressive detail but had little to say about who was actually producing it. Looking at the stakeholder network itself turns out to help close that gap, and in a fairly direct way: the unevenness is not just a statistical artifact of how the data happen to be aggregated, it is built into the structure of who talks to whom, who controls what, and who answers to no one in particular.

Start with the network's overall density. Using the typed-edge representation of the multigraph, the network density was 0.298 (simple directed density=0.290 after collapsing parallel ties), indicating a moderately interconnected governance network, consistent with the moderate range reported for other policy and health-governance networks [20, 21]. However, this density value on its own is not a dramatic finding. But it is worth pausing on what “moderate density” actually means here rather than treating it as a neutral descriptive statistic. A very sparse network would point to something

close to institutional anarchy – nobody coordinating with anybody. A very dense one would suggest the opposite, a tightly integrated system where information and authority move freely in every direction. What we have instead is neither: roughly three out of every ten possible relationships among the seventeen stakeholders are actually realized, and those realized relationships cluster heavily around a handful of actors – the Ministry of Health, medical universities, the Plan and Budget Organization – while thinning out considerably around others. That clustering is, we think, the more interesting fact than the density figure itself. It offers a plausible mechanism for exactly the paradox the introduction raised: national indicators can look tidy precisely because the actors who generate and report those indicators are well-connected to each other, while the actors closer to where a bed shortage is actually felt are not.

The most striking single finding to come out of the tie-type breakdown is how lopsided the network is toward sociopolitical relationships (43.2% of all ties) and away from regulatory ones (just 9.9%). It would be easy to read that gap as a distinctly Iranian pathology, but the broader literature on hospital governance suggests some caution is warranted. Hospitals have been described as complex adaptive systems in which outcomes depend as much on relational “software” – negotiation, informal norms, who owes whom a favor – as on the formal “hardware” of budgets and regulations [5]. Scarce resources allocated under competing claims tend to migrate toward exactly this kind of informal bargaining almost everywhere, because regulatory instruments are generally built to check compliance with a rule, not to adjudicate between two legitimate but conflicting demands [22]. So the general shape of the finding is not unique to Iran.

What does look more specific to this setting is the scale of the gap, and three features of the network help explain it. One is that the Ministry of Health combines the highest weighted out-degree in the entire network (27) with the second-highest betweenness centrality (0.221) – meaning the institution that sets policy and controls resources is, to a substantial extent, also the institution checking on itself. That kind of role concentration tends to crowd out exactly the sort of independent oversight channel a healthier system would need, a tension documented in other health systems where the ministry of health simultaneously directs resources and is expected to oversee their use [23]. A second feature is the weight carried by the Plan and Budget Organization (out-degree=18) and by individual politicians (out-degree=17) – both nearly on par with the Ministry of Health, and higher than medical universities, the actors who actually deliver the service. That is consistent with earlier evidence that Iranian health-resource decisions tend to cluster around a small set of central actors, often at the cost of weaker connections further out in the system [21, 24]. And a third is simply the thinness of the regulatory layer itself: with only 8 of the network's 81 ties coded as regulatory, there does not appear to be an actor positioned to monitor the process independently of the two bodies that already control it. Put those three

things together and the dominance of political and social channels over regulatory ones starts to look less like an anomaly and more like a fairly predictable consequence of how authority is currently distributed.

Medical universities present a genuinely puzzling case within this picture. They occupy the single highest betweenness score in the network (0.289), which fits the broader pattern of high-betweenness actors bridging policy and frontline levels of a health system [25]. Nearly everything that moves between the national level and the provincial or hospital level seems to pass through them. And yet their weighted out-degree (14) trails well behind the Ministry of Health, the Plan and Budget Organization, and influential politicians. In practice, this means medical universities are usually the first to see a local bed shortage and the last to have the authority to fix it on their own – they carry the operational weight of decisions made elsewhere without a matching share of the power to shape those decisions. That mismatch between informational centrality and financial authority is exactly the kind of position resource-dependence accounts of organizations would flag as unstable over time [26]. and it offers one plausible thread connecting this network structure to the persistent provincial and city-level disparities documented in earlier Iranian studies [13, 27].

It's worth pausing here on how much weight this particular finding can bear. The gap we're describing – universities see the problem but don't hold the purse strings – survived every robustness check we threw at it, so we feel comfortable treating it as a real feature of how this system works, not just a quirk of which interviews happened to mention which relationship. The same confidence doesn't extend to every corner of the network. Patient Support Groups/NGOs, in particular, moved around a lot across our perturbation iterations – some runs placed them well outside the top handful of brokers – and several of the more peripheral actors lost their footing in the network entirely once we demanded stronger evidence for every tie. We don't think this is a flaw unique to our data so much as a fairly predictable feature of studying stakeholder networks this way: the actors everyone talks to leave an obvious trail across interviews and documents, while the quieter, more peripheral ones are inherently harder to pin down with the same confidence [28]. So when we talk about who sits at the center of this network, we mean it fairly strongly; when we talk about who sits at the edges, that should be read as more of a tentative sketch than a settled fact.

The other end of the network tells a related story. Patients and the public sit at a moderate betweenness position (0.190) – closely followed by patient advocacy groups/NGOs (0.177), while the media's brokerage role is comparatively negligible (0.003) by comparison – and still well behind medical universities or the Ministry of Health – and they connect to the system almost entirely through sociopolitical and civil-society channels rather than through any formal seat at the policy or financing table [20]. What that suggests, practically, is that patient need tends to enter the decision-making process only

once it has become visible enough to generate media attention or public pressure, rather than being built into planning from the outset. It is not hard to see how that pattern connects back to something already documented in the introduction: a city like Shiraz can carry a Gini coefficient as high as 0.68-0.70 [13], and disparities of that size are the kind that typically become policy problems only after they have already become public ones. Meanwhile, actors with genuine service capacity but limited network reach – military health facilities, the Social Security Organization – remain on the periphery of directive influence despite the real resources they control, which is broadly consistent with the idea that structural gaps in a health network often mark the limits of formal integration rather than an absence of actual capacity [21].

Conclusion

Taken as a whole, this analysis suggests that inequity in hospital bed allocation in Iran is not simply a matter of too few beds or an imperfect population-based formula – it is, in real part, a governance problem. Directive authority sits with a small cluster of policy, budget, and political actors; the institutions best placed to see local need, medical universities chief among them, lack the authority to act on what they see; the regulatory channel meant to hold the system accountable is thin to the point of being almost notional; and the people the system is ultimately meant to serve enter the conversation mainly once their situation has already become a public one. None of this shows up in a bed-to-population ratio or a Gini coefficient, which is precisely why those measures, however carefully constructed, have not been able to explain why national equity and local inequity can sit side by side for as long as they have in Iran. If there is a practical takeaway, it is that closing this gap will likely require less emphasis on the number of beds and more attention to how authority, oversight, and participation are actually distributed among the people making these decisions – a question the existing literature on Iran's hospital system has, until now, largely left unasked.

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Ethical Considerations

Ethical approval was obtained prior to data collection, and written informed consent was secured from all

participants. Identifying information was removed from transcripts and reports, and findings are reported at the institutional rather than individual level to protect participant confidentiality. Participation was entirely voluntary, and all data were used solely for research purposes.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Authors' contributions

All authors contributed to the conception and design of the study, data collection and analysis, interpretation of results, drafting and revising the manuscript, and approved the final version of the manuscript.

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Reassessing the Origins of Christian Healthcare on the Eve of Nicaea's 1700th Anniversary

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Keywords

Council of Nicaea (325 AD) • Council of Seleucia-Ctesiphon (410 AD) • Roots of Christian Healthcare • History of hospitals • *Xenodochio*

Summary

On the eve of the 1700th anniversary of the Council of Nicaea (325 AD), this paper re-examines the widespread claim that the council instituted hospitals (xenodochia) throughout the Christian world. Through a critical analysis of the sources, it shows that this belief rests on later, spurious pseudo-canon transmitted via Arabic and Syriac traditions rather than on the authentic Nicene canons.

The paper also considers the Council of Seleucia-Ctesiphon (410 AD), concluding that, despite its historical importance, it had no normative influence on Western Christian hospitality.

The study argues that Christian healthcare institutions in the Latin West emerged independently, shaped by local ecclesial, monastic, and charitable traditions.

Introduction

The historical development of hospital institutions remains a valuable field of inquiry [1].

The 1700th anniversary of the First Council of Nicaea (325 AD) (Fig. 1) offers a timely opportunity to re-examine some widespread yet historically unfounded assumptions about the origins of Christian hospitality.

One particularly persistent claim is that the Council of Nicaea formally established the obligation to found hospitals (*xenodochia*) in every inhabited area of the empire. This reassessment gains further relevance in light of Pope Leo XIV's recent visit (November 2025) to Turkey to commemorate the anniversary of the Council. This paper also considers the Council of Seleucia-Ctesiphon (410 AD) (Fig. 2) – a genuine source often invoked in this debate – and examines why it too cannot serve as a normative basis for the emergence of Western hospitality institutions.

The context

The link between “need” and “hospitality” is a product of Christianity. After the fall of the Roman Empire, illness was seen as both divine punishment and a path to redemption, reflecting human weakness and the promise of spiritual growth through suffering.

Humanity was viewed as “infirm”, afflicted by a common weakness, members of a society unable to exert control over its own environment.

Indeed, charity and care were essential aspects of living according to the Gospel, as Saint Augustine affirmed: if the body is the instrument of the soul, it should be cared for. Illness, understood as a visible sign of sin, required spiritual intervention through the works of mercy.

Matthew (25:31-46) lists the corporal works of mercy – among which feeding the hungry, visiting the sick.

Fig. 1. A fresco depicting the First Council of Nicaea at the Vatican's Sistine Salon (public domain - Wikipedia commons).



Fig. 2. Ruined palace at Ctesiphon (public domain - Wikipedia commons).



The link between the works of mercy and the concept of hospitality is clearly illustrated in the Deed of Foundation of the Roman Hospital of Santo Spirito in Sassia, signed by Pope Innocent III in 1204: the friars had the special obligation to welcome and care for the sick and the poor, with special attention to women and children.

This trend peaked with the first Jubilee Year (1300), when crowds of pilgrims sought both spiritual salvation and physical healing in the most important sanctuaries. As a result, major pilgrimage routes were established, and many hospitality centres were built to practice the works of mercy.

The birth of hospitality

The earliest evidence of nosocomial structures or *xenodochia* (housing for the stranger) in Italy traditionally date back to the 4th century AD [1].

Many sources – including non-specialist ones – erroneously attribute the creation of hospitals to the Council of Nicaea, claiming that “the Council of Nicaea established that every inhabited centre should have a place designated for reception”. However, only one academic work – written in Italian and therefore largely overlooked – challenges this long-held belief [2].

In a recent master’s thesis – written in Dutch and accessible only online to a limited audience – one of the present co-authors revisits the issue and emphasizes the need to refine our historical understanding [3].

This latter research focuses on the economic aspects of late antique Christian sites (5–early 7 cent.) in the Eastern Roman Empire, starting with Qal’at Sem’an, the shrine of Simeon Stylites the Elder, about 30 km northwest of Aleppo, in the former province of Syria Prima, within the Antiochene territory. The large scale of both the buildings and the open courtyards suggest that the site was designed to accommodate considerable numbers of visitors [3].

One of its most significant facilities for visitors to the sacred place was the *xenodocheion* – a guesthouse offering free lodging and meals.

The presence of this evangelical recommendation is traditionally traced back to the Council of Nicaea in 325 [4].

Among the various authors who reported this data, Michele Voltaggio stated that *xenodocheia* were already a ‘well-established fact’ in the first quarter of the 4th century, citing as a proof the alleged 75th canon of the Council of Nicaea, of which he also gave a translation [5]: “*The building for [the care of] pilgrims, the poor and the sick, which are usually called xenodochia and hospitia, will be distinct in each city. The bishop will choose, among the monks living in the desert, somebody who will be stranger, coming from a far-off country, and far away from his family, who will have good reference about himself and who will not be sufficient, in order that they will be enough for any expenses he will raise them at any time, through the deacons from the believers*”.

However, as the author of the master’s thesis demonstrates,

this cannot be an authentic canon of the Council of 325, as only 20 canons were actually promulgated. For his translation, Voltaggio based himself on the text that can be found in the second part of the *Sacrorum conciliorum nova et amplissima collectio* compiled by J. D. Mansi, which is a “*nova ex arabico versione*” of the “*Magni Concilii Nicaeni: Canones LXXXIV*” that was compiled by Abraham Ecchellensis [4].

As the description already indicates, this is a Latin translation of an Arabic version of the so-called 84 canons of the Council of Nicaea.

Then, Voltaggio’s Latin translation dates from 1645 and is the translation of a series of Arabic texts, since different versions have been used – versions that are often not direct translations but rather recensions [6]. However, another Latin translation of these Arabic texts, which was made in 1578 by Francesco Torrès, is also included in the work of J. D. Mansi [4, 7].

The original Arabic texts date back indirectly to an early 5th-century Syriac original that some, including A. Vööbus, attribute to Maruta, bishop of Maipherqat in the early 5th century [8]. These are not the canons but “pseudo-canons” attributed to Nicaea but originating in the context of a synod, held in 410 in the Sassanid empire at Ctesiphon and are probably based on existing ecclesiastical legislative texts.

The translation of the Syriac version reads as follows [7]: “*It is the will of the general synod that xenodocheia shall be [established] in all towns. The bishop shall elect a man from the rank of monks who is far from his home country and family, and of whom there is good testimony - he shall be an 'aksenadakra (guest master). Beds and mattresses and other items which are required for the needs of the sick and needy shall be made*”.

Contrary to the initial dating of M. Voltaggio, it is generally held that the *xenodochia* did not emerge before the middle of the 4th century. The 4th and 5th centuries are regarded as a formative period, while the 6th and early 7th centuries mark its coming of age, managed by the monks under the guidance of the bishop, and financed mainly with funds from the Church, possibly integrated by the religious community.

The Case of Ctesiphon

The Synod of Ctesiphon, held in 410 AD within the Sassanid Empire, marks an important moment in the institutional development of the Church of the East. It sought to regularize its ecclesiastical hierarchy and establish doctrinal norms.

While the Synod of Ctesiphon is an authentic and significant ecclesiastical event, it must be understood in its proper geopolitical and ecclesial context. It addressed the needs of Christian communities under Persian rule and was not intended as a universal or ecumenical council. There is no historical evidence to suggest that its canons were ever received, transmitted, or applied in the Latin West.

As such, even if the Ctesiphon synod promoted

xenodochia, this cannot be taken as the foundation for Western Christian hospitality. The lack of transmission pathways, the absence of Latin references, and the different political-religious environment all support the conclusion that Western hospitality structures developed independently.

Conclusion

A careful and critical reading of the sources leads to three main conclusions:

1. The Council of Nicaea did not institute *xenodochia* or hospital care. Claims to the contrary rely on spurious, Arabic-transmitted canons that date to centuries later and have no authority in the original conciliar tradition.
2. The Synod of Ctesiphon (410 AD), while authentic, belongs to the Eastern Church under Persian rule and has no normative value for Western ecclesiastical or charitable practices. There is no evidence of its canons being known or applied in Italy or the Latin West.
3. The emergence of Christian hospitality in Italy must be understood as an autonomous development, shaped by local traditions, monastic spirituality, and episcopal leadership.

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Author's contribution

DL: conceived the study; DL and FB: designed the study; DL, FB, RD and MM drafted the manuscript, performed a search of the literature, revised the manuscript; DL and FB: methodology; FB and RD: investigation and data curation; DL, FB, RD and MM: review; FB, DL, RD and MM: editing.

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Female genital tuberculosis: the neglected history of a neglected disease and its implications for women's health

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Keywords

Genital tuberculosis • Extrapulmonary tuberculosis • History of medicine • Infertility • Morgagni

Summary

Female genital tuberculosis (FGTB) is a rare but significant form of extrapulmonary tuberculosis that is associated with infertility and gynaecological morbidity, particularly in low-income countries. Although this disease is clinically recognised, it has been neglected in the past both in clinical research and in scientific historiography. Our study analyses the evolution of knowledge about FGTB, from the first anatomical-pathological description by Giovanni Battista Morgagni in 1744 to the most recent diagnostic and therapeutic achievements. The historical analysis shows how interest in FGTB has only accelerated since the late 19th century, with important contributions from clinicians such as Ernesto Pestalozza and Arthur M. Sutherland, who promoted a

modern approach to diagnosis through histological, bacteriological and radiological investigations. Despite advances in imaging and molecular biology techniques, FGTB still poses a diagnostic challenge due to the non-specific clinical presentation and paucibacillary nature of the disease. Manifestations often lead to late diagnosis, the reason why it represents a paradigmatic example of how a disease can remain largely invisible despite its consequences for individual and public health. We believe that FGTB should be recognised as a neglected infectious disease with clinical, epidemiological and historical implications. Its scientific and historical rediscovery can stimulate further studies and an integrated approach to women's health.

Background, aims and methods

Tuberculosis (TB) is an airborne infection caused by organisms of the *Mycobacterium tuberculosis complex* and usually affects the lungs. However, *M. tuberculosis* can cause disease in almost any part of the body. Extrapulmonary manifestations therefore include: spondylodiscitis, meningitis, gastroenteritis, urinary tract infections and genital tuberculosis. The latter is a neglected disease that nowadays occurs mainly in low-income countries and can affect both female fertility and neonatal outcomes [1]. Female genital tuberculosis (FGTB) is an important cause of morbidity worldwide, with many patients having an indolent disease which is often only diagnosed after an investigation for infertility [2]. Communicable and neglected gynecological conditions are often underreported, misdiagnosed, and as a consequence largely untreated [3]. Moreover, FGTB has never been reviewed in the history of medicine and science.

The aim of the article is to briefly describe the disease and summarise the most important scientific discoveries about FGTB in the history of medicine since the first documented written description by Giovanni Battista

Morgagni in 1744. The paper will provide a new perspective on a disease that has been neglected in the history of science and still carries a significant morbidity burden today. Scientific databases (e.g. PubMed and Google Scholar) and historical records have been reviewed, including *De sedibus et causis morborum* English translation by Benjamin Alexander, 1769.

Female genital tuberculosis

Mycobacterium tuberculosis complex comprises several closely related species, with *M. tuberculosis* being the most important one that infects humans [4]. While *M. tuberculosis* is the main cause of TB worldwide, other species like *M. africanum* and *M. bovis* can also infect humans. The lipid-rich, hydrophobic cell wall of *M. tuberculosis* contributes significantly to its resistance to the host's immune defences and many antimicrobial agents [4].

Among the extrapulmonary manifestations of TB, FGTB is a rare manifestation that leads to infertility. In fact, infertility is the most common manifestation, affecting 60-80% of women with FGTB. This is primarily due

to obstruction or deformation of the fallopian tubes, intrauterine adhesions or damage to the ovarian tissue leading to a reduced ovarian reserve. Primary infertility (never having been pregnant before) is more common than secondary infertility (having been pregnant before) and accounts for 66%-85% of infertility cases in women with FGTB. In many patients, the diagnosis is only made after infertility testing, which indicates the indolent nature of the disease [2]. Approximately 40% of women with FGTB may be asymptomatic, making diagnosis difficult. Chronic abdominal and pelvic pain is frequently reported, often accompanied by menstrual irregularities, dysmenorrhoea or postmenopausal bleeding. Symptoms such as dyspareunia and abnormal vaginal discharge may also be present [5]. Approximately 35-50% of patients with FGTB may have a completely normal physical examination, which means that the absence of abnormal signs does not rule out the disease. In cases where abnormal findings are present, they may be vague and not correlate well with the patient's symptoms. These typically include adnexal masses or signs of ascites, which may indicate more severe disease. In menopausal women, FGTB may result in an enlarged, tense and tender uterus due to the formation of a pyometra, which may mimic other conditions such as endometrial cancer or gynecological malignancies. Physical examination

may reveal vaginal fistulas; moreover fistulous tracts can be present between the genital tract and adjacent organs such as the bowel or bladder, often due to complications such as rupture of a tuberculous pyosalpinx [6].

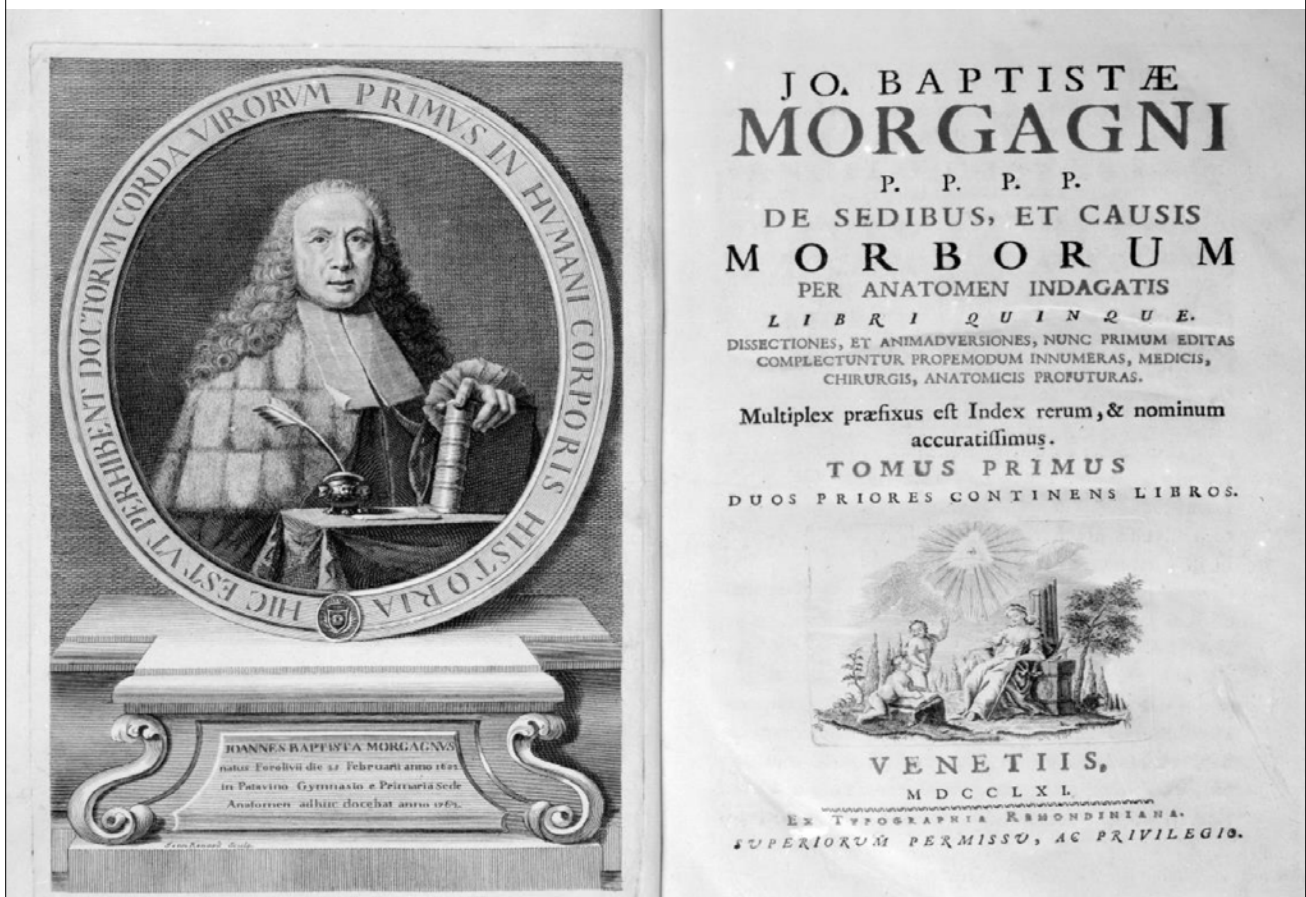
Due to its clinical presentation, FGTB can be misdiagnosed as a chronic pelvic inflammatory disease (PID) or even as a malignant disease such as ovarian and uterine cancer, as the symptoms overlap. Elevated serum CA-125 levels, which are often associated with malignancy, may also be elevated in FGTB, further complicating the diagnostic process [2, 5].

From an anatomopathological point of view, FGTB typically presents with granulomatous inflammation, which is characteristic of TB infection. In the endometrium, 46.7% of cases showed well-formed multicentric granulomas with varying degrees of caseous necrosis, indicating active infection. Granulomas can occur at different stages. The ovaries have the highest rate of acid-fast bacilli, followed by the fallopian tubes, endometrium and cervix [7].

The first written description of FGTB

It is widely accepted that the first reported FGTB was seen by Morgagni in the year 1744 and detailed in *De Sedibus et Causis Morborum* (Fig. 1), Letter XXXVIII,

Fig. 1. G.B. Morgagni, "De sedibus et causis morborum per anatomen indagatis", 1761. Wellcome Images (<http://catalogue.wellcomelibrary.org/record=b1204928>). Wikimedia Commons.



Number 34 [8, 9]. In the manual he reports about a: “*virgin of twenty years [...] having had no [...] menstrual discharges, for two years*”. The girl, before reaching the hospital of Padua, complained about “*pains*” and “*the belly began to be tumid. [...] for about a year*”. Moreover, he reports the patient complaining “*a slight fever, [...] fetid, and liquid, stools*”. After the symptoms description, Morgagni states “*she died about the middle of December, in the year 1744*”.

When describing the autopsy scan the first characteristic reported is cachexia: “*The body was emaciated*”. Later he writes about pathological findings of the abdomen: “*belly was very large, but not tense*”. As a consequence, he started the scan from there “*[...] being perforated at one side, a great quantity of water was gradually discharg’d [...] yellowish, and thin; the other less thin, and almost white. But when I examin’d [...] after [...] twenty-four hours, in a very large vessel [...] was pretty thick [...] pieces of the omentum being mix’d with it [...] neither the water, nor the body, had a putrid smell*” [10]. In the following pages he describes the inflammatory process of the peritoneum and the extension of the disease to the right and left hypochondriac region: “*The whole of the omentum [...] was torn into pieces [...] The liver [...] coher’d with the diaphragm [...] The spleen [...] was preternaturally increas’d [...] The same appearances were observ’d, here and there, on the interior surface of the peritoneum, and on the exterior of the intestines, especially of the small ones, in which, likewise, were hydatids. The largest of these was equal to the size of a small apple*” [10].

After this general description Morgagni’s move to adnexal organs and pelvis focusing on the “*peculiar disorder in the testes, the tubes, and the uterus itself*”. He reports about the macroscopic appearance of the

inflammatory process and the caseous material filling the uterus and fallopian tube. He reports the disease: “*was not discover’d in the uterus, without dissection; but in the testes, and the tubes, came spontaneously into view. For these parts had, equally on both sides [...] grown into a kind of tuberous, and shapeless mass, of a considerable size, that one could not, by any means, be known from the other [...] The surface of each of these masses was lacerated, for a considerable space, and was found to be spontaneously open*”. Interestingly, he follows describing the characteristics of the pelvic process: “*it consisted of a matter, which resembled nothing more than half-dried fuet: so white was it; of so unctuous a nature [...] it was quite inodorous*”. He proceeded to dissect the uterus with these words: “*when I cut pretty deeply into the fundus of the uterus [...] I saw that the remaining internal part of the substance [...] was converted into a matter which was similar to that just now describ’d*”. He writes the “*same matter the cavity of the fundus was filled [...] fall through the cervix, into the vagina, which was even now whitish, from the remains of this very matter*” [10].

As shown above, Morgagni’s first written description of a case of FGTB summarises most of the features of the disease, such as: tumour-like masses with caseous material, anatomical disruption of normal genital anatomy, peritoneal ascites, splenomegaly and vaginal discharge.

Main discoveries on FGTB in the following centuries

In 1857, Namias published a study full of observations on FGTB [11] and two years later, Calza gave a very accurate description of genital tuberculosis in a little girl. However, only in the late 1800s and early 1900s, research into FGTB started to be widespread. This disease was discussed at the International Congress in Rome in 1902 and in Munich in 1911 (Jung and Kronig) in relation to pregnancy. A fundamental contribution was later made by Italian clinicians. Ernesto Pestalozza (1860–1934), depicted in Figure 2, confirmed his extensive knowledge of the subject at the Congress of the Italian Society of Obstetrics and Gynaecology in 1921 [12]. “*Genital tuberculosis in infancy and prepuberty is far more common than is generally assumed*”, concluded Pestalozza in 1921 on the basis of his own anatomical and clinical observations and on the basis of an extensive world literature. He therefore considered it useful to spread awareness among general practitioners and paediatric specialists of such disease, not least because local forms of tuberculosis may leave after-effects whose influence may be largely felt in the woman’s subsequent sexual life [13].

As far as the treatment of FGTB is concerned, various invasive surgical techniques have been introduced since the late 19th century, together with heliotherapy, iodine therapy and serotherapy [12]. Interestingly different authors of the early 20th century advocated against

Fig. 2. Roberto Fantuzzi, “Ernesto Pestalozza and disciples”, 1934. Policlinico Umberto I in Rome. Courtesy by Policlinico Umberto I.



Fig. 3. Royal Samaritan Hospital and Southern General Hospital, where Arthur M. Sutherland worked. Both retrieved from Wikimedia Commons (attribution for the second image: wfmillar / Southern General Hospital / CC BY-SA 2.0.).



heliotherapy and conservative treatments in favour of surgery in genito-urinary TB [14].

A major contribution to FG TB was later made by Arthur M. Sutherland in 1944. The author wrote a thesis for his degree which was a case series and a literature review on the topic. Interestingly, he reported that the diagnosis was based solely on the histopathological examination of the endometrium and was supplemented by a bacteriological examination. He also wrote on the surgical and radiological examinations used. For example, dilation of the cervix and curettage of the uterus (with or without endometrial biopsy) were advocated. Tubal insufflation techniques and X-ray examinations were also well described [15]. Sutherland started to work in the Department of Obstetrics and Gynaecology at the Royal Samaritan Hospital and the Southern General Hospital in Glasgow (Fig. 3). Between 1 January 1950 and 15 June 1978, 638 women with proven tuberculosis of the genital tract were examined and monitored by the authoritative author. He reported that the treatment of choice at the time was a combination of rifampicin, ethambutol and isoniazid for 1 year. However, 7 different drug regimens were used to treat 581 patients. Apart from the most recent therapies, the best results were achieved with a combination of streptomycin, para-aminosalicylic acid and isoniazid for 18 months or 2 years. Interestingly, he stated that surgery should be performed if drug treatment failed [16]. Among other important publications in this field in the middle of the 20th century are those by Bret and Legros (1956), Ehrler (1966), Jameson (1935), Jedberg (1950), Ryden (1953), Schaefer (1956), ten Berge (1964) and Ylinen (1960). Each of these authors provides a detailed overview of the literature [12, 16].

Current state of the art

The nonspecific and often misleading clinical presentation of FG TB leads to frequent underdiagnosis and uncertainty regarding its true prevalence. Its occurrence is strongly associated with the prevalence of

pulmonary tuberculosis, ranging from less than 0.1% in the high-income countries to nearly 20% in India [8]. A recent meta-analysis considering different World Bank country income classification estimated the pooled prevalence of female genital tuberculosis (FGTB) at 20%. Among women with FGTB, the prevalence of overall infertility, primary infertility, and secondary infertility was 88%, 66%, and 34%, respectively [17]. FGTB is more commonly observed in low-resource settings, where HIV infection, immunosuppression, and limited access to healthcare act as additional risk factors [18, 19].

The condition primarily affects women of reproductive age and is frequently identified during infertility investigations [7]. Imaging modalities such as ultrasound, computed tomography, or magnetic resonance imaging may suggest FGTB when features like adhesions, calcifications, fibrosis, or abnormalities in endometrial thickness are present [20]. As with other forms of tuberculosis, definitive diagnosis requires the isolation of *M. tuberculosis* through culture, microscopic identification of acid-fast bacilli or PCR-based molecular assays. However, due to paucibacillary nature of FGTB, the microbiological confirmation is often difficult [8]. Histopathological examination, particularly the identification of caseating granulomas with multinucleated giant cells, provides additional diagnostic support [19]. Samples for microbiological and histopathological analysis are usually collected during hysteroscopic examination; hysterosalpingography as well is a key procedure in infertility assessment. Laparoscopy may also serve as a complementary or alternative tool [18]. While smear and culture of menstrual blood have been explored as a diagnostic option, their sensitivity remains low [21].

In cases of suspected FGTB, a comprehensive evaluation is essential to exclude TB involvement of other organs, with chest radiography routinely performed.

Overall, the diagnosis remains challenging and requires a high index of clinical suspicion, as FGTB is often misidentified as malignancy [18].

The treatment mirrors that of pulmonary tuberculosis

in terms of drug selection and total duration: 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid, rifampicin; often continuing to include pyrazinamide as part of the regimen (2HRZE/4HRZ) [22]. Drug-resistant cases follow specific guidelines. Surgery plays a role in severe cases, where abscesses drainage or adhesions breaking is needed [23, 5].

Discussion

FGTB poses a major clinical and diagnostic challenge, especially in low-income areas where tuberculosis is endemic. Unfortunately, many patients have an indolent disease which is often only diagnosed after an investigation for infertility. However, the importance of this disease has been underestimated in the past, both scientifically and clinically. In our opinion, FGTB should be considered a neglected infectious disease in daily clinical practice as much as in the history of medicine. Morgagni's description of a case of FGTB in 1744 summarises most of the features of the disease, focusing mainly on the anatomical disruption of the female genital tract and the presence of tumour-like masses. From the first documented description of macroscopic signs suggestive of FGTB to the contributions of scientists such as Pestalozza and Sutherland (Fig. 4), a slow but significant development of knowledge

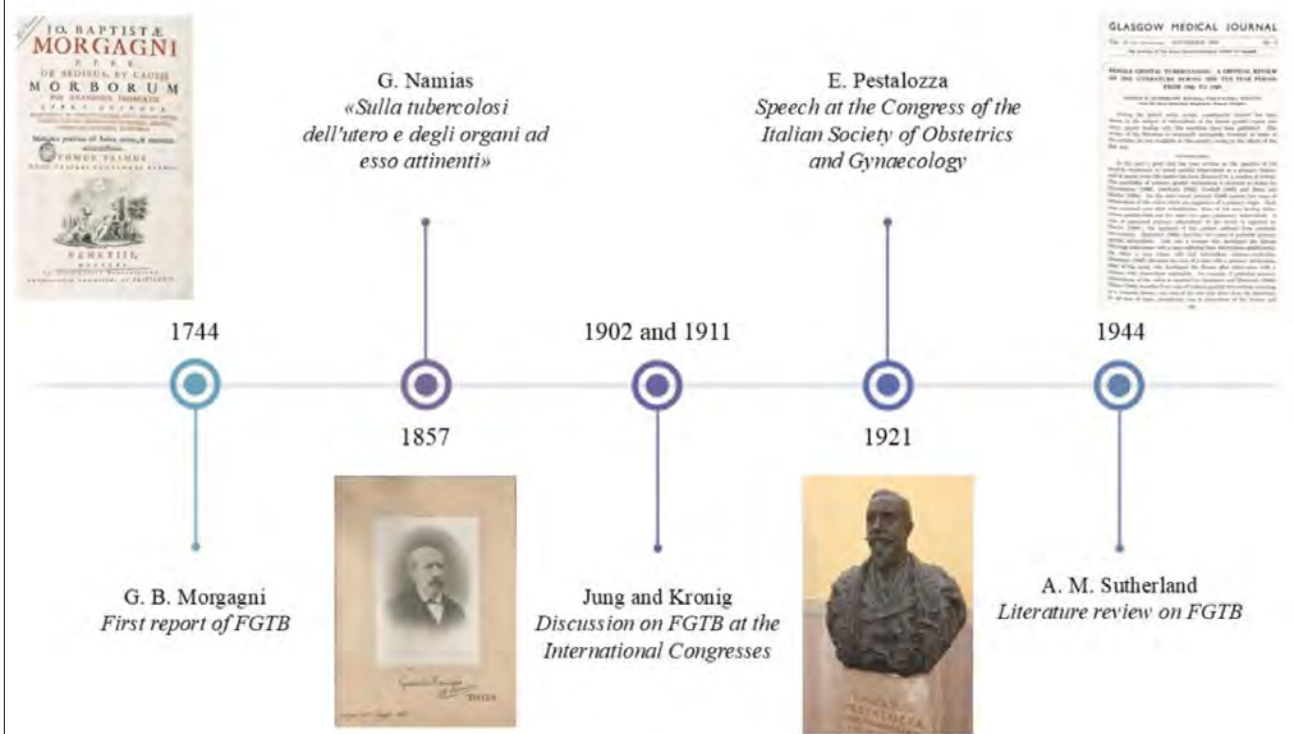
about FGTB can be observed; mainly since the late 19th century. Sutherland's work in particular provided a methodological framework for diagnosis based on histopathological, bacteriological and radiological examinations, some of which are still used today, albeit with modernized techniques.

Despite these advances, diagnosis remains problematic. The paucibacillary nature of the disease, the frequent absence of specific symptoms and the clinical overlap with other gynecological diseases make early identification difficult. Modern diagnostic tools such as PCR molecular techniques, advanced imaging and laparoscopy have increased sensitivity, but the index of clinical suspicion remains crucial. From a therapeutic point of view, the early attempts of heliotherapy, iodine therapy and serotherapy have given way to modern antitubercular therapies similar to those used in the pulmonary form (2HRZE/4HRZ). However, the clinical response can be variable and in some cases surgery is required to treat complications such as tubal abscesses or extensive adhesions.

Implications for women's health

Female genital tuberculosis (FGTB) represents a paradigmatic example of how a disease can remain largely invisible despite its potentially deep consequences for individual and public health. Although tuberculosis is

Fig. 4. Timeline of main achievements in the study of FGTB since the first documented report. Original image (created by the authors with BioRender Image and Illustration Software) adapted from: Morgagni de sedibus 1761 (Wikimedia Commons), Portrait photograph of G. Namias (held in the Historical Archive of the Istituto Veneto di Scienze, Lettere ed Arti), Photo of E. Pestalozza (for Himetop – The History of Medicine Topographical Database) and SUTHERLAND AM. Female genital tuberculosis: a critical review of the literature during the ten year period from 1940 to 1950. Glasgow Med J. 1950 Sep;31(9):279-95. PMID: 14778522; PMCID: PMC5970847.



often perceived as a disease of the past or as a condition primarily affecting the lungs, its extrapulmonary forms continue to pose important diagnostic and therapeutic challenges. Among these, FGTB is particularly meaningful because of its impact on reproductive health, fertility, pregnancy outcomes, and psychosocial well-being.

The persistence of FGTB in the twenty-first century features the complex interplay between infectious diseases, social determinants of health, and gender-related disparities in healthcare. In many settings, women affected by FGTB experience delayed diagnosis due to the nonspecific nature of symptoms, limited awareness among healthcare providers, and barriers to accessing specialized care. As a result, the disease frequently goes unrecognized for extended periods, delaying diagnosis and treatment. Consequently, many patients are diagnosed only at advanced stages of the condition, when substantial and often irreversible damage to the reproductive tract has already occurred.

FGTB offers an important lens through which to examine the principles of gender medicine. Historically, many aspects of women's health have received less scientific attention than conditions affecting the general population or predominantly male cohorts.

We believe that this “diagnostic invisibility” not only delays appropriate treatment but also increases the risk of severe long-term consequences, including infertility, chronic pelvic pain, and psychological distress.

Addressing this gap requires healthcare systems and research plans to adopt a more gender-sensitive approach, one that recognizes the unique manifestations of disease in women, prioritizes timely diagnosis, and ensures equitable access to care and scientific attention. The historical and scientific rediscovery of FGTB therefore extends beyond the study of a single disease. It encourages reflection on how medical knowledge is generated, which diseases attract scientific attention, and which patient populations may remain underserved.

Revisiting the history of FGTB reveals how changing epidemiological patterns, diagnostic technologies, and social attitudes toward women's reproductive health have shaped our current understanding of the disease. Addressing the persistent challenges associated with FGTB requires a truly multidisciplinary effort involving gynecologists, infectious disease specialists, microbiologists, pathologists, epidemiologists, public health professionals, and experts in gender medicine. Such collaboration is necessary to close existing knowledge gaps, improve epidemiological surveillance, and develop more accurate and accessible diagnostic strategies.

Furthermore, greater awareness among clinicians and policymakers can promote earlier recognition of the disease and facilitate timely intervention.

Increased investment in research on FGTB may not only improve prevention and treatment strategies but also contribute to a more comprehensive understanding of the relationship between infectious diseases and women's health. In this sense, FGTB serves as a reminder that

diseases affecting reproductive health should not be viewed as niche conditions, but rather as important components of global health and social well-being.

Finally, integrating historical perspectives, modern scientific advances, and the principles of gender medicine can help transform FGTB from a neglected condition into a recognized public health priority. Such an approach has the potential to reduce diagnostic delays, preserve reproductive health, improve quality of life, and promote a more equitable and inclusive model of healthcare for women worldwide.

Conclusion

FGTB remains a neglected condition with major consequences for women's reproductive health. Earlier diagnosis and a gender-sensitive multidisciplinary approach are essential to reduce its burden. History may help to recognize FGTB as a global health priority and promote equity in women's healthcare.

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Conflict 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.

Authors' contribution

OS, SDB: designed the study. OS, AST, VG, MCDS, LZ, VZ, MM: drafted the manuscript. OS, AST, VZ, MM: performed a search of the literature. OS, AP, MM: data curation. AP, MCDS, LZ, MM, SDB: revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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