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Retractions Associated with Kazakhstani Institutes in 2024/2025: Lessons for Medical Researchers in Kazakhstan

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Abstract

Medical researchers in Kazakhstan, empowered by a publication-based rewards system, may be tempted to engage in unethical behavior in order to achieve success. A recent (DOI: 10.1007/s10805-025-09624-0) assessment of 36 Scopus-indexed retractions from 2013–2023, peaking in 2016–2019, revealed that the most frequent cause of retractions was fake peer review, although some papers were also retracted due to engagement with paper mills. In a bid to offer some continuity to and expansion of that assessment, retractions of authors affiliated with Kazakhstani institutes were assessed using the Retraction Watch database for the 1 January 2024 to 3 April 2025 period. A total of 19 retractions were identified, nine each in Springer Nature and Wiley journals, and one in PLoS ONE, and with seven retractions having the affiliation "Al-Farabi Kazakh National University". The most common reason (89%) was compromised or manipulated peer review, while authors in 26% of retraction notices expressed disagreement with the retractions. Finally, 73% of emails listed for the corresponding authors were not institutional emails. The take-home message of this short analysis for medical researchers in Kazakhstan is to appreciate that the risks of abuses of the publication process far outweigh any benefits that may have accrued as a result of deceptive practices.

Key words: Central Asia, international collaboration, peer review, post-Soviet countries, retracted papers

Dear *Journal of Clinical Medicine of Kazakhstan* Editors,

The massive rise in scientific productivity by Kazakhstani authors in two of the largest scientific databases, Clarivate's Web of Science (WoS) and Elsevier's Scopus, especially in 2012–2024, can be attributed to – in large part – the ability to receive monetary rewards for publishing in journals indexed in these databases, following multiple reforms between 2011 and 2024 by the Ministry of Education and Science and the Ministry of Science and Higher Education of Kazakhstan, aspects that were debated in some length elsewhere [1]. Ultimately, a national desire to gradually shift away from the Soviet model and towards the European Union model of higher education also involved embracing rewards systems that are associated with research and publication [2 – 4]. Individual productivity would then also translate into amplification of the educational profile of Kazakhstani universities in international university rankings [5].

Such rewards-based productivity allowed the Republic of Kazakhstan (hereafter Kazakhstan) to achieve high productivity [6 – 10], including through collaborations with post-Soviet countries as well as Russia [11, 12], such that it was ranked third among eight Central Asian nations in terms of the volume of WoS-indexed papers [13].

However, this rewards system, which would eventually impact all spheres of academic achievement, such as academic titles, positions, research grants, awards, and scholarships, began to engender a "publish or perish" research and publishing culture [14], which, as expected, had the potential to lead to abuses of the system to amplify rewards, including publications in so-called "predatory" journals [15], even some that had presumably infiltrated scientific databases like Scopus [16]. Another dishonest strategy, which involved the purchase of papers, datasets, or authorship slots from "paper mills", as was documented in Russia [17, 18], often employed a fake email address for the corresponding author to game peer review, such

as the submission of fabricated peer reviewer reports i.e., fake peer review [19]. Finally, some of that productivity involved the reliance on plagiarism [20].

The logical consequence of gaming bibliometric indicators and the publication system [21] as a way to advance careers and rewards, or engaging in deceptive or unethical practices to achieve success, is that some of that activity will be detected, with negative consequences, the most tangible being in the form of retractions, i.e., the removal or scientific cancellation of a published document. Several studies in recent years on retractions by authors with a Kazakhstani affiliation indicated one or more peaks in the 2016–2019 period, primarily associated with a cluster of retractions of almost 50 papers published in *Elsevier's Thinking Skills and Creativity*, with most retractions being related to the abuse of or fake peer review, an association with paper mills, plagiarism, and self-plagiarism or duplication [22 – 24]. A recent analysis of retractions associated with Kazakhstani affiliations between 2013 and 2023 found that 26 of 36 Scopus-indexed retractions were associated with fake peer review, while none of the 36 retracted papers indicated an institutional email for the corresponding author [1].

To expand this discourse on retractions associated with Kazakhstani affiliations, the Retraction Watch database [25] was sourced between 25 March and 3 April 2025, to identify any documents, while the corresponding retraction notices (RNs) were consulted to ascertain the reasons for retraction and other aspects associated with the retractions. A total of 19 retractions were identified (Table 1). Of the 19 retractions, nine each were of papers published in Springer Nature and Wiley (including Hindawi) journals, and one in PLoS ONE (Table 1), 12 papers did not have international collaborations (i.e., only Kazakhstani affiliations were listed), and Al-Farabi Kazakh National University was associated with 7/19 or 37% of the retractions (Table 2). The most frequent reason for retraction, according to the RNs, was compromised or manipulated peer review in 17/19 (89%) of the cases, with at least one author expressing disagreement [26] with the retraction in five (26%) of the RNs, while the authors of the remaining retracted papers either did not respond, did not explicitly express disagreement with the retraction, or could not be contacted by the editor, journal or publisher (Table 2). Some of the RNs listed multiple reasons for retraction (Table 2), but the wording or the specificity of the issue was either vague, ambiguous, or euphemistic – such as a list of six possible but not clearly defined – reasons for three Wiley RNs, specifically associated with Hindawi journals, emphasizing that a crisis in the integrity of RNs, especially with respect to their transparency [27], may be emerging. Of the 26 email addresses listed for corresponding authors (including of papers where there were multiple corresponding authors and thus emails), 73% (19/26) were not institutional emails or several email addresses had suspect suffixes that did not correspond with the stated institution (for example, the suffix "in" in @murdoch.in suggesting an Indian source rather than a Kazakhstani affiliation), perhaps implying their association with paper mills [28]. Emails addresses not shown in Tables 1 and 2 for privacy reasons.

Kazakhstan has undergone a complex number of regulatory reforms since 2011 that have edged the higher education system closer to that of the EU, and further from the Russian and former Soviet systems. While those reforms were surely well-intentioned, they are strongly determined by bibliometric indicators, such as the Clarivate Impact Factor, or indexing in WoS or Scopus, driving a sector of the Kazakhstani academia to cheat or otherwise abuse trust in ethical norms to gain an academic advantage. Seven of the 19 retractions have a direct or indirect link with the medical sciences. The results of this small analysis send a strong but unambivalent message to medical researchers that engage in – or might be thinking of engaging in – such dubious research or publication practices to advance their careers and publication records, or curriculum vitae. Medical researchers need to appreciate that engaging in such practices might incur risks that outweigh the benefits if and when those abuses are discovered, and when ethical infractions translate into retractions. Those actions will then be converted into bruised institutional reputations, even though international institutional rankings have not yet begun to factor in retractions when assessing universities' educational and scientific performance [29].

Table 1 Background of the 19 retractions associated with Kazakhstani institutes [1]

#	Paper DOI	RN DOI	Journal	Publisher
1	10.1007/s42452-023-05405-9	10.1007/s42452-024-06435-7	*Discover Applied Sciences*	Springer Nature
2	10.1007/s11696-018-0539-y	10.1007/s11696-024-03801-y	*Chemical Papers*	Springer Nature
3	10.1007/s12029-020-00402-2	10.1007/s12029-024-01137-0	*Journal of Gastrointestinal Cancer*	Springer Nature
4	10.1371/journal.pone.0283251	10.1371/journal.pone.0309086	*PLoS One*	PLoS
5	10.1007/s10780-021-09434-4	10.1007/s10780-024-09518-x	*Interchange*	Springer Nature
6	10.1002/bsd2.226	10.1002/bsd2.354	*Business Strategy and Development*	Wiley
7	10.1002/bsd2.225	10.1002/bsd2.353	*Business Strategy and Development*	Wiley
8	10.1007/s11356-023-25836-6	10.1007/s11356-024-32823-y	*Environmental Science and Pollution Research*	Springer Nature
9	10.1007/s11356-022-19865-w	10.1007/s11356-024-32660-z	*Environmental Science and Pollution Research*	Springer Nature
10	10.1007/s11010-021-04314-y	10.1007/s11010-024-04972-8	*Molecular and Cellular Biochemistry*	Springer Nature
11	10.1002/ajmg.b.32893	10.1002/ajmg.b.32972	*American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*	Wiley
12	10.1007/s13198-021-01278-6	10.1007/s13198-024-02282-2	*International Journal of System Assurance Engineering and Management*	Springer Nature
13	10.1002/crq.21343	10.1002/crq.21425	*Conflict Resolution Quarterly*	Wiley
14	10.1111/ppl.13686	10.1111/ppl.14208	*Physiologia Plantarum*	Wiley
15	10.1002/num.22719	10.1002/num.23089	*Numerical Methods for Partial Differential Equations*	Wiley
16	10.1155/2022/5845870	10.1155/2024/9785806	*Journal of Food Quality*	Hindawi (Wiley)
17	10.1155/2022/2275517	10.1155/2024/9858153	*Journal of Food Quality*	Hindawi (Wiley)
18	10.1007/s10529-021-03193-z	10.1007/s10529-024-03470-7	*Biotechnology Letters*	Springer Nature
19	10.1155/2022/8615242	10.1155/2024/9849584	*Oxidative Medicine and Cellular Longevity*	Hindawi (Wiley)

[1] As assessed on the Retraction Watch database (see text for details)
Abbreviations: DOI, digital object identifier; RN, retraction notice

Table 2 Details of the 19 retractions associated with Kazakhstani institutes

#1	Affiliations (Kazakhstan)	Collaborating countries	Main reason(s) for retraction	Disagreement with retraction2
1	Al-Farabi Kazakh National University	Ethiopia, India, Oman, Peru	Compromised editorial handling and peer review process, inappropriate or irrelevant references or not being in scope of the journal or guest-edited issue	1 of 8
2	The Institute of Nuclear Physics of the Republic of Kazakhstan	Russia	Data (figure) concerns	1 of 6
3	Kazakh-Russian Medical University; Kazakh Research Institute of Oncology and Radiology	None	Compromised peer review	0 or not indicated
4	L.N. Gumilyov Eurasian National University; High School of Nature Science; Eurasian Center for Innovative Development; Toraighyrov University	Hungary	Concerns about authorship, competing interests, peer review, data; citations not supported by references	0 or not indicated
5	Abai Kazakh National Pedagogical University	None	Irregularities with authorship, peer review, and submission process	0 or not indicated
6	University of International Business; Kazakh-German University; Almaty Technological University; Almaty Management University	None	Compromised peer review	0 or not indicated
7	Baishev University; Narxoz University; Al-Farabi Kazakh National University; Kostanay Social and Technical University named after Academician Z. Aldamzhar; Toraighyrov University	None	Compromised peer review	0 or not indicated
8	Toraighyrov University	None	Irregularities with peer review and submission process	0 or not indicated
9	Nazarbayev University	Iran, USA	Data (figure) concerns	11 of 13
10	West Kazakhstan Marat Ospanov Medical University	None	Irregularities with authorship, peer review, and submission process; IRB missing	0 or not indicated
11	Al-Farabi Kazakh National University; Scientific Center of Obstetrics, Gynecology and Perinatology	None	Compromised peer review	0 or not indicated
12	Kazakh National Agrarian University	None	Compromised peer review; plagiarism	0 or not indicated
13	Eurasian Law Academy named after D.A. Kunaev; Suleyman Demirel University; Caspian University; Almaty City Bar Association	None	Compromised peer review	0 or not indicated
14	Institute of Plant Biology and Biotechnology	None	Compromised peer review	0 or not indicated
15	Zhetysu State University named after I. Zhansugurov; Al-Farabi Kazakh National University	None	Compromised peer review	1 of 2
16	Al-Farabi Kazakh National University	Ethiopia, India, Peru, Saudi Arabia	Compromised peer review and 5 other possibilities	0 or not indicated
17	Al-Farabi Kazakh National University	Ethiopia, India	Compromised peer review and 5 other possibilities	0 or not indicated
18	Republican Collection of Microorganisms of the Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan	None	Compromised peer review	1 of 5
19	Al-Farabi Kazakh National University	Australia, Chile, Ecuador, Hong Kong, India, Malaysia, Pakistan, Portugal, Romania, Spain	Compromised peer review and 5 other possibilities	0 or not indicated

[1] See Table 1 for background details
[2] Numbers indicate number of authors. For example, for #15, 1 of 5 authors explicitly disagreed with the retraction

Kazakhstani medical researchers would benefit from investing some time in appreciating the issue of retractions, especially considering that of a total of 129 retractions for Kazakhstan, using the Retraction Watch database, revealed that 13 (or about 10%) of them were related to medicine [30].

The analysis in this letter has a limitation: it only includes a sample size of 19 retractions. An updated and more comprehensive analysis of retractions in Kazakhstani research institutes relative to other post-Soviet nations might reveal some interesting trends.

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The Use of AI in the Diagnosis of Oral Diseases: a Bibliometric Analysis

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Abstract

This study presents a comprehensive bibliometric analysis of artificial intelligence (AI) applications in the diagnosis of oral diseases, aiming to explore publication trends, identify key contributors, and highlight emerging research directions. Utilizing data from the Web of Science and Scopus databases, we analyzed 90 relevant publications after refining an initial pool of 179 articles. The results reveal a significant increase in research output since 2016, with a peak in 2023, followed by a decline in 2024. Early research, dating back to 1996, focused on decision-support systems, while recent advancements emphasize deep learning, machine learning, and radiographic imaging for improved diagnostic accuracy. Keyword analysis identified "artificial intelligence," "deep learning," and "diagnosis" as central themes, reflecting the field's focus on technological innovation in oral healthcare. Geographically, China, the United States, and India emerged as leading contributors, with strong international collaborations observed between these countries and regions such as Europe and the Middle East. Despite the growing interest, challenges such as funding constraints and regulatory hurdles may have contributed to the recent decline in publications. This study underscores the transformative potential of AI in oral disease diagnosis and provides a roadmap for future research, emphasizing the need for global collaboration, inclusivity, and continuous monitoring of emerging trends to advance precision dentistry.

Keywords: Artificial intelligence, Oral health, Diagnoses, Machine Intelligence

Introduction

Artificial intelligence (AI), a subdomain of computer science, has revolutionized various fields, including healthcare, through its ability to mimic human cognitive processes such as reasoning, problem-solving, and decision-making [1, 2]. With rapid advancements in machine learning (ML), natural language processing, and computer vision, AI has become a critical component of modern medical research and clinical practice [3]. These technologies enable the analysis of vast amounts of data, improving disease prediction, diagnosis, and treatment accuracy, thus benefiting both patients and healthcare providers. Since 2019, there has been a substantial increase in publications dedicated to the application of AI in oral diseases, particularly in the analysis of imaging data and the diagnosis of conditions such as periodontitis, bone fractures, and dental caries [4, 5]. Recent studies have indicated that AI in dentistry is rapidly evolving, with a focus on developing medical devices and clinical decision support systems based on innovative AI algorithms to advance precision dentistry [6, 7].

The transformation is evident even in the field of oral health. Oral diseases, such as dental caries, periodontal diseases and oral cancers pose a major public health challenge globally [8-10]. Early diagnosis is imperative for the treatment and prevention of these diseases. By processing imaging data, medical records and clinical input from circulating data, AI technologies provide services that support dental professionals and assist in the diagnosis and management of oral diseases [11, 12].

Although the application of AI in healthcare—specifically in critical care, among other specialties—has received attention, the application of bibliometric analyses to better understand this field with respect to oral health is still lacking. Bibliometric analysis is a powerful method that can be utilized to identify

research trends, influential studies, important contributors, and international collaborations in a field [13]. The insights gained from analyzing the available literature will provide a roadmap for the continued development and application of AI in the diagnosis and management of oral diseases, offering valuable guidance to researchers, clinicians, and policy makers.

To address this gap, this study presents an in-depth bibliometric analysis of AI applications in diagnosing oral diseases. The goal is to explore publication trends, identify key authors and institutions, analyze the frequency of keywords, and highlight emerging research directions in this growing field. By doing so, this study provides a foundation for the further development and integration of AI technologies in oral healthcare.

Methods

Search strategy

This study was based on an extensive investigation utilizing the advanced search functionalities of the Web of Science and Scopus databases in January 2025. The data selection process commenced with a focused examination of article abstracts, titles, and keywords. Boolean and Wildcard search operators were applied to identify relevant keywords, as outlined in Table 1. Metadata extraction was guided by specific filters, including language (English) and article type, with no restrictions imposed on the publication year.

Table 1 Queries to search in Scopus and Web of Science databases for the bibliometric analysis of the use of AI in the diagnosis of oral diseases

No	Queries
#1	"Diagnoses" OR "Diagnose" OR "Diagnoses and Examinations" OR "Diagnoses and Examination" OR "Examination and Diagnoses" OR "Examinations and Diagnoses" OR "Antemortem Diagnosis" OR "Antemortem Diagnoses" OR "Diagnoses, Antemortem" OR "Diagnosis, Antemortem" OR "Postmortem Diagnosis" OR "Diagnoses, Postmortem" OR "Diagnosis, Postmortem" OR "Postmortem Diagnoses"
#2	"Artificial Intelligence" OR "Intelligence, Artificial" OR "Computer Reasoning" OR "Reasoning, Computer" OR "AI (Artificial Intelligence) " OR "Machine Intelligence" OR "Intelligence, Machine" OR "Computational Intelligence" OR "Intelligence, Computational" OR "Computer Vision Systems" OR "Computer Vision System" OR "System, Computer Vision" OR "Systems, Computer Vision" OR "Vision System, Computer" OR "Vision Systems, Computer" OR "Knowledge Acquisition (Computer) " OR "Acquisition, Knowledge (Computer) " OR "Knowledge Representation (Computer) " OR "Knowledge Representations (Computer) " OR "Representation, Knowledge (Computer)"
#3	"Oral health" OR "Health, Oral" OR "Disease, Mouth" OR "Diseases, Mouth" OR "Mouth Disease" OR "Oral Medicine" OR "Medicine, Oral" OR "Stomatology"
#4	#1 AND #2 AND #3

Table 2 Codes were used to merge Scopus and Web of Science exported data in RStudio

```
library(bibliometrix)
library(openxlsx)
## importing web of science dataset
web_data<-convert2df("abs.txt")
## importing scopus dataset
scopus_data<-convert2df("abs.
bib",dbsource="scopus",format="bibtex")
##combined both datasets
combined<-mergeDbSources(web_data,scopus_data,remove.
duplicated=T)
##exporting file
write.xlsx(combined,"combinedabs.xlsx")
```

To ensure a comprehensive and high-quality dataset, the analysis included peer-reviewed original and review journal articles that were accessible via institutional subscriptions to the Web of Science and Scopus databases. Conference papers, book chapters, and editorials were excluded to maintain a focus on primary research contributions. To ensure consistency in citation information amid the rapid updates of publications, the retrieval process was independently conducted by two researchers (M.A.K. and A.T.) within a single day (January 27, 2025). Any disagreements were resolved through discussions with a senior dentist (M.B.I.) until a consensus was achieved. To measure the agreement level between the two researchers regarding study inclusion and data extraction, the Cohen's kappa coefficient was computed. This statistic was determined by comparing the decisions of the researchers across all the studies assessed. The calculated Cohen's kappa coefficient was 0.80, reflecting a substantial level of agreement between the researchers.

Data extraction and analysis

The extracted metadata was stored in text and BibTeX formats and then consolidated into an Excel file using RStudio (Table 2). To ensure the accuracy and reliability of the primary dataset, a refinement process was undertaken. This involved removing duplicates and excluding articles with unrelated titles and abstracts. Bibliometric analysis and data management were subsequently conducted using the Bibliometrix package (version 4.1.3) and the Biblioshiny web application within the RStudio environment (version 2023.09.1+494, PBC, Boston, MA) [14]. As a result, the initial pool of 179 publications was refined to a final dataset of 90 documents (Figure 1).

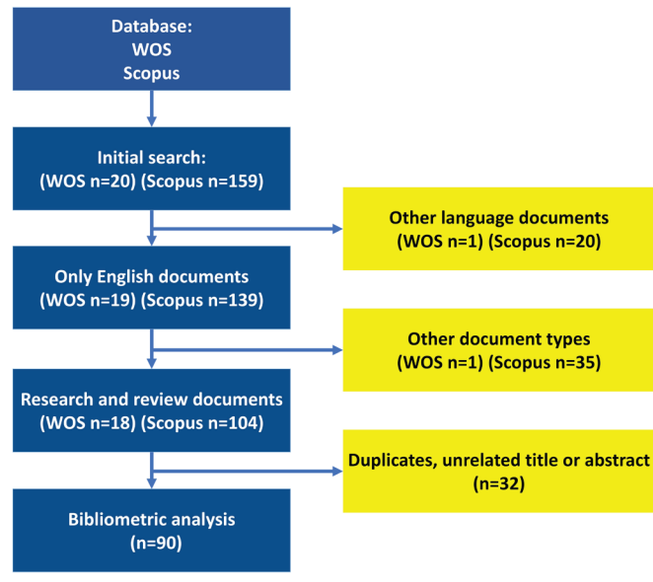

Figure 1 – Flow diagram for selecting articles in the bibliometric analysis of the use of AI in the diagnosis of oral diseases

Results

Growth in publications

The annual scientific production of articles related to AI in oral disease diagnosis is depicted in Figure 2. During the initial years, scientific production remained relatively low, with only sporadic publications. A few minor peaks around 1985 and 1995 indicate occasional research activity, but overall, the number of articles published annually was negligible. Between 2000 and 2015, a slow yet consistent increase in scientific output can be observed.

However, the rate of increase remained moderate, without any significant surges. A noticeable rise in the number of published articles began around 2016, reflecting a period of heightened research activity. This period marks a transition from steady growth to accelerated productivity. The most significant spike in scientific production occurred in 2023, reaching an all-time high. Following the peak in 2023, a sharp decline in the number of published articles is observed in 2024.

The analysis of highly cited studies on AI in oral disease diagnosis reveals that interest in this field dates back to 1996, much earlier than the recent surge in AI-driven dental research (Table 3).

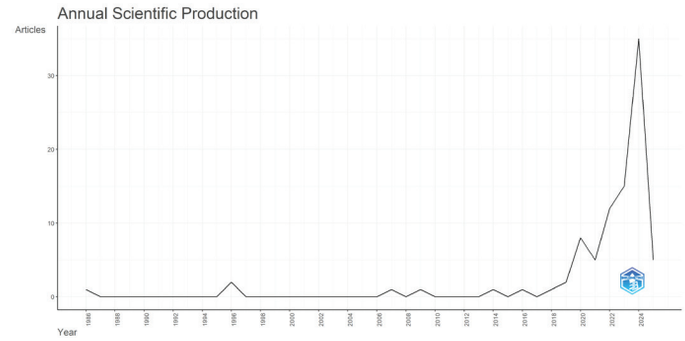

Figure 2 – Annual scientific production of articles related to AI in oral disease diagnosis

Table 3 Top 10 most cited papers relating to the use of AI in the diagnosis of oral diseases.

Ranking	Study references	Title of the document	Journal Name	Total citations	DOI
1	You W [16], 2020	Deep learning-based dental plaque detection on primary teeth: A comparison with clinical assessments	BMC Oral Health	98	10.1186/s12903-020-01114-6
2	Ahmed N [17], 2021	Artificial intelligence techniques: analysis, application, and outcome in dentistry - A Systematic review	Biomedical Research International	96	10.1155/2021/9751564
3	Leite A [21], 2020	Radiomics and machine learning in oral healthcare	Proteomics – Clinical Applications	84	10.1002/prca.201900040
4	Ezhov M [18], 2021	Clinically applicable artificial intelligence system for dental diagnosis with CBCT	Scientific Reports	80	10.1038/s41598-021-94093-9
5	Patil S [5], 2022	Artificial intelligence in the diagnosis of oral diseases: applications and pitfalls	Diagnostics	65	10.3390/diagnostics12051029
6	Muthu R K M [3], 2009	Automated classification of cells in sub-epithelial connective tissue of oral sub-mucous fibrosis—An SVM based approach	Computers in Biology and Medicine	52	10.1016/j.compbiomed.2009.09.004
7	Cui Y [23], 2022	Developments in diagnostic applications of saliva in human organ diseases	Medical Novel Technology and Devices	48	10.1016/j.medntd.2022.100115
8	Al K A [20], 2019	Detection of dental diseases from radiographic 2d dental image using hybrid graph-cut technique and convolutional neural network	MEAS J INT MEAS CONFED	44	10.1016/j.measurement.2019.06.014
9	White S [13], 1996	Decision-support systems in dentistry	Journal of Dental Education	36	PMID: 8594103
10	Cha J [17], 2021	Panoptic Segmentation on Panoramic Radiographs: Deep Learning-Based Segmentation of Various Structures Including Maxillary Sinus and Mandibular Canal	Journal of Clinical Medicine	29	10.3390/jcm10122577

The study by White S. [15] on decision-support systems in dentistry highlights that researchers have long recognized AI's potential in improving diagnostics and clinical decision-making. Although modern advancements in deep learning and machine learning have significantly enhanced AI applications, this early research laid the groundwork for the technology's evolution in dental healthcare.

In recent years, AI research in dentistry has expanded rapidly, with studies focusing on deep learning, machine learning, and radiographic imaging. The most cited studies, such as You W. [16] and Ahmed N. [17], highlight AI's role in dental plaque detection and systematic reviews of its applications. Other research, including Ezhov M. [18] and Cha J. [19], explores AI-powered imaging techniques like cone beam computed tomography (CBCT) and panoramic radiographs. Additionally, interdisciplinary approaches, such as hybrid AI techniques combining graph-cut methods with convolutional neural networks, reflect the diversity and innovation in this field [20].

Keywords

After filtering keywords based on a minimum occurrence threshold of three, 114 unique keywords were visualized to analyze their relevance and frequency. The visualization highlighted the most relevant keywords related to the study, including artificial intelligence, human, deep learning, diagnosis, and machine learning. These keywords represent critical themes in the research domain.

The distribution of keyword occurrences underscores artificial intelligence as the most frequently occurring keyword, appearing 70 times, followed by human with 55 occurrences. Other notable terms include diagnosis with 31 occurrences, deep learning with 30, mouth disease with 30, and machine learning with 28, reflecting the focus on technology-driven diagnostic methods for oral diseases.

Countries/regions and institutions

From 1996 to 2023, the production of articles on AI in dentistry has varied across countries, with notable trends observed for China, India, Iran, Saudi Arabia, and the USA. The USA consistently demonstrated high levels of publication, peaking in 2020. China exhibited rapid growth, with a sharp increase starting around 2020 and reaching its peak in 2023. India showed gradual growth, with a notable acceleration in recent years. Iran experienced moderate but steady growth, while Saudi Arabia displayed a slower yet consistent increase in publications. The trends highlight the growing global interest in AI applications within dentistry, with China and the USA emerging as leading contributors (Figure 4).

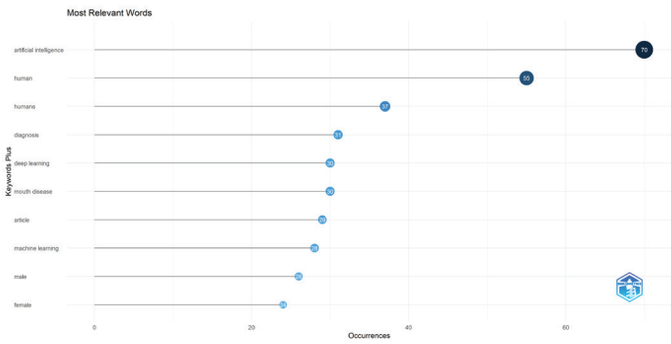

Figure 3 – Most relevant keywords based on their frequency of occurrence in studies related to AI applications in diagnosis of oral diseases

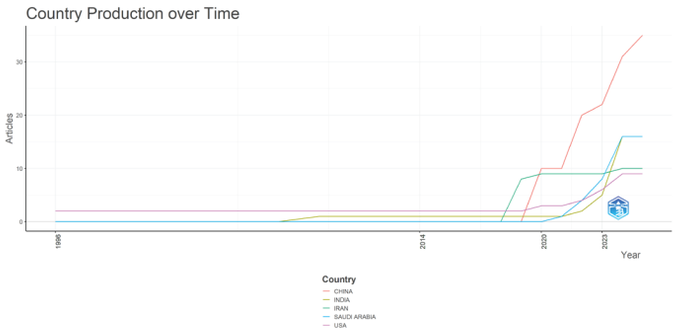

Figure 4 – Trends in AI in dentistry publications by country in diagnosis of oral diseases

Authors

The figure 5 illustrates the most relevant authors in AI research on diagnosis of oral diseases, based on the number of published documents. Among them, Li W stands out as the most prolific author, with four publications. Several other authors, including Araújo A, Jacobs R, Kowalski L, Lopes M, Martins M, Pearson A, Santos-Silva A, Vargas P, and Wang S, have each contributed three publications. The visualization highlights the key contributors in this research domain, demonstrating a relatively balanced distribution of publications among the top authors.

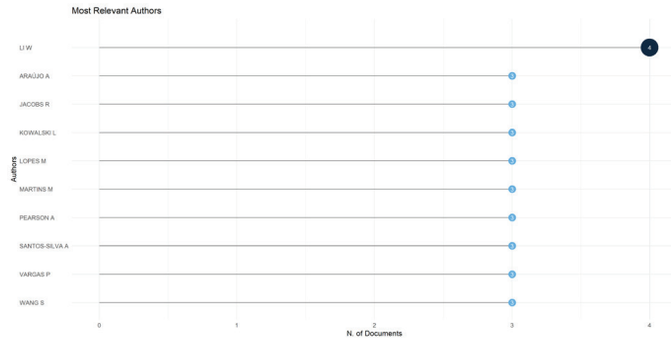

Figure 5 – Most relevant authors in AI research in diagnosis of oral diseases

Journals

The figure 6 presents the most relevant sources publishing research on AI in the diagnosis of oral diseases. The Journal of Oral Pathology and Medicine (impact factor, IF 5.9), Journal of Pharmacy and Bioallied Sciences (IF 1.4), and Oral Diseases (IF 7.6) are the top three sources, each contributing four publications. BMC Oral Health (IF 3.9) and the Journal of Clinical Medicine (IF 4.7) follow with three publications each. Additionally, several other journals, including Applied Sciences-Basel (IF 5.3), Bioengineering-Basel (IF 4.0), British Dental Journal (IF 3.1), Computers in Biology and Medicine (IF 11.7), and Diagnostics (IF 4.7), have published two articles each. This distribution highlights the key academic platforms for disseminating research in this field.

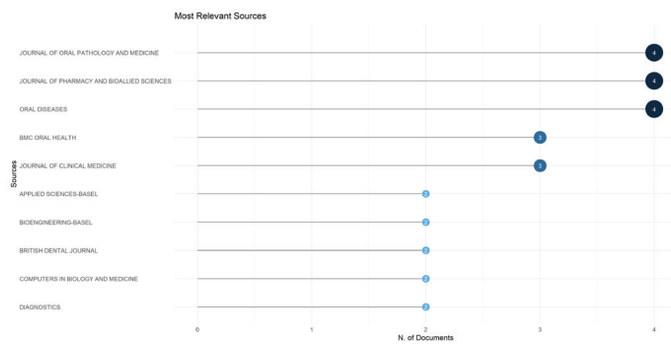

Figure 6 – Most relevant sources publishing research on AI in diagnosis of oral diseases

Countries collaboration

The Country Collaboration Map showcases international research partnerships, with darker colors denoting greater publication contributions (Figure 7). The most active countries are China, the United States, and India, which are involved in significant global collaborations. Strong research networks are observed between these countries and regions such as Europe, the Middle East, and South America. Notably, the United States and China maintain strong collaborations with multiple countries, reinforcing their role as key drivers of international research efforts. European countries such as the United Kingdom, Germany, and Italy also display significant involvement, contributing to interdisciplinary and multinational

research initiatives. This suggests a more diverse research environment, dominated now by developing countries, especially in Asia and South America. This trend indicates that emerging economies are becoming more engaged in scientific advancements and forming collaborations with leading research hubs.

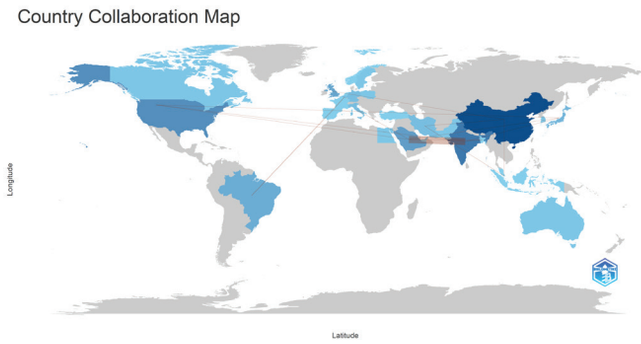

Figure 7 – Country collaboration map in AI applications in oral health

Authors collaboration

The co-authorship network visualization illustrates collaboration patterns among researchers in the field of artificial intelligence applied to oral disease diagnosis. Each node represents an author, while the edges between nodes indicate co-authorship relationships. The size of the nodes corresponds to the number of connections, highlighting the most influential authors within the research domain.

Distinct colors denote different collaboration clusters, suggesting the presence of research groups with frequent co-authorship. Notably, key contributors such as Araujo A, Kowalski L (University of São Paulo Medical School, Brazil), Lopes M (Department of Oral Diagnosis, Piracicaba Dental School, Brazil), Santos-Silva A (Department of Oral Diagnosis, Piracicaba Dental School, Brazil), and Vargas P (Department of Oral Diagnosis, Piracicaba Dental School, Brazil) exhibit high connectivity, indicating their significant role in shaping the research landscape. The visualization provides insights into the extent of interdisciplinary collaboration and potential research gaps, underscoring the necessity for broader international cooperation to enhance knowledge dissemination and innovation in this field (Figure 8).

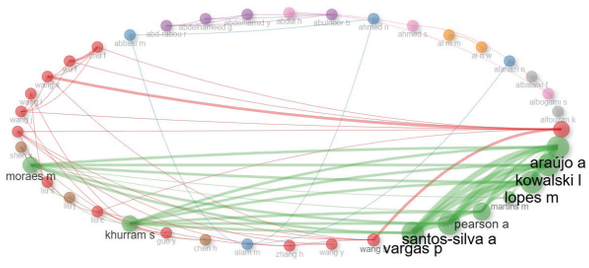

Figure 8 – Authors Collaboration Network

Institutional collaboration

The institutional collaboration network (Figure 9) visualizes the cooperative relationships between research institutions involved in studies on artificial intelligence applications in oral disease diagnosis. Notably, University Hospitals Leuven (Belgium), Taif University (Saudi Arabia), King's College London (UK), and University of Chicago (USA) emerge as key institutions with extensive research collaborations, suggesting

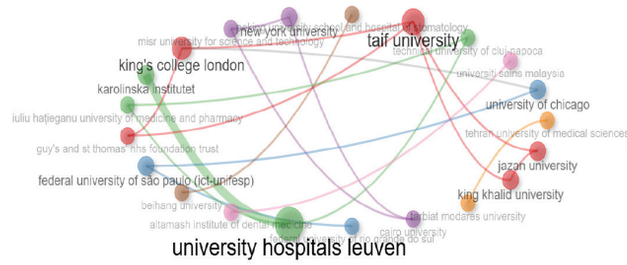

Figure 9 – Authors Collaboration Network

their central role in advancing knowledge in this domain. The presence of multiple interconnected clusters highlights the global nature of research in this field. However, certain institutions appear isolated or weakly connected, indicating potential opportunities for expanding international cooperation and fostering interdisciplinary partnerships to enhance research impact.

Frequency of AI Applications in Different Fields of Dentistry

The analysis of Table 4 highlights key trends and insights into how AI is being integrated into dental research and practice. The most frequently studied application of AI in dentistry is the diagnosis of dental diseases, including caries, periodontitis, gingivitis, and oral mucosal conditions, with 20 studies. This suggests that AI is widely utilized in assisting clinicians with the early detection and classification of common dental pathologies. Following closely, radiology and image processing (15 studies) represents another significant area, where AI is applied for CBCT analysis, X-ray interpretation, and tissue segmentation. The prevalence of AI in radiology underscores its crucial role in enhancing diagnostic accuracy and efficiency in dental imaging. Oncology, including oral cancer detection, leukoplakia identification, and other precancerous conditions, accounts for

Table 4 Frequency of AI Applications in Different Fields of Dentistry for the bibliometric analysis of the use of AI in the diagnosis of oral diseases

Ranking	Field of Application	Frequency
1	Diagnosis of dental diseases (including caries, periodontitis, gingivitis, and oral mucosal diseases)	20
2	Radiology and image processing (CBCT analysis, X-ray, tooth and tissue segmentation)	15
3	Oncology (oral cancer, leukoplakia, and precancerous conditions)	12
4	AI in dental education and expert systems	8
5	Prosthodontics and orthopedics	5
6	Teledentistry and remote monitoring	5
7	Temporomandibular disorders	3
8	Oral microbiome and its connection to systemic diseases	3
9	Ectopic eruption	2
10	Salivary gland diseases	2

12 studies. Given the importance of early diagnosis in cancer treatment, AI's ability to assist in the early identification of malignant and premalignant lesions is highly valuable. AI is also being explored in dental education and expert systems (8 studies), indicating a growing interest in AI-driven learning tools and decision-support systems for dental professionals. Additionally, teledentistry and remote monitoring (5 studies) highlight the increasing role of AI in providing virtual consultations and improving patient access to dental care, particularly in underserved areas. In the field of prosthodontics and orthopedics, AI is used in designing dental prostheses, optimizing occlusion, and assisting in treatment planning, though it is currently a less explored domain with only 5 studies.

Discussion

The findings of this bibliometric analysis indicate a growing interest and significant development of artificial intelligence for oral disease diagnosis [21]. The volume of research literature in this field has substantially increased over the past 20 years, especially since 2016. The introduction of advanced technologies such as machine learning, deep learning, and computer vision in dental diagnosing is driving the performance, efficiency and decision-making processes of healthcare-workers and dental practitioners to a greater extent.

The dramatic rise in the number of publications, especially in 2023, highlights the advancing role of AI in oral healthcare. The decrease in 2024, however, raises potential challenges, such as funding constraints, regulatory challenges, or shifts in research focus. A slow but steady rise in AI-driven technology adoption in our profession was as apparent as the steady growth we observed from 2000 to 2015. It is also important to note that the observed decline in 2024 might be attributed to the delay in indexing newly published articles. Indexing in databases such as Web of Science and Scopus does not happen immediately, and some journals have a lag time of several months. Given that the search was conducted in January 2025, it is likely that not all relevant publications from 2024 were included in the dataset, which could partially explain the observed decrease.

Highly cited studies indicate that AI applications in oral disease diagnosis date back to at least 1996 [15]. While early research focused on decision-support systems, recent advancements emphasize deep learning techniques and radiographic imaging analysis. Notable contributions include AI-powered dental plaque detection, automated radiograph interpretation, and hybrid AI models that integrate multiple analytical approaches [16, 17, 21]. These developments reflect the continuous evolution of AI applications, emphasizing improved diagnostic accuracy and personalized treatment strategies.

Keyword analysis reveals that artificial intelligence, deep learning, and machine learning are central to the field, demonstrating a strong emphasis on technological innovation. The prominence of terms such as 'diagnosis,' 'oral health,' and 'machine learning' suggests that AI research primarily targets diagnostic enhancement and disease management. This aligns with the broader trend of AI adoption in medical imaging, data analysis, and clinical decision support [4].

The global distribution of research on AI in oral health demonstrates significant contributions from China, the United States, and India, with emerging participation from Iran, Saudi Arabia, and European nations. The dominance of China and the USA in this domain reflects their strong investments in AI research and healthcare innovation. Moreover, increasing research output from developing countries highlights the global shift toward AI-driven dental diagnostics, expanding access to advanced healthcare technologies in diverse regions [22, 23].

The country collaboration map illustrates extensive international partnerships, particularly between China, the United States, and European nations. These collaborations indicate a growing emphasis on interdisciplinary and multinational research initiatives, which facilitate knowledge exchange, shared resources, and the development of standardized AI applications for oral disease diagnosis. The involvement of emerging economies further suggests that AI research in dentistry is becoming more inclusive and globally integrated [24].

While this bibliometric analysis provides valuable insights into the application of AI in the diagnosis of oral diseases, several limitations should be acknowledged. The study relied on the Web of Science and Scopus databases, which are among the most comprehensive and reliable bibliographic sources [25]. However, this approach may have excluded AI-related research indexed in specialized databases, such as IEEE Xplore for computer science and engineering-focused studies. Reasons for excluding IEEE Xplore is that it lacks the advanced filtering options and raw data export features for article metadata (such as abstracts, titles, and keywords) that are available in Web of Science and Scopus, influencing our decision to focus on the latter databases for this analysis.

The analysis was restricted to English-language publications, potentially leading to language bias [26]. Geographically, the study identified leading contributors but may not have fully captured institutional and regional disparities in AI research. Encouraging global collaboration and analyzing non-Western publications could provide a more equitable assessment of research contributions [27]. The rapid advancements in AI technologies necessitate ongoing bibliometric updates to track emerging trends. Future studies should consider real-time tracking and dynamic dashboards to monitor AI developments in dentistry continuously.

Certain fields have received minimal attention in AI research, including temporomandibular disorders (3 studies), oral microbiome and systemic disease connections (3 studies), ectopic eruption (2 studies), and salivary gland diseases (2 studies). The lower number of studies in these areas may be due to the complexity of these conditions, limited availability of comprehensive datasets, or the early stage of AI application in these fields.

This analysis highlights several promising research directions and clinical applications. While AI research is primarily focused on diagnostics, expanding its use in treatment planning, particularly in prosthodontics and orthodontics, could lead to more personalized dental care. AI also holds great potential for improving access to remote dental services, especially in underserved and rural areas. Additionally, the link between the oral microbiome and systemic diseases remains an underexplored field where AI could drive significant advancements. Furthermore, AI-driven research in rare and complex dental conditions, such as salivary gland diseases and temporomandibular disorders, is essential for improving diagnostic accuracy and treatment strategies.

Despite these limitations, this study offers a valuable foundation for understanding the evolving landscape of AI applications in oral disease diagnosis. Addressing these challenges in future research will further enhance the accuracy, inclusivity, and applicability of bibliometric analyses in this field.

Future research directions should focus on several key areas. First, the integration of AI with multimodal diagnostic data, such as clinical records, genetic markers, and salivary biomarkers, holds promise for improving diagnostic precision. Second, the ethical and regulatory challenges associated with AI-driven dental diagnostics need further exploration, particularly regarding data privacy, bias mitigation, and standardization of AI models. Third, efforts should be directed toward developing AI tools that are accessible and applicable in low-resource settings to reduce healthcare disparities. Finally, interdisciplinary collaboration between AI researchers, dental practitioners, and policymakers is crucial for translating AI innovations into clinical practice effectively. Addressing these research gaps will help optimize AI-driven diagnostic systems and improve oral healthcare outcomes globally.

Conclusion

This bibliometric analysis provides valuable insights into the evolution, key contributors, and emerging trends in AI applications for oral disease diagnosis. While substantial progress has been made, challenges such as regulatory constraints, data standardization, and clinical validation must be addressed to ensure the effective integration of AI in dental practice. Future research should focus on developing standardized datasets, enhancing model interpretability, and fostering interdisciplinary collaborations between AI researchers and dental professionals. Additionally, establishing clearer regulatory guidelines and ethical frameworks will be essential for facilitating clinical adoption. Continuous monitoring of emerging trends and sustained global cooperation will be crucial in advancing AI-driven precision dentistry and improving patient outcomes.

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HIV Prevention and Awareness Among People with Substance Use Disorders in Kazakhstan: A Systematic Review

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Abstract

The aim of this review is to assess the available research on HIV prevention and awareness efforts among individuals with substance use disorders in Kazakhstan, in order to identify primary themes and subthemes. A systematic search of five databases was conducted using a pre-defined search strategy, according to the established guidelines. Key populations of interest: people who inject drugs, novel psychoactive substance users, youth substance use, men who have sex with men, female sex workers and migrant workers. Forty studies were included. Within the people who inject drugs cohort, research themes were categorized into four groups: Project Renaissance, Project Bridge, optimized HIV case finding and no project. Among novel psychoactive substance users, research focused on novel psychoactive substance and polydrug use, prevalence rates, associated influences, and the impact of COVID-19. Studies involving youth substance users addressed the Kazakhstani Families Together intervention and COVID-19's effects. For men who have sex with men, investigations included HIV prevention trials with themes of novel psychoactive substance and polydrug use, HIV testing, early sexual experiences, and chemsex. Research on female sex workers examined interventions like Project Nova and Aegida. For migrant workers, research included the Silk Road Health Project with the following themes: alcohol abuse, sexual risk behaviors, and limited healthcare access. Despite Kazakhstan's initiatives in HIV prevention, research gaps remain, particularly concerning novel psychoactive substance users, overdose prevention, bio-behavioral interventions, mHealth approaches, and illicit drug use pattern analyses.

Keywords: HIV; preventive medicine; awareness; substance-related disorders; systematic review; drug users; HIV testing; sexual and gender minorities.

Introduction

According to estimates from World Health Organization (WHO), by 2023, 39.9 million people were living with HIV [1]. While the global incidence of HIV infection decreased by 32% in 2022 compared to 2015, the European region, which includes Kazakhstan, saw a 10% increase [2]. The Republic of Kazakhstan, situated at the crossroads of Eastern Europe and Central Asia, has experienced a concentrated HIV epidemic, predominantly affecting key populations such as people who inject drugs (PWID), men who have sex with men (MSM), sex workers, and individuals in closed settings. As of early 2024, there were 32,659 reported cases of people living with HIV in Kazakhstan, with estimates suggesting the actual number could be around 40,000 [3]. In 2023 alone, the country reported 3,862 new HIV infections [3]. Notably, HIV prevalence among MSM and PWID is significantly elevated, estimated at approximately 8.8% and 7%, respectively [3].

In response to the evolving epidemic, Kazakhstan has implemented various HIV prevention and harm reduction initiatives. The government has augmented state funding for HIV prevention and established a regulatory framework for methadone procurement, resulting in the enrollment of 490 PWID into opioid agonist therapy (OAT) programs [4]. Additionally, pre-exposure prophylaxis (PrEP) programs have been integrated into national clinical protocols and receive government funding; in 2023, nearly 5,000 high-risk individuals accessed PrEP services [4].

Despite these efforts, challenges persist. Stigma and discrimination against key populations hinder access to prevention and treatment services. UNAIDS

national estimates suggest the MSM population in Kazakhstan is approximately 71,000 individuals based on HIV testing surveillance [3]; however, population size estimation studies indicate this number could be substantially higher, at around 154,000 individuals [5]. Moreover, the expansion of OAT has been minimal since its introduction in 2008, primarily due to policy and funding constraints [6]. The COVID-19 pandemic has further disrupted harm reduction and HIV service delivery, exacerbating existing barriers [7]. The use of novel psychoactive substances (NPS) is on the rise, with substance abuse-related hospitalizations due to NPS reaching 10% in 2018 [8], to 3.9% of the general young population reporting NPS consumption in 2021 across Kazakhstan [9].

The primary mode of HIV transmission in Kazakhstan has evolved over time. Initially, injecting drug use was the predominant route; however, by 2016, heterosexual transmission accounted for 62.5% of new HIV cases [10]. This shift underscores the complex interplay between substance use and sexual risk behaviors, necessitating comprehensive prevention strategies.

Despite growing recognition of this issue, there remains a paucity of synthesized evidence concerning HIV prevention and awareness strategies tailored to individuals with substance use disorders in Kazakhstan. The challenges faced by this group are multifaceted, involving not only biological risks but also significant socio-psychological and behavioral barriers to adopting preventive measures. Therefore, it is imperative to critically examine the existing body of literature on HIV prevention and awareness among individuals with substance use disorders within the context of Kazakhstan. The primary aim of this systematic review is to synthesize and critically assess the available research on HIV prevention and awareness efforts among individuals with substance use disorders in Kazakhstan. Specifically, this review seeks to identify the primary themes and subthemes in HIV prevention and awareness research among key populations and vulnerable groups with substance use disorders in Kazakhstan, with the goal of identifying potential research gaps and future research directions.

Methods

The study protocol is registered with PROSPERO, the International prospective register of systematic reviews of the National Institute for Health and Care Research [11] (ID: CRD42024622743).

Search strategy

An initial search in the PROSPERO database did not reveal registration of any similar study protocols. Following this, a comprehensive systematic search was conducted across following electronic databases: PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search was initiated on October 01, 2024, and completed on December 01, 2024. The search strategy incorporated the following keywords: "HIV" OR "Human immunodeficiency virus" OR "AIDS" OR "Acquired Immunodeficiency Syndrome" AND "Drug" OR "Substance" OR “Alcohol” AND "Kazakhstan." No restrictions on publication dates were applied. Filters were set to limit the search results to articles or research articles where applicable. In the ScienceDirect database, the search was conducted within titles, abstracts, or keywords, while in Google Scholar, the search was restricted to titles only.

Eligibility criteria

The types of studies to be included were determined using the following eligibility criteria: based on participants (population) in the study and based on the types of study to be included. Inclusion criteria based on participants: 1. Studies on HIV prevention and awareness research among individuals with substance use disorders including alcohol, recreational drugs, and over-the counter medicine misuse. 2. Studies on adult population in Kazakhstan. Exclusion criteria based on participants: 1. Absence of the information on HIV prevention or awareness or substance use. 2. Studies in several countries or in Central Asia. Inclusion criteria based on the types of studies: 1. Observational studies including cohort studies, cross-sectional studies, and case-control studies; qualitative studies; mixed-methods research studies; randomized controlled trials (RCT); modeling studies; case-reports. 2. Studies published in English. Exclusion criteria based on the types of studies: 1. Absence of the information on HIV prevention or awareness or substance use. 2. Reviews, editorials, commentaries, study protocols and conference abstracts. 3. Studies published in languages other than English. 4. Studies presenting identical results and themes as those already included.

Selection of studies and data extraction

The literature review and data extraction were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. Using the keywords, an initial search of titles was conducted across all databases by two authors (A.I.I. & M.R.). The results were then compared and agreed upon. After duplicates were removed, the two authors independently screened the titles and abstracts of the search results to assess their relevance. Full texts of titles that passed the initial screening were retrieved and evaluated against the predefined inclusion and exclusion criteria described above. Data extracted from eligible studies included the first author’s last name, publication year, region, key population or vulnerable group, study design, sample size and key implications for HIV prevention and awareness. The theme and subthemes of the research were then developed. Two authors (A.I.I. & M.R.) independently extracted data from the selected articles, and any discrepancies in data extraction were resolved through consultation with a third author (B.T.) and consensus among the three researchers (A.I., M.R. and B.T.) responsible for study selection and data extraction.

Risk of bias (quality) assessment

The assessment of risk of bias was conducted using the Mixed Methods Appraisal Tool (MMAT). The MMAT includes two initial screening questions to determine the eligibility of studies for further evaluation. For each study design category—qualitative research, quantitative randomized controlled trials, quantitative non-randomized studies, quantitative descriptive studies, and mixed-methods studies—an overall quality score was assigned based on five specific criteria. For qualitative studies, the criteria included: 1) appropriateness of the method to answer the study question, 2) adequacy of data collection, 3) adequacy of data findings, 4) sufficiency of data to interpret results, and 5) coherence between all parts of the analysis. For quantitative randomized trials, the criteria were: 1) appropriateness of the randomization, 2) comparability of groups, 3) completeness of outcome data, 4) blinding of assessors, and 5) adherence of participants to

the intervention. For quantitative non-randomized studies, the criteria were: 1) representativeness of the target population, 2) appropriateness of measurements, 3) completeness of outcome data, 4) accountability of confounders, and 5) administration of the intervention or assessment of exposure as intended. For quantitative descriptive studies, the criteria included: 1) relevance of the sampling strategy, 2) representativeness of the sample, 3) appropriateness of measurements, 4) mitigation of non-response risk bias, and 5) appropriateness of the statistical analysis. For mixed-methods research, the criteria were: 1) adequateness of the rationale for using the chosen method, 2) effectiveness of the integrated research components to answer the research question, 3) adequateness of the interpretation, 4) adequateness of addressing inconsistencies between the research methods, and 5) adherence of different research components to corresponding quality criteria. Each study was evaluated to ascertain the percentage of quality criteria met, ranging from 0% to 100%. Studies that met at least 60% of the quality criteria were considered eligible for inclusion in the systematic review.

Strategy for data synthesis

To determine the themes and subthemes of the HIV prevention and awareness research among individuals with substance use disorders in Kazakhtan the thematic synthesis process proceeded in three phases. During the first phase, we identified the following key populations or vulnerable groups of interest: people who inject drugs (PWID), novel psychoactive substance users (NPS), youth substance use, men who have sex with men (MSM), female sex workers and migrant workers. Within each group we identified the main theme of the research. To minimize researcher bias in theme development process, a collaborative approach was employed to enhance objectivity and rigor. Two independent researchers (I.K. and M.R.) conducted the theme development process separately, and then compared the results. Any disagreements were resolved through a consultation with the third researcher. Thematic analysis results are presented as forest plots, along with the number of studies corresponding to each theme. A maximum of three themes per study were agreed upon.

Results

Included study characteristics

The initial database search yielded 1,015 articles; after removing 601 duplicates, 414 unique titles remained for screening. Of these, 228 were excluded as non-relevant, resulting in 186 articles subjected to full-text review. Upon thorough assessment, 40 articles met the inclusion criteria. The excluded studies addressed various topics: 25 focused on Central Asia or multiple countries including Kazakhstan; 22 were reviews, abstracts, study protocols, or commentaries; 17 centered on HIV prevention research and testing; 15 examined HIV epidemiology; 12 investigated MSM; 11 explored issues related to migrants; 8 delved into stigma and mental health; and 7 addressed various co-infections. Additionally, 23 studies were excluded for other reasons, and 4 were excluded due to reporting similar results and themes as already included studies [13–16]. The study selection process is detailed in the PRISMA flow diagram (Figure 1) [12].

A comprehensive summary of the studies, along with key implications for HIV prevention and awareness, is provided in Table 1, divided into the following groups: PWID, NPS users, youth substance use, MSM, female sex workers and migrants.

A total of 21 studies were identified focusing on HIV prevention and awareness among PWID. Of these, 12 studies

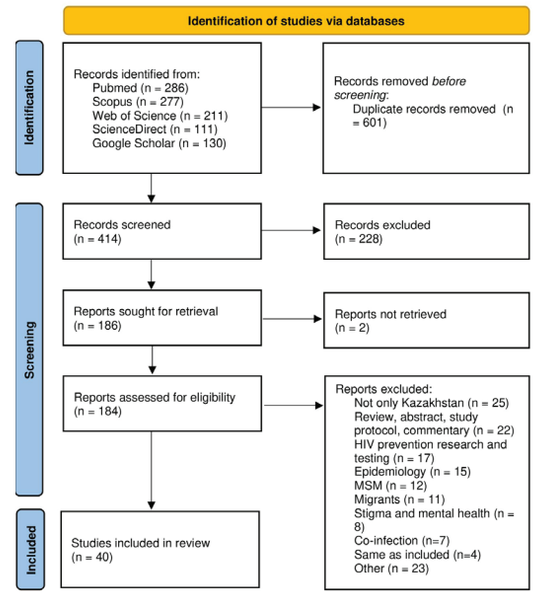

Figure 1 – PRISMA flow diagram of study selection process

specifically report findings from Project Renaissance, a randomized controlled trial conducted between 2009 and 2012. This project evaluated the efficacy of a couple-based HIV/STI risk-reduction intervention (CHSR) involving heterosexual couples in Almaty. Three studies centered on Project Bridge, a stepped-wedge cluster trial implemented from 2017 to 2020 across 24 needle and syringe programs (NSPs) in three Kazakhstani cities, aiming to enhance the HIV care continuum. One study presented results from an optimized HIV case-finding intervention, executed in Almaty during 2018 and 2019, which employed a social network strategy to facilitate HIV testing among at-risk populations. The remaining five studies, independent of these projects, comprised one cross-sectional genetic testing study, three qualitative studies, and one cross-sectional survey.

Three independent studies addressed NPS users: a case-control study, a cross-sectional study, and a registry data analysis. These investigations provided insights into the prevalence and patterns of NPS use, associated risk behaviors, and implications for HIV transmission within this demographic.

Two studies focused on youth substance use. One was the Kazakhstani Families Together (KFT) trial, a computer-assisted, family-focused drug prevention intervention targeting at-risk youth in Almaty. The other was a cross-sectional analysis examining substance use prevalence and its correlation with HIV awareness among the youth.

Three studies investigated MSM populations with substance use. Two reported data from an HIV prevention trial aiming to increase engagement of MSM who use substances in the HIV care continuum across three Kazakhstani cities. The third was a qualitative study exploring barriers and facilitators to HIV prevention and care within this group.

Nine studies concentrated on female sex workers who use drugs in Kazakhstan. Seven utilized data from Project Nova, a randomized controlled trial conducted between 2014 and 2017. This project combined HIV risk reduction with financial literacy training, vocational training, and microfinancing for female sex workers who use drugs, recruiting 400 participants across two cities [56]. The remaining two studies derived data from the Aegida intervention, initiated in 2020 in two Kazakhstani cities, promoting HIV self-testing through education, peer support, stigma reduction, and linkage to care.

Table 1 Included study characteristics

First author, year	Region	Study design	Sample size	Key implication	Project
People who inject drugs					
Bobkov, 2004 [17]	Pavlodar, Shymkent, Karaganda	Cross-sectional (genetic testing)	43 heterosexual couples	The study confirmed the spread of the same subtype A virus across former Soviet Union countries	No project
Gilbert, 2010 [18]	Shu	RCT	40 heterosexual couples	CHSR is effective in reducing the drug and sexual HIV risks	Project Connect adaptation (pre-implementation of Project Renaissance
El-Bassel, 2014 (a) [19]	Almaty	RCT	300 heterosexual couples	Risk reduction intervention is more effective than wellness promotion intervention	Project Renaissance
El-Bassel, 2014 (b) [20]	Almaty	Cross-sectional analysis of the baseline data from RCT	364 heterosexual couples	HIV prevalence was found to be 30.1% among FWID and 10.4% among female partners of MWID who do not inject drugs	Project Renaissance
Famouri, 2014 [21]	Almaty	Cross-sectional analysis of the baseline data from RCT	68 heterosexual couples	Partner notification of HCV status was 68%. This rate was higher among respondents who participated in needle syringe programs. To improve partner notification rates, and improve HIV/HCV testing it is crucial to address and eliminate the structural barriers that hinder access to needle syringe programs.	Project Renaissance
Shaw, 2016 [22]	Almaty	Cross-sectional analysis of the baseline data from RCT	364 heterosexual couples	Depression is high among PWID, however there are significant gender associated differences.	Project Renaissance
Davis, 2018 [23]	Almaty, Karaganda & Temirtau, and Shymkent	Qualitative study	57, 32 women, 25 men	Suboptimal ART adherence cannot be separated from poverty and stigma, and individual-, interpersonal- and structural-level facilitators and barriers influence the ART adherence	No project
el-Bassel, 2018 [24]	Almaty	Cross-sectional analysis of the baseline data from RCT	364 heterosexual couples	The prevalence of HIV among PWID was 28%, and 25% of those who were positive were unaware of their status.	Project Renaissance
Gilbert, 2018 [25]	Almaty	RCT	479 individuals were selected from 364 heterosexual couples	Incorporating overdose prevention into a couple-based HIV/HCV intervention could be a valuable approach for addressing the combined challenges of opioid overdose, HIV, and HCV in Kazakhstan.	Project Renaissance
Jiwattram-Negron, 2018 [26]	Almaty	Cross-sectional analysis of the baseline data from RCT	364 heterosexual couples	18% of screened WHID experience SAVA, and HIV prevalence is 22%. There is a need to deliver direct supportive services to the community.	Project Renaissance
Marotta, 2018 (a) [27]	Almaty	Cross-sectional analysis of the baseline data from RCT	510 329 – male 181 - female	Drug crime convictions among PWID, especially female PWID, are linked to high-risk behaviors, Hepatitis C virus (HCV) infection, and more severe substance use disorders	Project Renaissance
Marotta, 2018 (b) [28]	Almaty	Latent class analysis from RCT data	510 329-males 181-females	Power inequities exist within intimate relationships of PWID. Enhancing risk reduction and safe sex self-efficacy may help lower drug and sexual risk behaviors, thereby reducing HIV transmission.	Project Renaissance
Shaw, 2018 [29]	Almaty	Cross-sectional analysis of the baseline data from RCT	364 heterosexual couples	Access to NSP and a regular physician are associated with both access to HIV testing and treatment. Criminal record is associated with access to testing, but not treatment	Project Renaissance
Davis, 2019 [30]	Almaty	Qualitative study	20 PWID (HIV+), 18 of their intimate partners, and 7 AIDS Center healthcare providers	Adherence to ART treatment is suboptimal. The feasibility of providing quantitative drug levels should be evaluated.	No project
Stringer, 2019 [31]	Almaty, Shymkent, and Karaganda & Temirtau	Mixed methods research	Focus groups with 57 PWID and survey of 80 nurses	The drivers of stigma that could be acted upon are negative opinions and moral judgements.	Project Bridge (pre-implementtation)

Marotta, 2020 [32]	Almaty	Structural equation modeling	432 – 216 heterosexual couples	Criminal justice involvements significantly impacts the drug and sexual HIV risks	Project Renaissance
El-Bassel, 2022 (a) [33]	Almaty, Shymkent, and Karaganda & Temirtau	A cluster trial	1015 841 males	Bridge HIV continuum intervention in Needle and Syringe Programs is effective in HIV care and prevention	Project Bridge
McCrimmon, 2022 [34]	Almaty, Shymkent, and Karaganda & Temirtau	Qualitative study	24 nurses	NSP need recognition as essential organizations and additional equipment	ProjectBridge
Primbetova, 2022 [35]	Kazakhstan	Cross-sectional analysis	56 nurses (17) and outreach workers (37)	Evaluating the varying attitudes of nurses compared to outreach workers, male versus female staff, and HIV-positive versus HIV-negative personnel, along with providing ongoing training, can help reduce stigma and enhance participation in harm reduction programs.	No project
Denisiuk, 2023 [36]	Almaty	Cross-sectional analysis	5983 4032 - males 1933 females	Optimized HIV case finding through assisted self-testing and social network strategies is crucial for reaching key populations and improving access to HIV testing and care.	Optimized HIV case finding introduction
Neuenschwander, 2024 [37]	Almaty	Qualitative study	20	Barriers and facilitators of the ART adherence were indicated at the individual, interpersonal and structural level. Integrating dyad approaches into ART adherence interventions is crucial	No project
NPS users					
Prilutskaya, 2017 [38]	Pavlodar and Almaty	Naturalistic case-control study	190 - 170 male 20 female	Regular use of synthetic cannabinoids delays recovery from opioid use disorder and extends withdrawal and craving symptoms. Tailored detoxification treatments are needed for polydrug use conditions.	No project
Prilutskaya, 2020 [8]	Kazakhstan (16 state reginal centers and three clinics)	Cross-sectional analysis	345 - 285 males 59 females	The prevalence of NPS has risen from 3.91% in 2016 to 10.01% in 2018, with the highest prevalence in Nur-Sultan, Almaty, and North Kazakhstan, and cathinones being the most prevalent.	No project
Akkuzinova, 2024 [39]	Kazakhstan	Registry data analysis	Over a four-year period, there were 471,807 cases reported, comprising 399,359 males and 72,448 females.	During the pandemic period the use other stimulants including alcohol, caffeine and other stimulants, and multiple drug use and the use of other psychoactive substances significantly increased compared to pre-pandemic period.	No project
Youth substance use					
Ismayilova, 2018 [40]	Almaty	Mixed-methods research	181 - 111 boys 70 girls	A family-based, computer-assisted KFT intervention is a cost-effective, scalable measure for preventing HIV and substance abuse among at-risk youth	KFT intervention
Konstantinov, 2020 [41]	Kostanay	Cross-sectional analysis	466 154 males 312 females	Substance use pattern among students did not significantly change during COVID-19	No project
MSM					
Lee, 2022 [42]	Almaty, Nur-Sultan, Shymkent	Cross-sectional analysis of the stepped wedge HIV prevention trial	304	HIV testing is associated with polydrug use, and lower sexual risk	HIV prevention trial
Laughney, 2023 [43]	Almaty, Nur-Sultan, Shymkent	Secondary analysis of self-report data	902	MSM who experienced their first sexual encounter between the ages of 13 and 15 were significantly more likely to engage in lifetime binge drinking, illicit drug use, and recent binge drinking behavior. Substance use risk prevention interventions should take early sexual debut into account.	HIV prevention trial
Lunchenkov, 2024 [44]	Almaty	Qualitative study	21	Engaging in chemsex acts as a strategy to cope with minority stress among despite significant health risks. The use of new substances and synthetic cathinones is increasing	No Project

Female sex workers					
Mergenova, 2019 [45]	Almaty and Temirtau	Cluster-randomized, controlled trial	354	Implementation of a combination of HIV-prevention interventions and microfinance interventions among female sex workers is feasible	Project Nova
el-Bassel, 2020 [46]	Almaty and Temirtau	Cross-sectional analysis of the RCT data	400	Violence against female sex workers is associated with non-fatal overdose	Project Nova
Velez-Grau, 2021 [47]	Almaty and Temirtau	Cross-sectional analysis of the RCT data	400	52.5% of participants reported suicidal ideation. There is a need to include mental health component to HIV interventions	Project Nova
Mukherjee, 2022 [48]	Almaty	Latent class analysis	255	In Kazakhstan, female sex workers who use drugs frequently encounter police violence, which exacerbates their vulnerability to HIV. Experiencing multiple forms of police violence correlates with increased HIV susceptibility. Implementing police sensitization workshops that combine law enforcement with harm reduction strategies, along with decriminalizing drug use, could help address the HIV epidemic in Kazakhstan.	Project Nova
Cordingley, 2023 [49]	Almaty and Taldykorgan	Qualitative study	30	Implementing HIV self-testing for women who engage in sex work and use drugs can effectively reduce stigma and overcome barriers to HIV testing	Aegida intervention
Mukherjee, 2023 [50]	Almaty and Temirtau	Cross-sectional analysis of the RCT data	400	Intimate partner and client violence against female sex workers is high and exchanging sex for drugs being associated with higher odds of violence. HIV prevention programs should address partner violence.	Project Nova
Witte, 2023 [51]	Almaty and Temirtau	Cluster-randomized, controlled trial	354	A combined HIV risk reduction and microfinance intervention could more effectively decrease gender-based violence from paying and intimate partners among female sex workers than HIV risk reduction interventions alone.	Project Nova
Yang, 2023 [52]	Almaty and Temirtau	Cross-sectional analysis of the RCT data	400	The findings of this study highlight the critical need for economic empowerment or support programs alongside HIV risk reduction options, ensuring that women do not have to choose between survival and safety.	Project Nova
McCrimmon, 2024 [53]	Almaty and Taldykorgan	Qualitative study	30	Participants were unaware of and unfamiliar with PrEP	Aegida intervention
Migrant workers					
Ismayilova, 2014 [54]	Almaty	Cross-sectional analysis	450 225 males, 225 females	Half of migrant workers have limited access to healthcare, and alcohol abuse is prevalent among them.	No project
El-Bassel, 2018 [55]	Almaty	Cross-sectional analysis	1342 (all male)	Hazardous drinking is a predictor of sexual risk behaviors such as engaging in commercial sex and sex under influence of alcohol and drugs.	Silk Road Health Project

Abbreviations: ART - antiretroviral therapy; CHSR - couple-based HIV/STI risk-reduction intervention; FWID – females who inject drugs; HIV – Human Immunodeficiency Virus; KFT - Kazakhstani Families Together; MSM – men who have sex with men; MWID - males who inject drugs; NPS – novel psychoactive substances; PWID – people who inject drugs; SAVA – substance abuse, violence and HIV.

Two studies focused on alcohol abuse among migrant workers. One study reported findings from the Silk Road Health Project, while the other was a cross-sectional study. The Silk Road Health Project was conducted between 2010 and 2013 among 1,342 male migrant and non-migrant market workers in Almaty, Kazakhstan [57].

Themes of HIV prevention and awareness research

The themes of HIV prevention and awareness research among PWID are delineated in Figure 2 (a, b, c, d) and are categorized into four groups: Project Renaissance, Project Bridge, optimized HIV case finding, and studies not associated with any specific project. For studies analyzing data from Project Renaissance, the following themes were identified: couple-based HIV/STI risk-reduction intervention (CHSR) description, HIV prevalence, partner notification of hepatitis C virus (HCV) status, mental health, overdose prevention, the Substance Abuse, Violence, and HIV (SAVA) syndemic, drug crime conviction, power inequalities, access to needle and syringe programs (NSP), and criminal justice involvement. Studies utilizing data from Project Bridge highlighted the themes of NSP effectiveness and stigma. The study focusing on optimized HIV case finding examined the theme of HIV self-testing. Among the five studies not linked to any specific project, one study covered two themes [23], while the others each addressed individual themes. The derived themes were antiretroviral therapy (ART) adherence, stigma and HIV subtype.

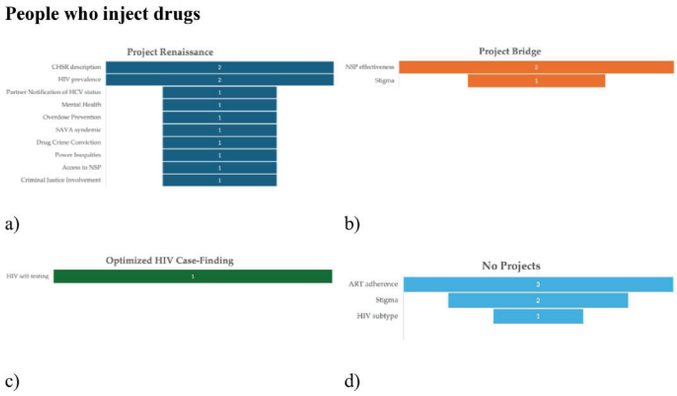

Figure 2 – Themes of HIV prevention and awareness research among PWID: a) Project Renaissance; b) Project Bridge; c) Optimized HIV-Case-Finding; d) No projects

Abbreviations: ART - antiretroviral therapy; CHSR - couple-based HIV/STI risk-reduction intervention; HCV – hepatitis C virus; HIV – Human Immunodeficiency Virus; NSP – Needle and Syringe Programs; PWID – people who inject drugs; SAVA – substance abuse, violence and HIV.

The themes of HIV prevention and awareness research among NPS users and youth substance use are illustrated in Figure 3 (a, b). Studies focusing on NPS users identified several key themes: NPS and polydrug use, the prevalence of NPS use, the influence of NPS use, and the impact of COVID-19. All three studies covered polydrug use along with NPS use. Among those studies, a study conducted by Akkuzinova and colleagues encompassed three themes: polydrug use, the prevalence of NPS use and the impact of COVID-19 [39]. Research on youth substance use emphasized themes such as KFT intervention and the influence of COVID-19 on youth substance use.

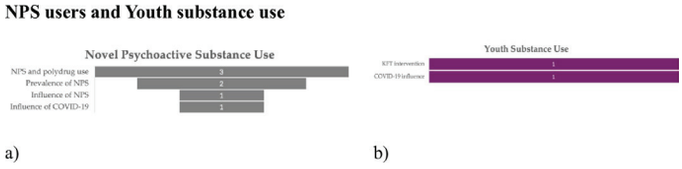

Figure 3 – Themes of HIV prevention and awareness research: a) NPS users; b) Youth substance use

Abbreviations: HIV – Human Immunodeficiency Virus; KFT - KFT - Kazakhstani Families Together; NSP – novel psychoactive substances.

The themes of HIV prevention and awareness research among MSM with substance use are presented in Figure 4 (a, b). For studies analyzing data from HIV prevention trials, two studies were identified, each focusing on two themes: NPS nad polydrug use, HIV testing, and early sexual encounters. Additionally, a study not affiliated with any projects also explored two themes, categorized as NPS and polydrug use and chemsex [44].

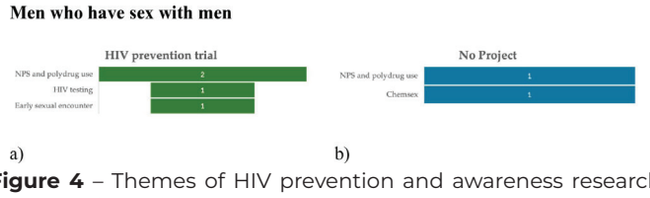

Figure 4 – Themes of HIV prevention and awareness research among MSM; a) HIV prevention trial; b) No project

Abbreviations: HIV – Human Immunodeficiency Virus; MSM – men who have sex with men; NSP – novel psychoactive substances.

The themes of HIV prevention and awareness research among female sex workers who use drugs are illustrated in Figure 5 (a, b). Analyzing data from Project Nova, several themes were identified: partner violence, project description/adaptation, police violence, suicidal ideation, non-fatal overdose, and economic empowerment. A study by el-Bassel and colleagues (2020) had two themes: partner violence and non-fatal oversode [46]. Studies analyzing data from the Aegida intervention highlighted themes such as HIV self-testing and pre-exposure prophylaxis (PrEP) awareness.

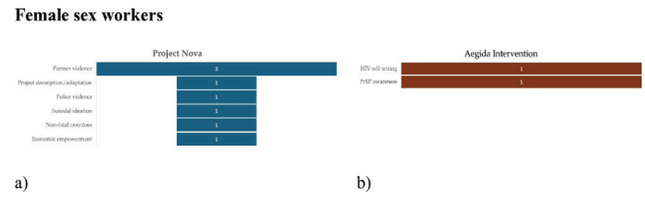

Figure 5 – Themes of HIV prevention and awareness research among female sex workers: a) Project Nova; b) Aegida intervention

Abbreviations: HIV – Human Immunodeficiency Virus; KFT - KFT - Kazakhstani Families Together; NSP – novel psychoactive substances.

The themes of HIV prevention and awareness research among migrant workers with substance use are illustrated in Figure 6 (a, b). Analyzing data from the Silk Road Health Project, two themes were identified: alcohol abuse and sexual risk behavior, with one study encompassing both themes [55]. Additionally, a study not affiliated with any specific projects also explored two themes, categorized as alcohol abuse and limited access to healthcare [54].

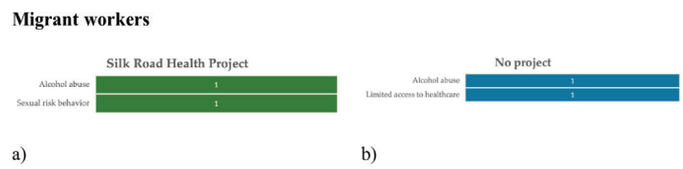

Figure 6 – Themes of HIV prevention and awareness research among migrant workers: a) Silk Road Health Project; b) No project

Risk of bias (quality) assessment

Table 2 summarizes the results of the risk of bias (quality) assessment. All included studies met at least 80% of the MMAT quality criteria, indicating high quality and a low risk of bias. Most of the studies had strong international collaborations and secured funding, which may explain the rigorous methodology employed in the included studies.

Discussion

There is a plethora of research on HIV prevention and awareness in the context of substance use in Kazakhstan. Our systematic review critically evaluated HIV prevention and awareness initiatives among individuals with substance use disorders in Kazakhstan, encompassing 40 studies that targeted key populations: people who inject drugs (PWID), new psychoactive substance (NPS) users, youth substance users, men who have sex with men (MSM), female sex workers who use drugs, and migrants. Within the PWID cohort, research

Table 2 MMAT risk of bias (quality) assessment results

First author, year	MMAT criteria used	1	2	3	4	5	MMAT quality criteria met (%)
People who inject drugs							
Bobkov, 2004 [17]	Quantitative descriptive	20%	20%	20%	0%	20%	80%
Gilbert, 2010 [18]	RCT	20%	20%	20%	20%	20%	100%
El-Bassel, 2014 (a) [19]	RCT	20%	20%	20%	20%	20%	100%
El-Bassel, 2014 (b) [20]	RCT	20%	20%	20%	20%	20%	100%
Famouri, 2014 [21]	RCT	20%	20%	20%	20%	20%	100%
Shaw, 2016 [22]	RCT	20%	20%	20%	20%	20%	100%
Davis, 2018 [23]	Qualitative study	20%	20%	20%	20%	20%	100%
el-Bassel, 2018 [24]	RCT	20%	20%	20%	20%	20%	100%
Gilbert, 2018 [25]	RCT	20%	20%	20%	20%	20%	100%
Jiwattram-Negron, 2018 [26]	RCT	20%	20%	20%	20%	20%	100%
Marotta, 2018 (a) [27]	RCT	20%	20%	20%	20%	20%	100%
Marotta, 2018 (b) [28]	RCT	20%	20%	20%	20%	20%	100%
Shaw, 2018 [29]	RCT	20%	20%	20%	20%	20%	100%
Davis, 2019 [30]	Qualitative study	20%	20%	20%	20%	20%	100%
Stringer, 2019 [31]	Mixed methods	20%	20%	20%	20%	20%	100%
Marotta, 2020 [32]	RCT	20%	20%	20%	20%	20%	100%
El-Bassel, 2022 (a) [33]	Quantitative non-randomized	20%	20%	20%	20%	20%	100%
McCrimmon, 2022 [34]	Qualitative study	20%	20%	20%	20%	20%	100%
Primbetova, 2022 [35]	Quantitative descriptive	20%	20%	20%	0%	20%	80%
Denisiuk, 2023 [36]	Quantitative descriptive	20%	20%	20%	0%	20%	80%
Neuenschwander, 2024 [37]	Qualitative study	20%	20%	20%	20%	20%	100%
Novel psychoactive substance users							
Prilutskaya, 2017 [38]	Quantitative descriptive	20%	20%	20%	0%	20%	80%
Prilutskaya, 2020 [8]	Quantitative descriptive	20%	20%	20%	0%	20%	80%
Akkuzinova, 2024 [39]	Quantitative descriptive	20%	20%	20%	0%	20%	80%
Youth substance use							

Ismayilova, 2018 [40]	Mixed-methods	20%	20%	20%	20%	20%	100%
Konstantinov, 2020 [41]	Quantitative descriptive	20%	20%	20%	0%	20%	80%
Men who have sex with men							
Lee, 2022 [42]	Quantitative non-randomized	20%	20%	20%	20%	20%	100%
Laughney, 2023 [43]	Quantitative non-randomized	20%	20%	20%	20%	20%	100%
Lunchenkov, 2024 [44]	Qualitative study	20%	20%	20%	20%	20%	100%
Female sex workers							
Mergenova, 2019 [45]	RCT	20%	20%	20%	20%	20%	100%
el-Bassel, 2020 [46]	RCT	20%	20%	20%	20%	20%	100%
Velez-Grau, 2021 [47]	RCT	20%	20%	20%	20%	20%	100%
Mukherjee, 2022 [48]	RCT	20%	20%	20%	20%	20%	100%
Cordingley, 2023 [49]	Qualitative study	20%	20%	20%	20%	20%	100%
Mukherjee, 2023 [50]	RCT	20%	20%	20%	20%	20%	100%
Witte, 2023 [51]	RCT	20%	20%	20%	20%	20%	100%
Yang, 2023 [52]	RCT	20%	20%	20%	20%	20%	100%
McCrimmon, 2024 [53]	Qualitative study	20%	20%	20%	20%	20%	100%
Migrant workers							
Ismayilova, 2014 [54]	Quantitative descriptive	20%	20%	20%	0%	20%	80%
El-Bassel, 2018 [55]	Quantitative descriptive	20%	20%	20%	0%	20%	80%

Abbreviations: MMAT - Mixed Methods Appraisal Tool.

themes were categorized into four groups: Project Renaissance, Project Bridge, optimized HIV case finding and no project, and included topics such as couple-based HIV/STI risk-reduction interventions, HIV prevalence, partner notification of HCV status, mental health, overdose prevention, the SAVA syndemic, drug crime convictions, power inequalities, access to NSP, criminal justice involvement, NSP effectiveness, stigma, HIV self-testing, ART adherence, and HIV subtypes. Notably, stigma emerged as a recurring theme. Among NPS users, research focused on NPS and polydrug use, prevalence rates, associated influences, and the impact of COVID-19. Studies involving youth substance users addressed the KFT intervention and COVID-19's effects. For MSM, investigations included HIV prevention trials with themes of NPS and polydrug use, HIV testing, early sexual experiences, and chemsex. Research on female sex workers who use drugs examined interventions like Project Nova and Aegida, covering partner violence, intervention descriptions and adaptations, police violence, suicidal ideation, non-fatal overdose, economic empowerment, HIV self-testing, and pre-exposure prophylaxis awareness. For migrant worker population with substance use issues, research included the Silk Road Health Project with the following themes: alcohol abuse, sexual risk behaviors, and limited healthcare access, with alcohol use being a recurrent theme. Notably, multiple international interventions and collaborations such as Project Renaissance, Project Bridge, Project Nova, Aegida, The Silk Road Project have been instrumental in improving HIV prevention, monitoring and awareness efforts among key populations and vulnerable groups. However, persistent issues like stigma, limited access to NSP, political and structural barriers, and criminal justice involvement continue to impede effective HIV prevention efforts.

When juxtaposed with global research trends, the findings from Kazakhstan reflect similar challenges observed in other regions with concentrated HIV epidemics among substance users. For instance, the underutilization of OAT like methadone in Kazakhstan, despite their proven efficacy in reducing HIV transmission among opioid users, mirrors trends seen in various countries where scale-up has been minimal due to policy and funding constraints [6,58]. Additionally, the intersection of substance use and sexual risk behaviors among MSM, female

sex workers and migrants underscores a syndemic framework, where co-occurring epidemics exacerbate HIV vulnerability, a pattern consistent with findings in other Central Asian nations [59].

The review highlights critical research gaps, particularly concerning the emerging patterns of NPS and polydrug use and their implications for HIV transmission. Recent studies emphasize the significant public health challenges posed by increased risks of overdose and the complex treatment needs associated with polydrug and NPS use [60]. Bio-behavioral interventions promoting harm reduction, condom use, sexual communication skills, and safe sex practices and behavioral therapy have demonstrated efficacy in various settings, suggesting their potential applicability in Kazakhstan [61–63]. Kazakhstan's pilot community-based PrEP program has shown promise, indicating the feasibility of expanding such initiatives to encompass broader harm reduction and prevention services [64]. Leveraging mobile health (mHealth) interventions, such as text messaging and mobile applications, offers innovative opportunities to disseminate information, provide medication adherence reminders, and connect individuals with medical, psychological, and social services[15,40]. Furthermore, analyzing drug compounds and their metabolites in wastewater presents a novel approach to understanding illicit drug consumption patterns within specific population groups [65].

Future research should prioritize strategies to mitigate immediate threats, such as overdose prevention among polydrug users and behavioral interventions to reduce HIV transmission linked to risky sexual behaviors. Longitudinal studies are essential to evaluate the long-term effectiveness of current interventions and to explore innovative strategies, including the integration of HIV services with harm reduction programs like OAT, the expansion of community-based PrEP initiatives and community involvement, and the facilitation of self-testing and linkage to care. Additionally, there is a pressing need to investigate the influence of structural factors, including policy environments, healthcare infrastructure, performance of service providers and healthcare provider attitudes, on the accessibility and efficacy of HIV prevention services for substance users.

Several limitations inherent to the studies included in the review warrant cautious interpretation of the findings. The predominance of cross-sectional analysis limits causal inferences, and the reliance on self-reported data may introduce social desirability and recall biases. Furthermore, the exclusion of non-English publications could result in the omission of region-specific insights, potentially skewing the comprehensiveness of the synthesis.

In conclusion, while Kazakhstan has implemented various initiatives targeting HIV prevention among individuals with substance use disorders, critical research gaps persist. These gaps include insufficient focus on NPS and polydrug users, overdose prevention strategies, bio-behavioral interventions, behavioral therapy, mHealth interventions, and analyses of illicit drug use patterns. Persistent challenges such as stigma, limited harm reduction services, and policy barriers continue to hinder progress. Addressing these issues through evidence-based, culturally sensitive, and integrated approaches is imperative to curb the HIV epidemic among key populations in the region. Collaborative efforts involving policymakers, healthcare providers, and community stakeholders are essential to enhance the effectiveness and reach of HIV prevention and awareness programs among substance users.

Abbreviations

The following abbreviations are used in this manuscript:

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
CHSR	Couple-based HIV/STI risk-reduction intervention
FWID	Females who inject drugs
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
KFT	Kazakhstani Families Together
MMAT	Mixed Methods Appraisal Tool
MSM	Men who have sex with men
MWID	Males who inject drugs
NPS	Novel psychoactive substances
OAT	Opioid agonist therapy
PrEP	Pre-exposure prophylaxis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PWID	People who inject drugs
SAVA	Substance abuse, violence and HIV
WHO	World Health Organization

Author Contributions: Conceptualization, I.K.; methodology, I.K. and M.R.; validation, I.K. and B.T.; formal analysis, I.K.; investigation, I.K.; resources, I.K. and B.T.; data curation, I.K.; writing – original draft preparation, I.K. and B.T.; writing – review and editing, I.K., B.T. and M.R.; visualization, I.K.; supervision, I.K.; project administration, I.K. and M.R.; funding acquisition, I.K. and B.T. All authors have read and agreed to the published version of the manuscript.

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Data availability statement: The corresponding author can provide the data supporting the study's conclusions upon request. Due to ethical and privacy constraints, the data are not publicly accessible.

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Educational Interventions to Reduce Antibiotic Prescribing for Children with Respiratory Tract Infections in Primary Care: a Systematic Review

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Abstract

Antibiotic resistance is a serious public health threat that is driven by overuse of antibiotics. The latter may occur in the management of children with mild self-limiting respiratory tract infections. Educational interventions to tackle the issue of antibiotic overuse targeted at parents and clinicians may help reduce unnecessary antibiotic use for respiratory tract infections. This systematic review sought to assess the effectiveness of educational interventions targeted at parents and clinicians in reducing antibiotic prescribing for children with respiratory tract infections in primary care settings.

A literature search was conducted in Medline, Cochrane Library, APA PsycInfo, and CINAHL for relevant published studies between 2000-2024. Inclusion criteria included studies of educational interventions for parents and/or clinicians, with regards to the management of respiratory tract infections in children under 18 years of age, in primary care settings. The risk of bias in RCTs was assessed utilizing the RoB 2 tool, whereas non-RCTs, before-and-after studies, and studies with historical controls were evaluated utilizing the ROBINS-I tool. A narrative synthesis was used to synthesize findings, and different techniques such as grouping, tabulation, textual descriptions of studies, and transforming data into a common rubric were utilized.

A total of 293 studies were identified, and 16 studies met the eligibility criteria. Two studies targeted only parents, five only clinicians, and nine both parents and clinicians. Overall, included studies were of low quality. Contradictory results were observed among studies investigating parent educational interventions, whereas some evidence of positive impact was identified among studies exploring educational interventions targeted at clinicians, and combined parent-clinician interventions.

There was insufficient evidence to provide a firm conclusion about the effectiveness of parent, clinician, and combined educational interventions. Additionally, the quality of evidence was not strong. Therefore, further high-quality research is recommended.

Keywords: anti-bacterial agents; child; parents; clinicians; respiratory tract infections; primary health care.

Introduction

Antibiotic resistance takes place when microorganisms adapt and acquire the capability to grow and spread despite the presence of antibiotics that would normally kill or retard their growth [1]. This makes infections with antibiotic resistant microorganisms more difficult and expensive to treat, as well as leads to prolonged hospitalizations and higher mortality rates [2]. The number of people infected with antibiotic-resistant microorganisms is increasing significantly, and the WHO reports this problem is rising to dangerous levels worldwide [2]. For instance, according to the CDC, more than two million people are infected with antibiotic-resistant microorganisms in the US annually [3].

The spread of antibiotic resistance threatens children worldwide. 254000 children under the age of 5 died due to antibiotic-resistant infections in 2019 globally [4]. Particularly in Europe, multi-drug-resistant infections among children represent about

30% of the total cases [5]. A study carried out in Sweden analyzed nasopharyngeal cultures of 340 children between 0–10 years with respiratory tract infections (RTIs) for resistant strains [6]. It revealed that 22% of 178 cultures with the growth of either S.pneumoniae or H.influenzae or both were resistant to beta-lactam antibiotics [6].

There are several causes of the antibiotic resistance crisis but the overuse of antibiotics is the most important one [7]. Global antibiotic consumption increased by 65% between 2000 and 2015, reaching 34.8 billion defined daily doses (DDDs) [8]. Children in particular were three times more likely to consume antibiotics than adults [9]. It is common for children to be prescribed antibiotics for mild self-limiting diseases such as for RTIs in primary care settings. Most RTIs are caused by viral agents for which there is little evidence of their effectiveness [10]. For example, a study carried out in the US observed that emergency departments prescribed antibiotics in 61% of all visits for acute RTIs [11].

Parental factors may have contributed to the high rates of antibiotic use in children with RTIs. According to one US study, 70% of parents assumed that antibiotics were required for yellow or green nasal discharge, and about half of them had decided on the necessity of antibiotics even before visiting a clinician [12]. Another study reported that a quarter of parents demanded antibiotics during primary care visits putting clinicians in a difficult situation [13]. The main cause for this was attributed to parental misinformation regarding antibiotic use [13].

Additionally, inadequate knowledge and misconceptions regarding antibiotic prescribing were also recognized among primary care clinicians [14]. One study conducted in the UK reported that general practitioners decided to prescribe an antibiotic when they were not able to differentiate between a viral or bacterial infectious disease [15].

These studies indicate that one possible approach to tackling the issue of antibiotic overuse could be to educate parents and primary care clinicians on reducing unnecessary antibiotic use.

Three systematic reviews on the effectiveness of educational interventions to reduce antibiotic prescribing for children with RTIs in primary care have been carried out so far [16–18]. One review [16] focused solely on parents, whilst another review [18] focused on only clinicians. The third systematic review [17] included all types of educational interventions that targeted parents, clinicians, and parents and clinicians combined. However, the review results were based upon data from a decade ago, and the effectiveness of interventions then was unclear. Therefore, an up-to-date systematic review on the effectiveness of educational interventions to reduce antibiotic prescribing for children with RTIs in primary care settings is needed.

Methods

A systematic literature search was carried out of four electronic databases (Medline via Ovid, Cochrane Central Register of Controlled Trials, APA PsycInfo and CINAHL) for relevant primary intervention studies published between 2000 and 2024. Studies investigating educational interventions on judicious antibiotic use targeting parents, clinicians, or parents and clinicians combined were eligible. The full list of search terms used are detailed in Supplement 1.

This review included studies on children and adolescents under the age of 18 who were treated for RTIs. Studies of children with signs and symptoms of other diseases, chronic conditions and serious co-morbidities were excluded. Additionally, studies involving only children diagnosed with otitis media were excluded.

The types of studies included were randomized controlled trials (RCTs), cluster-RCTs, non-RCTs, before-and-after studies, and studies with historical controls were included. Letters, editorials, commentaries, systematic reviews, narrative reviews, meta-analysis, meta-synthesis, study protocols were excluded. Trials involving pharmacological, diagnostic interventions, and vaccines were excluded. Clinician interventions providing financial incentives for reducing the number of prescribed antibiotics were excluded. Additionally, interventions that concentrated solely on communication training or electronic support systems were excluded.

Studies carried out in primary care settings such as family practice and pediatric primary care centers were included. Trials conducted in inpatient facilities and day care health facilities were excluded.

Studies comparing educational interventions with no intervention, usual care, or alternative intervention were eligible. Studies with historical controls and those comparing pre- and post-intervention outcomes were also included.

The primary outcome sought was a change in the frequency of prescribed antibiotics. No secondary outcome was examined. Studies that did not report on the primary outcome were excluded from this systematic review.

The search was restricted only to publications in English. A screening of reference lists of included articles was also performed as an additional method of searching for relevant studies. Furthermore, included studies of existing systematic reviews were screened to exclude the risk of missing relevant primary studies.

The literature search was conducted in accordance with the PRISMA reporting of reviews (See Figure 1. PRISMA flow diagram). Firstly, search results from different databases were combined, and duplicates of the same study were removed. Secondly, the titles and abstracts of the studies were assessed for inclusion. If it was not clear whether to include the study, the full text was reviewed. Thirdly, the full texts of all conceivably relevant trials were retrieved and assessed for eligibility. Multiple reports of the same study were integrated at this stage.

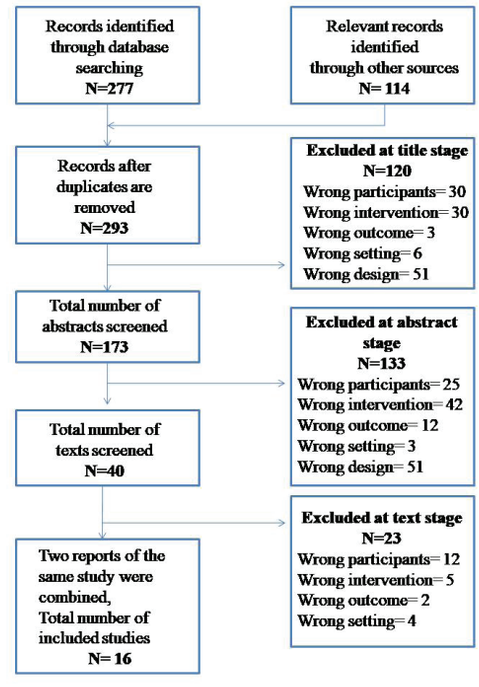

Figure 1 – PRISMA flow diagram

The Cochrane data collection form for intervention reviews for randomized and non-randomized controlled trials was utilized to extract data from studies that met the inclusion criteria (Supplement 2). The article screening and data extraction process was performed by two researchers, and where there was any uncertainty, this was resolved through discussion.

The risk of bias in each RCT was also assessed utilizing the RoB 2 tool. Additionally, the risk of bias in non-RCTs, before-and-after studies, and studies with historical controls was evaluated utilizing the ROBINS-I tool. The researcher's judgments about each risk of bias domain were presented in a risk of bias figure (e.g., Figure 2).

The findings of included studies were brought together narratively as considerable heterogeneity was expected. Different techniques were utilized to synthesize data narratively: grouping, tabulation, textual descriptions of studies, and transforming data into a common rubric. The included studies were organized by classifying them into three groups according to the intervention target: parents, clinicians, and combined.

Two common rubrics were constructed to transform data: odds ratio (OR) and mean difference (MD). Dichotomous outcomes were summarized utilizing OR. The mean difference was used as the summary statistics for continuous outcomes. 95 % confidence intervals (CIs) were calculated for both summary statistics, and the results were considered statistically significant when the p-value was <0.05. Additionally, the chi-squared and I2 tests were used to evaluate heterogeneity across included studies.

Results

Study selection

The search of databases provided a total of 277 studies. A further 114 potentially relevant articles were found through backreferencing. A total of 293 records remained after removing duplicates. 253 ineligible studies were excluded at the title and abstract stages. The full texts of the remaining 40 records were reviewed, of which 23 that did not satisfy the inclusion criteria were discarded. The list of studies excluded at the text stage with the indication of reasons for exclusion is illustrated in Supplement 3. Two reports of the same study were integrated [34, 35]; as a result, 16 studies were finally included in this systematic review.

Characteristics of studies

1. Studies targeting parents only

Two studies targeting only parents were identified [19, 20]. One study was a RCT [19], whereas the second was a historical control study [20]. Both studies were carried out in the US [19, 20]. The studies included a total of 1219 children, and parents of 972 children were assigned to an intervention group [19, 20], whilst 247 were assigned to a control group [20]. Parent educational interventions consisted of informational pamphlets and videos in one study [19] and of posters in the second [20]. Detailed study characteristics and descriptions of the interventions are provided in Tables 1 and 2 respectively.

2. Studies targeting clinicians only

Five studies targeting only clinicians were identified [21–25]. Three studies were cluster-RCTs [21, 22, 24], one was a non-RCT [23], and another was a before-and-after study [25]. Three trials were conducted in the US [21, 23, 24], one in Israel [25], and one in the UK [22]. Four studies included a total of 121 primary care practices [21, 22, 24, 25], of which 74 were assigned to an intervention group, and 47 were assigned to a control group. Additionally, one study included 30 clinicians [23], of which 21 were allocated to an intervention group and 9 to a control. All five studies consisted of an educational session [21–25]. Audit and feedback on prescribing for viral and bacterial RTIs were provided in three trials [21, 22, 24].

3. Studies targeting both parents and clinicians

Nine studies targeting parents and clinicians were identified [26-34]. Eight studies were cluster-RCTs [26–31, 33, 34], and one study was a non-RCT [32]. Five trials were carried out in the US [28–30, 32, 33], one in Israel [26], one in the Netherlands [27], one in the UK [31], and another in China [34]. Eight studies included a total of 499 practices [26–32, 34], of which 110 were assigned to an intervention group, whereas 389 were assigned to a control group. Additionally, one RCT involved 216 clinicians: 154 of them were in the intervention group, and 62 were in the control [33].

Clinician educational training was carried out in seven trials [26–31, 34]. Five trials provided feedback on antibiotic prescribing by clinicians [28–30, 32, 33]. Booklets [26, 27, 31], pamphlets [26, 28, 29, 33], posters [26, 28–30, 32], brochures [30, 32], flyers [28], handouts and stickers [30], reference cards [32], letters [33], leaflets and video [34] on antibiotics were utilized as parent educational materials.

Four studies reported the barriers to implementing educational interventions [27, 28, 31, 32]. The first mentioned a lack of interest and a high workload among clinicians [32], whereas the second indicated physicians' medical leave of absence and relocating the clinic [27]. Moreover, technical issues in the patient database were highlighted in the third [28], and a lack of time during the patient consultation was noted in the fourth study [31].

Risk of bias within studies

Overall, the quality of included studies was low in ten studies [19, 21, 22, 24, 26, 27-30, 33], and moderate in two [31, 34]. There was some concern regarding potential risk of bias for some domains for most of the RCTs (Figure 2A; Full details of the risk of bias assessment is provided in Supplement 4).

For non-RCT, before-and-after studies, and studies with historical controls, the overall quality of included studies was judged to be low in three studies [20, 23, 25] and moderate in one [32].

See Figure 2B for the risk of bias summary of non-RCTs, before-and-after studies, and studies with historical controls (Also see Supplement 5 for the completed risk of bias assessment form).

Results of individual studies and synthesis of results

The mean difference was calculated in two studies [19, 33], whereas the OR was estimated in five studies [20, 25, 27, 31, 34]. It was not possible to measure the mean difference or OR for the remaining studies as their statistics were reported incompletely.

1. Studies targeting parents only

The studies targeting only parents demonstrated mixed results (Table 3). No significant difference (MD - 0.30, p>0.05; OR - 0.76, p>0.05)was identified in antibiotic prescribing between the intervention and control groups of two studies evaluating the impact of educational pamphlets with a video [19] and posters [20]. On the contrary, one trial assessing the effectiveness of educational pamphlets with an informative letter reported a significant difference in the percentage of episodes with antibiotics (MD - 9.00, p<0.05) between the intervention and control groups [33].

Table 1 Characteristics of included studies

Author/ year	Country	Intervention target	Study Design	Study setting	Sample size		Age of children (mean ± SD, average age, median, or range)		Illnesses of children
					IG	CG	IG	CG	
Taylor, 2005	the USA	Parent	RCT	Primary care pediatric offices	252	247	8.8 m ± 6.3	8.8 m ± 5.9	URIs, otitis media, sinusitis
Ashe, 2006	the USA	Parent	A historical control study	Private pediatric group practices	720		average age = 4.2 yrs		URTIs, otitis media, sinusitis, pharyngitis, etc.
Juzych, 2005	the USA	Clinician	NRCT	Primary care clinics	21	9	79.8 % < 15 yrs	85.6 %<15 yrs	bronchitis, otitis media, pharyngitis, URIs
Razon, 2005	Israel	Clinician	Before-and-after study	Community child healthcentres	27		between 3 m to 18 yrs		otitis media, pharyngitis/ tonsillitis, sinusitis, URTIs
Gerber, 2013	the USA	Clinician	Cluster-RT	Primary care pediatric practices	9 practices	9 practices	median =5 yrs	median = 4 yrs	sinusitis, streptococcal pharyngitis, pneumonia
Gulliford, 2019	the UK	Clinician	Cluster-RCT	General practices	41 practices	38 practices	< 15 yrs		cough, bronchitis, otitis media, rhinosinusitis, sore throat, common colds
Kronman, 2020	the USA	Clinician	Cluster-RT	Primary care pediatric practices	19 practices, 57 clinicians. Wedge 1 -7 Wedge 2 - 16 Wedge 3 - 18 Wedge 4 - 16		Median baseline age- 4.24 yrs Median post-intervention age-2.80 yrs		otitis media, bronchitis, pharyngitis, sinusitis, URTIs
Mainous, 2000	the USA	Combined	RCT	Private or hospital-based primary care practice	PE=53 F=49 PE+F=52	62	<18 yrs		otitis media, sinusitis, pharyngitis, pharyngitis/ tonsillitis, rhinitis, common cold/ URTIs, bronchitis
Finkelstein, 2001	the USA	Combined	Cluster-RCT	Practices affiliated with managed care organizations	6 practices	6 practices	between 3 to 72 months		otitis, pharyngitis, pneumonia, sinusitis, bronchitis, cold
Doyne, 2004	the USA	Combined	Cluster-RCT	Federally qualified health centers and traditional private practices	6 practices	6 practices	N/A		N/A
Gonzales, 2005	the USA	Combined	NRCT	Managed care organizations	5 practices	281 practices	between 0 and 17 yrs		otitis media, sinusitis, pharyngitis, bronchitis pneumonia, nonspecific URI
Finkelstein, 2008	the USA	Combined	Cluster-RCT	ambulatory and emergency departments	8 practices	8 practices	between 3 to 72 months		N/A
Francis, 2009	the UK	Combined	Cluster-RCT	General practices	30 practices	31 practices	5.1 yrs ± 3.9	5.3 yrs ± 3.8	cough, earache, runny nose, sore throat, fever, unwell look
Regev-Yochay, 2011	Israel	Combined	Cluster-RCT	Primary care pediatric solo practices	26 practices	26 practices	5.6 yrs±0.02	5.9 yrs±0.02	URTIs, fever, otitis media, pharyngitis, common cold, pneumonia
Wei, 2017	China	Combined	Cluster-RCT	Primary care township hospitals	12 practices	13 practices	between 2 and 14 yrs		nasopharyngitis, sinusitis, pharyngitis, tonsillitis, laryngitis, URI
Dekker, 2018	Netherlands	Combined	Cluster-RCT	General practice	17 practices	18 practices	4.7 yrs ± 4.4	4.4 yrs ± 4.1	fever, earache, runny nose, sore throat, cough

Abbreviations: the USA - the United States of America, the UK - the United Kingdom, RCT - randomized controlled trial, NRCT – non-randomized controlled trial, RT- randomized trial, m - month, yrs – years, PE – patient education, F-feedback.

Table 2 Description of interventions

Study ID	Intervention description		Control	Duration	Delivered by
	Parent	Clinician			
Taylor, 2005	1. Educational pamphlets "Your Child and Antibiotics". 2. A video featuring the child's pediatric practice physician, in which the main points discussed in the pamphlet were reinforced.	No	Placebo - copies of pamphlets of the "Towards Injury Protection Program"	12 months	Study coordinator
Ashe, 2006	Educational posters, summarizing the causes of a runny nose, treatment of viral respiratory infections, antibiotics, and conditions when they are required, were placed in the reception area of each practice.	No	Historical controls	1 month	N/A
Juzych, 2005	No	Half-day educational sessions on antimicrobial resistance, which utilized guidelines and case study presentations to review appropriate treatment and diagnosis of RTIs. A guideline document and various articles on antimicrobial resistance were received.	No intervention	4 months	N/A
Razon, 2005	No	1. Seminar on the diagnosis and treatment of pediatric RTIs. 2. A written summary of the recommendations.	Pre-intervention outcome	1 day	An expert in paediatric infectious diseases
Gerber, 2013	No	1. One 1-hour on-site clinician education session. 2. 1 year of personalized, quarterly audit and feedback of prescribing for bacterial and viral acute RTI.	Usual care	2.5 year	Physician member of the study team
Gulliford, 2019	No	1. A six-minute brief training on the importance of antimicrobial drug resistance and the use of the trial interventions. 2. A monthly updated feedback of data for counts of respiratory consultations and antibiotic prescriptions for that practice, in comparison with the preceding 12 months. 3. Decision support tools providing patient information sheets and advice on the positive indications for antibiotic prescription during consultations for RTI.	Usual care	12 months	A champion general practitioner
Kronman, 2020	No	Module 1: 1. 25-minute online tutorials about best practices for both parent-clinician communication practices and antibiotic prescribing. 2. Live or recorded 40-minute webinars on the same topics. 3. Four individualized feedback reports presenting antibiotic prescribing rates during ARTI visits. Module 2: 1. Two booster video vignettes on the same topics. 2. Antibiotic prescribing feedback for the module 1 period Module 3: 1. One booster video vignette 2. Antibiotic prescribing feedback for the module 2 and 3 period	Pre-intervention outcome	2 years 8 months	Study staff
Mainous, 2000	1. A letter 2. Patient education pamphlets "Your Child and Antibiotics."	1. The feedback with a prescribing profile included a listing of the total number of episodes of care for pediatric respiratory conditions, the number that received antibiotics, and the corresponding proportion that received antibiotics. Physicians were provided with their percentile rank for antibiotic prescribing compared to their peers. 2. A letter indicating little evidence of antibiotics for RTIs.	No intervention	1 month	N/A

Finkelstein, 2001	1. Patient education pamphlets "Your Child and Antibiotics." 2. A cover letter signed by the child's pediatrician. 3. Additional CDC pamphlets and posters in the waiting and examination rooms.	1. "Academic detailing" summaries promoting judicious antibiotic prescribing. 2. 90-minute small group educational session on antibiotic resistance and potential ways to prevent overuse of antibiotics. 3. Antibiotic prescribing feedback (bar graphs of practitioner and practice-level antibiotic prescribing rates) from the previous year.	Unclear	1 year	Peer leaders Study coordinators
Doyne, 2004	Pamphlets, posters, and flyers on illness prevention, when to seek care, what to expect from office visits, the limited role of antibiotic treatment for some conditions, and the dangers of unnecessary antibiotic use, plus recommendations for the prescription of antibiotics for common disorders affecting young children.	1. Evidence-based clinical practice guidelines. 2. Educational seminar on antibiotic resistance and its implications, antibiotics for common disorders, tools to reduce antibiotic use, alternative treatments, results of the parental focus groups, and advice on how to say "no" to parental demand for antibiotics. 3. Quarterly provided report cards detailing antibiotic-prescribing data	Guidelines and practice -specific report cards were distributed twice by mail	12 months	Study investigator, Local leader
Gonzales, 2005	1. A bilingual introductory letter. 2. CDC brochures on antibiotic resistance. 3. A refrigerator magnet. 4. A reference card providing easy-to-read facts about symptoms and treatments for ARIs. 5. CDC posters and patient reference cards. 6. Examination room posters.	1. Antibiotic prescribing profiles and practice guidelines were mailed.	Unclear	N/A	N/A
Finkelstein, 2008	1. Brochure "Kids and Antibiotics" with general information about antibiotic use and resistance. 2. Newsletters mailed twice each winter to address key topics related to antibiotic use and to combat misconceptions that were found to be prevalent in these communities. 3. Website and interactive activities for parents and children. 4. Posters, illness-specific handouts, and stickers. 5. Counter-top displays with handouts and stickers in pharmacies. 6. Training (in year 3) of local child care center directors and teachers on antibiotic resistance and appropriate exclusion policies for upper respiratory illnesses.	1. Bimonthly faxed or emailed briefs (1 page) on a topic related to antibiotic use, respiratory tract infections, or antibiotic resistance. 2. Feedback about prescribing by practice. 3. 2 face-to-face meetings focusing on diagnosis and treatment of infections. 4. Study coordinator visits.	No intervention	3 cold seasons	Educational coordinators
Francis, 2009	An eight-page booklet on respiratory tract infections in children.	Online training on the use of the booklet.	Usual care	1,5 year	N/A
Regev-Yochay, 2011	Posters, pamphlets, and coloring booklets	1. Three workshops on non-judicious antibiotic prescription, parent-physician communication, and antibiotic prescription rate feedback. 2. Development of evidence-based guidelines for the diagnosis and management of RTIs. 3. A seminar on RTIs diagnostic skills and tools. 4. Distribution of relevant abstracts from leading journals. 5. Development of a campaign for parents and children. 6. A simulation seminar on parent-physician communication and physician leadership.	No intervention	3 years	Local leaders

Wei, 2017	Leaflets and video educating caregivers about antibiotics.	1. The guidelines covering best practice in clinical assessment, diagnosis, and treatment of respiratory diseases or upper respiratory tract infections. 2. A 2-hour interactive training session covering the use of the guidelines, communication skills, and case study-based role-plays to correctly diagnose children with viral upper respiratory tract infections and explain to caregivers why antibiotics were not needed for such infections. 3. Monthly peer-review meetings during which doctors' antibiotic prescribing rates were assessed.	Usual care	6 months	N/A
Dekker, 2018	A written information booklet on the epidemiology of RTI, their predominant viral cause, self-limiting prognosis, the rationale to withhold antibiotics and antibiotic-related problems, including bacterial resistance, self-management strategies, and signs and symptoms that require GP consultation.	1. Online training on the prevalence of prudent antibiotic use and problems related to it, RTI guidelines, and communication skills. 2. Videos of consultation techniques.	Usual care	N/A	N/A

Table 3 Effects of interventions. Abbreviations: OR – odds ratio, RR – rate ratio, MD – mean difference.

Study ID	Outcome	Intervention	Control	OR [95% CI] or RR [95% CI]	Difference	Significance
Studies targeting parents only						
Taylor, 2005	Total number of prescriptions for antibiotics	2.2 ± 2.6	2.5 ± 2.9	-	MD: 0.30 [-0.78 to 0.18]	0.22
Ashe, 2006	Proportion of visits that resulted in a prescription for an antibiotic	151/360 [41.9%]	175/360 [48.6%]	0.76 [0.57 to 1.02]	-	0.07
Studies targeting clinicians only						
Juzych, 2005	Changes in antibiotic prescribing rates	-25.9%	-4.8%	-	21.1%	<0.05
Razon, 2005	Proportion of visits that resulted in a prescription for an antibiotic	1) AOM - 1848/2114 [87.4%] 2) Pharyngitis/ tonsillitis - 1196/1434 [83.4%] 3) Sinusitis - 160/186 [86.1 %] 4) URTI - 97/846 [11.5%]	1) AOM - 1606/1727 [93 %] 2)Pharyngitis/ tonsillitis -1348/1610 [83.7 %] 3) Sinusitis - 143/166 [86.1 %] 4) URTI - 119/861 [13.8 %]	1) 0.52 [0.42 to 0.66] 2) 0.98 [0.81 to 1.18] 3) 0.99 [0.54 to 1.81] 4) 0.81 [0.61 to 1.08]	-	1) <0.05 2) 0.81 3) 0.97 4) 0.14
Gerber, 2013	Change in overall proportion of broad-spectrum antibiotic prescriptions	12.5%	5.8%	-	6.7%	0.01
Gulliford, 2019	Antibiotic prescribing rate per 1000 patient-years	139.3 [55 557]	139.8 [47 509]	RR: 0.96 [0.82 to 1.12]	-	-
Kronman, 2020	Rate ratios of antibiotic prescribing	1) Module 1 - 0.96 [0.93 to 0.99] 2) Module 2 - 0.84 [0.81 to 0.88] 3) Module 3 - 0.89 [0.86 to 0.92] 4) post-intervention - 0.93 [0.90 to 0.96]	Reference	-	1) Module 1 decreased 4% [1% to 7%] 2) Module 2 - 16% [12% to 19%] 3) Module 3 - 11% [8% to 14%] 4) Post-intervention - 7% [4% to 10%]	-

Studies targeting both parents and clinicians						
Mainous, 2000	Percentage of episodes with antibiotics	1) Patient education - 44.5 ± 25.6 2) Feedback - 43.6 ± 28 3) Combined - 49.7 ± 22.3	53.5 ± 26.8	-	1) -9.00 [-9.40 to -8.60] 2) -9.90 [-10.30 to -9.50] 3) -3.80 [-4.20 to -3.40]	<0.05
Finkelstein, 2001	Change in antibiotic use per person-year 3 months < 36 months 36 months < 72 months	 18.6% 15%	 11.5% 9.8%	-	 7.1% 5.2%	<0.05
Doyne, 2004	The ratio of antibiotic prescriptions filled to the number of office visits	0.82 [0.71 - 0.95]	0.86 [0.77 - 0.95]	-	0.04	NS
Gonzales, 2005	Changes in antibiotic prescribing rates	-4%	Local control: -2% Distant control: 1%	-	-2% -5%	0.18 0.48
Finkelstein, 2008	Change in antibiotic dispensing rates 3 months < 24 months 24 months < 48 months 48 months < 72 months	 21.2% 14.5% 9.3%	 20.7% 10.3% 2.5%	-	 0.5% 4.2% 6.7%	 0.69 0.01 <0.05
Francis, 2009	Antibiotic prescribed at index consultation	50/256 [19.5%]	111/272 [40.8%]	0.35 [0.24 to 0.52]	-	<0.05
Regev-Yochay, 2011	Number of antibiotic prescriptions per 100 patient-years	1) year 0 (baseline) - 78.38 [43677] 2) year 1 (baseline) - 65.57 [44702] 3) year 2 -46.93 [42495] 4) year 3 - 48.18 [46046] 5) year 4 - 48.99 [49341] 6) year 5 - 45.91 [49998]	1) year 0 (baseline) - 76.32 [44453] 2) year 1 (baseline) - 70.95 [45195] 3) year 2 - 59.34 [45918] 4) year 3 - 57.58 [48023] 5) year 4 - 59.60 [48323] 6) year 5(post-intervention) - 54.56 [47701]	RR: 1) 1.12 [0.91 to 1.36] 2) 0.91 [0.89 to 0.93] 3) 0.77 [0.75 to 0.78] 4) 0.81 [0.79 to 0.83] 5) 0.81 [0.79 to 0.83] 6) 0.84 [0.82 to 0.86]	-	-
Wei, 2017	Proportion of visits that resulted in a prescription for an antibiotic At 6 months follow-up At 18 months follow-up	 943/2351 [40%] 2748/5084 [54%]	 1782/2552 [70%] 2772/3685 [75%]	 0.29 [0.26 to 0.33] 0.39 [0.35 to 0.43]	-	<0.05
Dekker, 2018	Proportion of visits that resulted in a prescription for an antibiotic	102/475 [21.4%]	176/531 [33.2%]	0.55 [0.42 to 0.73]	-	<0.05

2. Studies targeting clinicians only

The results of studies targeting only clinicians were also varied. No significant difference (RR – 0.96, p>0.05) was observed between the intervention and control groups in one of the trials investigating the effect of brief training, prescribing feedback, and a decision support tool [22]. However, the remaining four trials reported a significant difference between the groups [21, 23-25]. The largest difference of 21.1% (p<0.05) was identified in a study exploring the impact of half-day educational sessions [23]. Another considerable difference of 16% (p<0.05) was found after the implementation of booster activities following the main ones, such as online tutorials, webinars, and prescribing feedback [24]. The remaining three studies investigating the impact of educational sessions and prescribing feedback demonstrated an effect size of up to 10% [21, 25, 33]. However, of note, in one of these trials, evidence of intervention effectiveness was found for only acute otitis media (OR - 0.52, p<0.05), whereas no evidence of intervention effectiveness (OR – 0.98; 0.99; 0.81, p>0.05) was observed for pharyngitis/tonsillitis, sinusitis, and upper RTIs [25].

The antibiotic prescribing rates in the post-intervention period were analyzed in one study [24]. As a result, the 2-8-month post-intervention follow-up analysis demonstrated a 7% decrease (95% CI, 4%-10%) in the probability of antibiotic prescribing for acute RTIs [24].

3. Studies targeting both parents and clinicians

The studies targeting both parents and clinicians gave mixed results. No evidence of a difference (MD - 0.04, p>0.05; MD - 2%, 5%, p>0.05) was detected in two studies [28, 32]. Additionally, one study demonstrated no evidence of intervention effectiveness (MD - 0.5%, p>0.05) for the group of children who are under 24 months [30]. The remaining trials presented a significant difference in antibiotic prescribing between the intervention and control groups. The most considerable difference of 30% (p<0.05) was observed in a study investigating

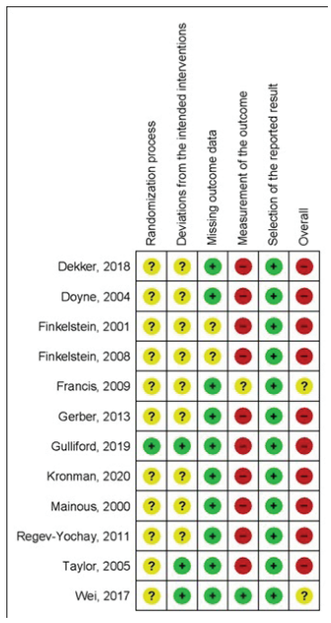

Figure 2a – Risk of bias summary of non-randomized controlled trials, before-and-after studies, and studies with historical controls. Green color indicates a low risk of bias, yellow- no information, and red-serious risk

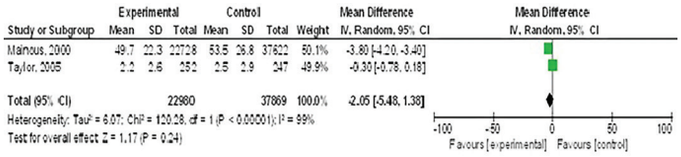

Figure 3a – Antibiotic prescribing rates at the end of the study, intervention versus control group

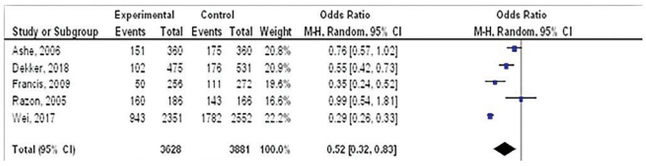

Figure 3b – Antibiotic prescribing rates at the end of the study, intervention versus control group. Second part

the impact of patient and clinician educational materials, clinician training sessions, and peer-review meetings [34]. Another significant difference of 21.3% (OR - 0.35, p<0.05) was observed in another study exploring the effect of online training for clinicians and a patient booklet [31]. A similar effect (OR - 0.84, p<0.05) was observed in a study consisting of several programs such as workshops, seminars, educational materials, and developing a campaign and evidence-based guidelines [26]. The remaining four studies observed an effect size of around 10% [27, 29, 30, 33].

The antibiotic prescribing rates in the post-intervention period were analyzed in two studies [26, 34]. A one-year follow-up analysis illustrated that the intervention effect was maintained with the RR 0.84 (95% CI, 0.82 to 0.86, p<0.05) after the study period in one study [26]. Similarly, the intervention effect was sustained in another study at the 18-month follow-up with the OR 0.39 (95% CI, 0.35 to 0.43, p<0.05) [34].

Additional analysis

It was not possible to conduct a meta-analysis as the populations, interventions, outcomes, and study designs of included studies were considerably diverse. Moreover, different effect measures were used by studies, and statistics were not available to enable further analysis. Statistical heterogeneity and inconsistency was also observed across studies (See Figure 3).

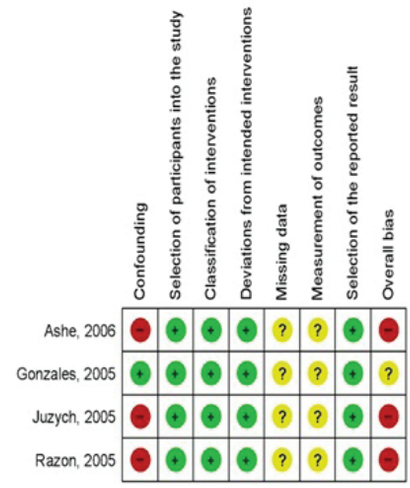

Figure 2b – Risk of bias summary of randomized controlled trials. Green color indicates a low risk of bias, yellow- some concerns, and red-high risk of bias

Discussion

the number of studies exploring clinician and combined parent-clinician educational interventions was limited. There is some evidence that these educational interventions might have a positive effect, but the effect size for the majority of studies was small (<10%) and it is questionable if this is significant for reducing antibiotic overuse in a population level. Notably, the evidence was not strong as most studies were of high risk of bias. The clinical and methodological diversity made it difficult to compare studies, for instance, a one-day intervention [25] versus another which lasted two years and eight months [24].

The evidence base for educational interventions targeting only parents was even more limited compared to those targeting clinicians or both. Once again, there were very few primary studies and there was considerable heterogeneity. Therefore, firm conclusions regarding the effectiveness of parent, clinician, or combined parent-clinician educational interventions can not be reliably made.

There are however a couple of different observations made by this systematic review compared to previous ones. Vodichka et al.'s review concluded that interventions targeting only parents do not seem to change antibiotic prescribing rates for children significantly [17]. However, this review suggests such a conclusion cannot be drawn due to the paucity of primary studies to corroborate this view. Similarly, Vodichka et al. stated the existence of moderate evidence of greater effectiveness of combined intervention compared to others [17]. However, this review indicates that despite the presence of some low-quality evidence on the effectiveness of combined interventions, the evidence-base seems to be insufficient to infer this conclusion.

Implications for practice

Whilst the evidence base for educational interventions is limited, it does hint at possible efficacy of educational interventions targeting clinicians, or possibly parents and clinicians together. Real world evidence gathering for this would be helpful and could be achieved through robust monitoring and evaluation of any such interventions that are subsequently developed and delivered in practice. Other modalities of antibiotic stewardship may be more efficacious, e.g., antibiotic prescribing guidelines, requirement for prior authorization for restricted antibiotics, prescribing audits and feedback, self-directed antibiotic reassessments (a.k.a "antibiotic timeouts"), and antibiotic dose as well as duration optimization [36]. That

said, it would be of value to compare the relative efficacies of these modalities versus clinician and parent education to inform prioritization of interventions.

The national guideline may contain recommendations about which educational interventions should be implemented to reduce antibiotic use. The prioritization process should be carried out: evaluation of antibiotic resistance in a specific region, assessment of the particular educational intervention's effect, cost-effectiveness analysis, and ethical considerations. Further, decision-makers and healthcare professionals decide on the best interventions, improve them, and allocate resources.

Implications for research

The paucity of robust studies in this topic area calls for more research, especially for studies of educational interventions targeting parents. In addition, this review only examined antibiotic use with regards to RTIs, and it may be of value exploring antibiotic use for other common infections such as gastrointestinal and urinary tract infections for example. Also, this review was limited to primary care settings only, and analyzing the intervention effect in the inpatient departments may have influenced the reduction of antibiotic use. Furthermore, almost all studies were carried out in high-income countries. Thus, further high-quality research is strongly recommended, especially in middle and low-income countries.

Notably, whilst the type of intervention reviewed was defined to be educational, its components and characteristics were heterogeneous, e.g., in terms of what the intervention consisted of, its contents, mode of delivery, who delivered it, or duration of delivery. It is therefore difficult to say what type of educational intervention would be most efficacious, or in which contexts (e.g., young ill child versus older ill child, rural versus urban settings, etc.). Neither is it clear which modality is most efficient and cost-effective, which are essential considerations for policymakers. Consequently further research is required to elucidate these key aspects further.

Limitations

there are several limitations with this review. The primary limitation was the low quality of included studies. Only three trials were of unclear risk of bias, whereas the remaining thirteen were of high risk of bias [19-30, 33]. Another important limitation was clinical and methodological diversity which was seen by variation in characteristics of included studies. For instance, population characteristics such as age, sex, ethnicity, types of RTIs that children have, and severity of illness varied widely or were not reported by the primary studies. Additionally, as mentioned above, the educational interventions used were diverse. The duration of interventions, providers, comparators, and time points of outcome measurement differed considerably or were not described by the primary studies. This heterogeneity made it challenging to compare trials with each other. Whilst the included studies examined the frequency of antibiotic use, it was not possible to ascertain the appropriateness of antibiotic prescribing. The field of antibiotic resistance is also diverse and complex, and there are multiple drivers. For example, the relative contributions of animal versus human use of antibiotics, broad spectrum versus narrow spectrum antibiotic use, short versus long duration antibiotic use, and primary care versus hospital prescribing.

Conclusions

overall, the evidence-base was limited but there is some suggestion that educational interventions targeted at clinicians, and possibly parent-clinician combinations too, might work. These measures are unlikely to sufficient to address the growing antibiotic resistance problem, and it is likely that a basket of interventions including both policy and practice interventions will be required. In the absence of any new potent antibiotic discoveries, these measures will need to be amply resourced and sustained in order to maintain the efficacy of existing antibiotics against many infections.

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Supplement 1 Search strategies

MEDLINE via Ovid, last searched in June 7th, 2024(74 results):

1	exp Child/	2095827
2	exp Adolescent/	2186188
3	youth*.mp.	98283
4	teen*.mp.	34374
5	kid*.mp.	954140
6	young.mp.	1450053
7	pediatric.mp.	359550
8	paediatric.mp.	70899
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	5020952
10	exp Patient Education as Topic/	88438
11	exp Patient Education Handout/	5553
12	exp Health Education/	259292
13	clinician education.mp.	405
14	educational intervention*.mp.	13908
15	exp Education/	881252
16	training.mp.	542158
17	10 or 11 or 12 or 13 or 14 or 15 or 16	1274176
18	reduc*.mp.	4077995
19	decreas*.mp.	2812076
20	minimiz*.mp.	210470
21	minimis*.mp.	24275
22	prevent*.mp.	2692996
23	18 or 19 or 20 or 21 or 22	7977548
24	exp Anti-Bacterial Agents/	792958
25	antimicrobial*.mp.	214012
26	antibiotic*.mp.	436588
27	antibacterial*.mp.	97099
28	antibiotic prescribing.mp.	3498
29	antibiotic prescription*.mp.	3790
30	24 or 25 or 26 or 27 or 28 or 29	1121356
31	exp Respiratory Tract Diseases/	1636077
32	exp Respiratory Tract Infections/	559531
33	respiratory illness*.mp.	8155
34	exp Pneumonia/	280716
35	exp Bronchitis/	30996
36	exp Cough/	17940
37	chest infection*.mp.	1478
38	exp Sinusitis/	22648
39	exp Common Cold/	4374
40	exp Tonsillitis/	8182
41	exp Laryngitis/	4087
42	exp Bronchiolitis/	9483
43	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42	1639634
44	exp Primary Health Care/	185146
45	exp Family Practice/	66658
46	exp General Practice/	77755
47	gp.mp.	47515
48	primary care.mp.	137906
49	44 or 45 or 46 or 47 or 48	362294
50	9 and 17 and 23 and 30 and 43 and 49	86
51	limit 50 to (english language and yr="2000 - 2024")	74

Cochrane Library, Cochrane Central Register of Controlled Trials, last searched in June 12th, 2024 (107 results):

1	child*	196238
2	adolescent*	149026
3	youth*	9505
4	teen*	3607
5	teenager*	1222
6	kid*	63662
7	Young	126869
8	Paediatric	57564
9	Pediatric	57571
10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	423040
11	Education	91741
12	educational intervention	20573
13	patient education	36490
14	patient medication education	5348
15	educational session	4217
16	patient counseling education	5208
17	health education	51534
18	clinician education	2202
19	staff education	5565
20	Training	109584
21	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20	184379
22	reduc*	462365
23	prevent*	265725
24	decreas*	253739
25	minimis*	6796
26	minimiz*	15298
27	#22 or #23 or #24 or #25 or #26	745419
28	antibiotic*	35764
29	antibacterial*	14755
30	antimicrobial*	12613
31	antibiotic prescribing	949
32	antibiotic prescription	1286
33	#28 or #29 or #30 or #31 or #32	49413
34	primary care	113970
35	primary healthcare	15868
36	general practice*	28032
37	family practice*	13549
38	Gp	11442
39	#34 or #35 or #36 or #37 or #38	143917
40	respiratory tract infection*	13053
41	respiratory tract disease*	11762
42	respiratory illness	6310
43	Pneumonia	19445
44	Bronchitis	4701
45	Bronchiolitis	1673
46	Cough	11287
47	Sinusitis	3371
48	chest infection	3346
49	common cold	2838
50	Tonsillitis	1199
51	Laryngitis	287
52	#40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51	55578
53	#10 and #21 and #27 and #33 and #39 and #52 with Publication Year from 2000 to 2024, with Cochrane Library publication date Between Jan 2000 and Jan 2024, in Trials (Word variations have been searched)	107

APA PsycInfo, last searched in June 13th, 2024 (2 results):

1	child*.mp.	867898
2	adolescent*.mp.	474608
3	youth*.mp.	122618
4	teenager*.mp.	10084
5	teen*.mp.	25428
6	young.mp.	372013
7	kid*.mp.	19896

8	paediatric.mp.	5177
9	pediatric.mp.	3655
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	1342039
11	exp Primary Health Care/	20122
12	primary care.mp.	35203
13	general practice.mp.	5624
14	family practice.mp.	5844
15	gp.mp.	4714
16	11 or 12 or 13 or 14 or 15	48354
17	exp Health Education/	2015
18	patient education.mp.	14044
19	exp Educational Programs/	9746
20	exp Parent Training/	771
21	exp Education/	465222
22	educational intervention*.mp.	6362
23	clinician education.mp.	82
24	exp Training/	84916
25	staff education.mp.	566
26	exp Personnel Training/	17736
27	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	519011
28	reduc*.mp.	482699
29	prevent*.mp.	266431
30	minimis*.mp.	3091
31	minimiz*.mp.	30721
32	decreas*.mp.	287086
33	28 or 29 or 30 or 31 or 32	910955
34	exp Antibiotics/	2581
35	antimicrobial*.mp.	716
36	antibacterial.mp.	175
37	antibacterial agent*.mp.	28
38	exp "Prescribing (Drugs)"/	4124
39	antibiotic* prescribing.mp.	157
40	34 or 35 or 36 or 37 or 38 or 39	7268
41	respiratory tract infection*.mp.	784
42	respiratory infection*.mp.	714
43	respiratory tract disease*.mp.	310
44	respiratory illness*.mp.	408
45	exp Pneumonia/	696
46	bronchitis.mp.	397
47	bronchiolitis.mp.	65
48	cough.mp.	1373
49	chest infection.mp.	19
50	sinusitis.mp.	230
51	common cold.mp.	328
52	tonsillitis.mp.	72
53	laryngitis.mp.	45
54	41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53	4741
55	10 and 16 and 27 and 33 and 40 and 54	2

CINAHL, last searched in June 13th, 2024 (94 results):

1	children or adolescents or youth or child or teenager or teens or young people or kids or paediatric or pediatric
2	reduce or decrease or minimize or prevent
3	antibiotics or antibacterial or antimicrobials
4	primary care or primary health care or primary healthcare or general practice or gp
5	respiratory illness or respiratory infection or pneumonia or bronchitis or cough

Supplement 2 A completed data extraction form.

Study ID	Dekker, 2018
Date form completed	16.06.2024
Name/ID of person extracting data	Aizhan Baltabay
Study author contact details	a.r.j.dekker-8@umcutrecht.nl
Country	Netherlands
Notes	
Methods	**Methods**
Aim of study	to reduce antibiotic prescribing for children with RTI by online training for general practitioners (GPs) and information for parents
Design	pragmatic cluster randomized controlled trial
Unit of allocation	the general practice
Start date	N/A
End date	N/A
Setting	general practice
Notes	trial with measurements before and after the intervention
Participants	**Participants**
Population description	children younger than 18 years with signs and symptoms of RTI (nose, ear, throat and/or lower RTI symptoms), presenting at their general practice during the winter season
Inclusion criteria	to register 40 consecutive consultations of children younger than 18 years with signs and symptoms of RTI (nose, ear, throat and/or lower RTI symptoms), presenting at their general practice during the winter season 2013–14
Exclusion criteria	GPs registered less than 10 patients in total per general practice
Total no. randomised (or total pop. at start of study for NRCTs)	35 practices were randomised
Number in intervention group	17 practices number of GPs - 40
Number in control group	18 practices number of GPs – 35
Age of children (mean)	intervention = 4.7 yrs ± 4.4 control = 4.4 yrs ± 4.1
Sex	N/A
Race/Ethnicity	N/A
Illnesses	symptoms: fever, earache, runny nose, sore throat, cough
Severity of illness	intervention = 1.6 control =1.9 1 is not ill, 5 is severely ill
Subgroups reported	N/A
Control	usual care
Notes	

Intervention group	Intervention group
Description of clinician intervention	Online training for GPs was designed to promote positive expectations and self-confidence in GPs and patients to manage the infection without antibiotics. The online training consisted of three parts. The first part was a general background about the relevance of prudent antibiotic use and information about antibiotic-related problems. The second part informed about the child-specific parts of the four national RTI guidelines of the Dutch College of GPs, including assessment of disease severity, risk factors, signs and symptoms, when to prescribe antibiotics and the advised first- and second-choice antibiotic treatment. The third part focused on training in enhanced communication skills, supported by videos of consultation techniques.
Description of patient intervention	The booklet contained the following information in text and pictograms: epidemiology of RTI, their predominant viral cause, self-limiting prognosis, rationale to withhold antibiotics and antibiotic-related problems, including bacterial resistance, self-management strategies, signs and symptoms that require GP consultation.
Duration	N/A
Providers	N/A
Notes	
Outcomes	Outcomes
Outcome name	Primary outcome - the antibiotic prescription rate per general practice in the follow-up audit, as documented on the consultation report forms filled in by the GPs.
Time points measured	N/A
Time points reported	N/A
Unit of measurement	percentage of prescribed AB

Data analysis	Generalized linear model for Poisson distributed count outcomes.
Number included in the analysis	In the intervention group: 15 practices - 475 consultations In the control group: 17 practices - 531 consultations
Notes	Pharmacy antibiotic dispensing data were retrieved per practice.
Results	Results
Baseline audit	During the baseline audit 1009 consultations of children with symptoms of RTI were registered by 75 GPs from 35 general practices. The mean antibiotic prescription rate from this baseline audit was 29.6% (35.7%, SD 4.8 in the control group versus 24.2%, SD 4.3 in the intervention group).
Intervention compliance	The training was completed by all 40 GPs of the intervention group. Their median time logged-in was 1 h and 18 min.
Withdrawals and exclusions from the analysis	Lost to follow up in the intervention group is 2 as they did not register consultations. Lost to follow up in the control group is 1 as they registered only 6 consultations. 3 consultations were excluded due to lacking the primary outcome
Primary outcome	In 21.4% of consultations an antibiotic was prescribed in intervention practices, compared with 33.2% in the control group. Intervention group - 102/475 Control group - 176/531
Notes	
Other information	
Study funding sources (including role of funders)	Netherlands Organisation for Health Research and Development. Study was conducted independently.
Possible conflicts of interest (for study authors)	N/A
Notes	

Supplement 3 The list of studies excluded at the text stage

Reason for exclusion: wrong participants
Camacho M, Nogales M, Manjon R, Del Granado M, Pio A, Ottmani S. Results of PAL feasibility test in primary health care facilities in four regions of Bolivia. The International Journal of Tuberculosis and Lung Disease [Internet]. 2007 Nov 1;11(11):1246-52.
Chazan B, Turjeman RB, Frost Y, Besharat B, Tabenkin H, Stainberg A, Sakran W, Raz R. Antibiotic consumption successfully reduced by a community intervention program. IMAJ-RAMAT GAN [Internet]. 2007 Jan 1;9(1):16.
Gjelstad S, Høye S, Straand J, Brekke M, Dalen I, Lindbæk M. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study). Bmj [Internet]. 2013 Jul 26;347.
Hickman DE, Stebbins MR, Hanak JR, Guglielmo BJ. Pharmacy-based intervention to reduce antibiotic use for acute bronchitis. Annals of Pharmacotherapy. 2003 Feb [Internet];37(2):187-91.
Llor C, Bjerrum L, Munck A, Cots JM, Hernández S, Moragas A. Access to point-of-care tests reduces the prescription of antibiotics among antibiotic-requesting subjects with respiratory tract infections. Respiratory Care [Internet]. 2014 Dec 1;59(12):1918-23.
Reyes-Morales H, Flores-Hernandez S, Tome-Sandoval P, Perez-Cuevas R. A multifaceted education intervention for improving family clinicianphysicians' case management. Family medicine [Internet]. 2009 Apr 1;41(4):277-84.
Butler CC, Simpson SA, Dunstan F, Rollnick S, Cohen D, Gillespie D, Evans MR, Alam MF, Bekkers MJ, Evans J, Moore L. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. Bmj [Internet]. 2012 Feb 2;344.
van der Velden AW, Kuyvenhoven MM, Verheij TJ. Improving antibiotic prescribing quality by an intervention embedded in the primary care practice accreditation: the ARTI4 randomized trial. Journal of Antimicrobial Chemotherapy [Internet]. 2016 Jan 1;71(1):257-63.
Hallsworth M, Chadborn T, Sallis A, Sanders M, Berry D, Greaves F, Clements L, Davies SC. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. The Lancet [Internet]. 2016 Apr 23;387(10029):1743-52.

Guthrie B, Kavanagh K, Robertson C, Barnett K, Treweek S, Petrie D, Ritchie L, Bennie M. Data feedback and behavioural change intervention to improve primary care prescribing safety (EFIPPS): multicentre, three arm, cluster randomised controlled trial. Bmj [Internet]. 2016 Aug 18;354.
Stewart J, Pilla J, Dunn L. Pilot study for appropriate anti-infective community therapy. Effect of a guideline-based strategy to optimize use of antibiotics. Canadian Family clinicianPhysician [Internet]. 2000 Apr 1;46(4):851-9.
Esmaily HM, Silver I, Shiva S, Gargani A, Maleki-Dizaji N, Al-Maniri A, Wahlstrom R. Can rational prescribing be improved by an outcome-based educational approach? A randomized trial completed in Iran. Journal of Continuing Education in the Health Professions [Internet]. 2010 Dec;30(1):11-8.
Reason for exclusion: wrong intervention
Rolf von den Baumen T, Crosby M, Tadrous M, Schwartz KL, Gomes T. Measuring the impacts of the Using Antibiotics Wisely campaign on Canadian community utilization of oral antibiotics for respiratory tract infections: a time-series analysis from 2015 to 2019. Journal of Antimicrobial Chemotherapy [Internet]. 2021 Sep;76(9):2472-8.
Strumann C, Steinhaeuser J, Emcke T, Sönnichsen A, Goetz K. Communication training and the prescribing pattern of antibiotic prescription in primary health care. PloS one [Internet]. 2020 May 19;15(5):e0233345.
Vervloet M, Meulepas MA, Cals JW, Eimers M, Van Der Hoek LS, Van Dijk L. Reducing antibiotic prescriptions for respiratory tract infections in family practice: results of a cluster randomized controlled trial evaluating a multifaceted peer-group-based intervention. NPJ primary care respiratory medicine [Internet]. 2016 Feb 4;26(1):1-6.
Freer J, Ally T, Brugha R. Impact of Centor scores on determining antibiotic prescribing in children. International Journal of Health Care Quality Assurance [Internet]. 2017 May 8. Høye S, Gjelstad S, Lindbæk M. Effects on antibiotic dispensing rates of interventions to promote delayed prescribing for respiratory tract infections in primary care. British Journal of General Practice. 2013 Nov 1;63(616):e777-86.
Reason for exclusion: wrong setting
Belongia EA, Sullivan BJ, Chyou PH, Madagame E, Reed KD, Schwartz B. A community intervention trial to promote judicious antibiotic use and reduce penicillin-resistant Streptococcus pneumoniae carriage in children. Pediatrics [Internet]. 2001 Sep 1;108(3):575-83.
Belongia EA, Knobloch MJ, Kieke Jr BA, Davis JP, Janette C, Besser RE. Impact of statewide program to promote appropriate antimicrobial drug use. Emerging infectious diseases [Internet]. 2005 Jun;11(6):912.
Perz JF, Craig AS, Coffey CS, Jorgensen DM, Mitchel E, Hall S, Schaffner W, Griffin MR. Changes in antibiotic prescribing for children after a community-wide campaign. Jama [Internet]. 2002 Jun 19;287(23):3103-9.
Hennessy TW, Petersen KM, Bruden D, Parkinson AJ, Hurlburt D, Getty M, Schwartz B, Butler JC. Changes in antibiotic-prescribing practices and carriage of penicillin-resistant Streptococcus pneumoniae: a controlled intervention trial in rural Alaska. Clinical Infectious Diseases [Internet]. 2002 Jun 15;34(12):1543-50.
Reason for exclusion: absence of results
Altiner A, Berner R, Diener A, Feldmeier G, Köchling A, Löffler C, Schröder H, Siegel A, Wollny A, Kern WV. Converting habits of antibiotic prescribing for respiratory tract infections in German primary care–the cluster-randomized controlled CHANGE-2 trial. BMC Family Practice [Internet]. 2012 Dec;13(1):1-7.
Bjerrum L, Munck A, Gahrn-Hansen B, Hansen MP, Jarboel D, Llor C, Cots JM, Hernández S, López-Valcárcel BG, Pérez A, Caballero L. Health alliance for prudent prescribing, yield and use of antimicrobial drugs in the treatment of respiratory tract infections (HAPPY AUDIT). BMC Family Practice [Internet]. 2010 Dec;11(1):1-7.

Supplement 4 A completed risk of bias assessment form for randomized controlled trials.

Study ID: Dekker, 2018
Abbreviations: Y- yes, PY – probably yes, N- no, PN – probably not, NI – no information.

Signalling questions	Comments	page number	Response
Domain 1: Risk of bias arising from the randomization process			
Was the allocation sequence random?	Simple random allocation was performed by a computer-generated list on general practice level.	3	Y
Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Information is not provided		NI
Did baseline differences between intervention groups suggest a problem with the randomization process?	Practices of the intervention and control groups were comparable with respect to their total list size and numbers of listed children. Consultations were comparable between the intervention and control groups with respect to children's age, duration of illness before consultation, illness severity and presentation with fever	4	N
Risk-of-bias judgement	Some concerns		
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)			
Were participants aware of their assigned intervention during the trial?	Participating clinicianphysicians completed the short online evaluation of the GP training, which was assessed by study investigators.	3	PY
Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Information is not provided		NI
If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Information is not provided		NI

If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			
If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			
Was an appropriate analysis used to estimate the effect of assignment to intervention?	The primary analysis was according to the principle of intention-to-treat.	3, 4	Y
If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			
Risk-of-bias judgement	Some concerns		
Domain 3: Missing outcome data			
Were data for this outcome available for all, or nearly all, participants randomized?	Three consultations lacked the primary outcome and were excluded from analyses. Data for the rest of consultations was available.	4	Y
If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?			
If N/PN to 3.2: Could missingness in the outcome depend on its true value?			
If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			
Risk-of-bias judgement	Low risk		
Domain 4: Risk of bias in measurement of the outcome			
Was the method of measuring the outcome inappropriate?	The method of measuring the outcome was appropriate. The analysis was according to the principle of intention-to-treat. The numbers of total dispensed antibiotics were analysed using a generalised linear model and controlled for the numbers of dispensed antibiotics in the year preceding the intervention and the numbers of children in the practice.	3	N
Could measurement or ascertainment of the outcome have differed between intervention groups?	Total and types of dispensed antibiotic courses for all children under 18 years were collected via the Dutch Foundation for Pharmaceutical Statistics. Therefore, the likelihood that measurement or ascertainment of the outcome differed between the groups is low.	4	N
If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Information is not provided		NI
If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Information is not provided		NI
If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Information is not provided		NI
Risk-of-bias judgement	High risk		
Domain 5: Risk of bias in selection of the reported result			
Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The data was analysed in accordance with a pre-specified analysis plan.	3,4	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from... 5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The numerical result is not likely to be selected on the basis of the results from multiple eligible outcome measurements.	4	N
5.3 ... multiple eligible analyses of the data?	The numerical result is not likely to be selected on the basis of the results from multiple eligible analyses of the data.	4	N
Risk of bias judgement	Low risk		
Overall risk of bias	High risk		

Supplement 5 A completed risk of bias assessment form for non-randomized controlled trials, before-and-after studies, and studies with historical controls.

Study ID: Juzych, 2005
Abbreviations: Y- yes, PY – probably yes, N- no, PN – probably not, NI – no information.

Signalling questions	Comments	Page number	Response
Risk of bias due to confounding			
1.1 Is there potential for confounding of the effect of intervention in this study? If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	Anti-pneumococcal vaccine may be a confounder.	4	Y
If Y/PY to 1.1: 1.2. Was the analysis based on splitting participants' follow up time according to intervention received? If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, proceed to question 1.3.	The analysis was not based on splitting participants' follow up time according to intervention received.	2	N
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)			
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Time (baseline vs study year), patient gender, and years since residency training (categorized as in practice >15 years or <15 years) were controlled. However, anti-pneumococcal vaccine was not controlled.	2	PN
1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?			
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Information is not provided		NI
1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	Information is not provided		NI
1.8. If Y/PY to 1.7: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?			
Risk of bias judgement	Serious risk		
The risk of selection bias			
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No, all four clinics of the Wellness Plan were included in the study. All of the participants had a baseline year before the intervention. Moreover, the clinics were assigned to the intervention group based on geographic proximity in order to limit the overlap of both clinicianphysicians and patients between the intervention and control locations.	1, 2	PN
If N/PN to 2.1: go to 2.4 2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?			
2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?			
2.4. Do start of follow-up and start of intervention coincide for most participants?	The baseline period for all participants was between November 16, 1999 and March 31, 2000. The study period for all participants was between November 16, 2000 and March 31, 2001.	2	PY
2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?			
Risk of bias judgement	Low		
The risk of bias due to classification of interventions			

3.1 Were intervention groups clearly defined?	The program of the intervention group consisted of half-day educational sessions covering antimicrobial resistance, and utilized guidelines and case study presentations to review appropriate treatment and diagnosis of bronchitis, pharyngitis, sinusitis, and otitis media. In addition to the presentations, the course participants received a number of patient educational materials, a guideline document, and various articles on antimicrobial resistance. The control group did not receive any intervention.	2	Y
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	The information used to define intervention groups seems to be recorded at the start of the intervention.	2	PY
Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Classification of intervention status does not seem to be affected by knowledge of the outcome or risk of the outcome.	2	PN
Risk of bias	Low		
The risk of bias due to deviations from intended interventions			
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Deviations from the intended intervention are not observed.	2	PN
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?			
Risk of bias	Low		
The risk of bias due to missing data			
5.1 Were outcome data available for all, or nearly all, participants?	Information is not provided		NI
5.2 Were participants excluded due to missing data on intervention status?	Information is not provided		NI
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Information is not provided		NI
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?			
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?			
Risk of bias	NI		
The risk of bias due to measurement of outcomes			
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Information is not provided		NI
6.2 Were outcome assessors aware of the intervention received by study participants?	Information is not provided		NI
6.3 Were the methods of outcome assessment comparable across intervention groups?	The same method of outcome assessment was used across intervention groups. Prescribing data were extracted from a pharmacy database and linked to each patient visit by date of prescription. Subsequently, the proportion of incident office visits at which the patient received an antibiotic prescription was calculated.	2	Y
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Information is not provided		NI
Risk of bias	NI		
The risk of bias due to selection of the reported result			
Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome measurements within the outcome domain?	The reported effect estimate is not likely to be selected from multiple outcome measurements within outcome domain.	2, 3	PN
7.2 ... multiple analyses of the intervention-outcome relationship?	The reported effect estimate is not likely to be selected from multiple analyses of the intervention-outcome relationship.	2, 3	PN
7.3 ... different subgroups?	The reported effect estimate is not likely to be selected from different subgroups.	2, 3	PN
Risk of bias	Low		
Overall risk	Serious risk		

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Epidemiological Transition and the Phenomenon of Depression in Indonesia: a Narrative Review

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Abstract

Indonesia is experiencing a macro transition (i.e., socio-demographic, economic) that co-occurs with the micro transitions, including epidemiological transitions in health. This transition is shown by the increase in non-communicable diseases (NCDs) and decrease in communicable diseases (CDs). Depression is one of the NCDs that has become more prevalent in Indonesia over the last 20 years. The many possible causes of depression, which include biology, environment, culture, and the interaction between these factors, may be explained by this transition. This review discussed how this change could lead to an increase in depression in Indonesia. The way genes, environment, and culture interact could be an interesting topic, according to the current epidemiological transition in Indonesia in relation to depression occurrence.

Keywords: depression, epidemiological transition, socio-cultural transition, prevalence, Indonesia.

Introduction

As a unique country with diverse ethnicity and socio-demographic conditions [1–2], Indonesia is facing transition in both macro and micro aspects. The macro transition includes changes in society, demographics, the economy, and politics. Transitions in the macro aspect tend to affect the micro aspect, such as health [2]. A notable phenomenon in the domain of public health is the epidemiological transition, which is characterized by a shift in disease prevalence from communicable diseases (CD) to non-communicable diseases (NCD). Following this situation, the increase in the prevalence of NCDs, particularly depression, has emerged as a serious concern.

Depression is now a global issue and serious NCD problem, which is predicted to be the leading cause of disability [3–6]. In 2015, depression was the most significant contributing factor to global disability, accounting for an estimated 7.5% of all-year disability. Additionally, depression was the primary cause of suicide, responsible for 800,000 deaths annually. Furthermore, major depression has emerged as one of the top five global health problems, with a prevalence of 268,172 cases and an incidence of 274,704 cases in 2016 [7-8]. The global prevalence of depression ranges from 2 to 6%. These results are consistent with those of surveys conducted in 1993, 2000, and 2007, which showed that the prevalence of depressive disorders was 2.2%, 2.8%, and 2.6%, respectively [9].

Therefore, I review this phenomenon and bring a critical point of view on how this epidemiological transition could affect the potential increase of depression prevalence in Indonesia. I believe that this may contribute to the complexity of depression etiologies and prove that it is not only a single biological consequence but also involves the socio-cultural factors that may interact with biological factors and evolve to increase the prevalence of depression.

Methods

This review was conducted using the narrative method and included supporting literature from several databases, including Google Scholar, ScienceDirect, PubMed, and other relevant sources. The following keywords were utilized in the search query: “epidemiological transition,” “depression,” “socio-cultural transition,” and “Indonesia.” The inclusion criteria for the present study were as follows: articles were to be peer-reviewed and written in either English or Indonesian. The inaccessible articles were excluded from the review. There is no rigid criterion for the selection of articles by year of publication. Nonetheless, priority is given to articles that provide substantive support for the review's core concepts. Concurrently, a range of official reports, books, and book chapters were incorporated to provide supplementary data and theoretical support. The final list of eligible literature for review included 38

journals. Moreover, the extant supporting literature includes seven official reports, two books, and three book chapters.

Epidemiological transition in Indonesia

The systemic transition from macro to micro cannot be separated from Thompson's effects on the demographic transition of the population. This effect is explained by the change in the numbers of births and deaths as societies move from rural to industrial settings. The consequence of this effect affects the change in age structure, urbanization and socio-demographic shift, including increasing productivity age, educational and job support [2, 10–13].

The other macro-level impact of the demographic transition is economic and political transformations. Since the reform era of 1998, Indonesia has experienced substantial economic development, particularly at the middle-income level. The country has undergone a continuous increase in Gross Domestic Product (GDP) and interest in the industrial and service sectors [2, 14, 15].

These transitions can influence health at the micro level, as illustrated in Figure 1. Developmental progress during the transition period has improved the quality of life for the Indonesian population, as shown by the increase in life expectancy and decrease in mortality rates [2]. However, the transition may also have adverse effects on health.

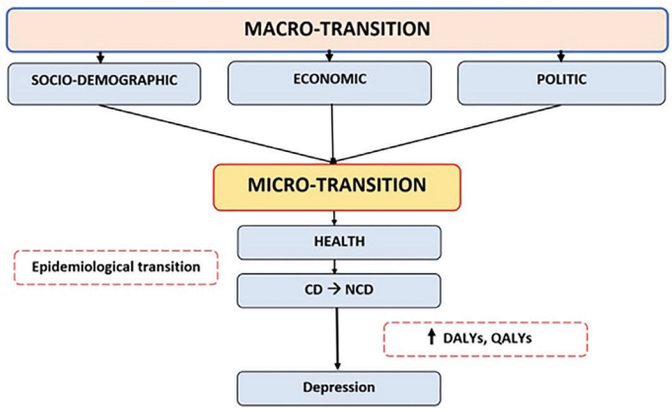

Figure 1 – A macro-transition, defined as a significant shift in the larger societal structure, is the catalyst for a micro-transition, which is, in turn, a smaller-scale societal shift. This micro-transition is influenced by macro-level factors, including socio-demographic, economic, and political developments. The epidemiological transition is defined as the shift from a prevalence of communicable diseases (CD) to a prevalence of non-communicable diseases (NCD) in terms of health. As a result of this transition, depression has been observed to increase in both DALYs and QALYs.

Omran's epidemiological observations have demonstrated the negative impact of demographic transitions on health, using socio-economic, political, and cultural factors as determinants. The results show a shift in disease from communicable to non-communicable, called an epidemiological transition (Figure 1). Caldwell introduced the term "health transition," which concerns survival and ability to function, where social, cultural, and behavioral changes can cause a shift from health to morbidity, affecting DALY and QALY [16–20].

The potential impact of epidemiological transition on depression

The increase of depression prevalence

The emergence of epidemiological transition in Indonesia, which has increased the trend of NCDs over the CDs. The reports of IHME in 2013 show the significant increase of NCDs prevalence from 1990 to 2010, which is in parallel with the decrease of CDs prevalence. This issue can be a challenge for Indonesia in the future, as the NCDs involve more complicated predisposing and precipitating factors. The challenge may be in the socio-cultural context, such as the inevitability of competition and social inclusion (Figure 2) [2, 21].

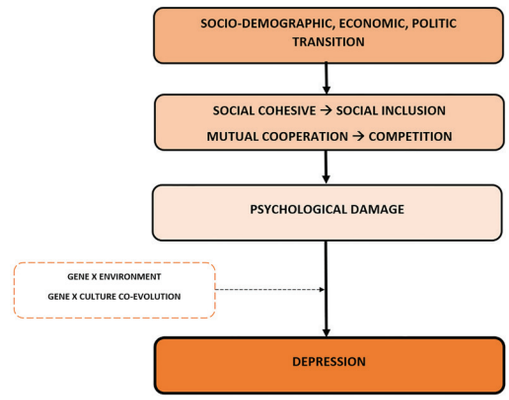

Figure 2 – The transition of the socio-demographic, economic, and political situation in Indonesia has given rise to a socio-cultural phenomenon characterized by a shift from a cohesive and cooperative (collectivist) to an inclusive and competitive (individualist) societal paradigm. This transition has exerted a significant influence on psychological well-being, giving rise to psychological distress, including depression. This phenomenon can be attributed to the interaction between genes and environment, as well as the co-evolution of genes and culture.

The increase of educated people and high migration rates to the capital city for employment could lead to quality issues and social challenges. This can trigger depression, which has increased in Indonesia over the past two decades. According to the Global Burden of Disease (GBD) data for 1999-2010, major depression was the main cause of lost DALYs, reaching 3.2% in 2010. Indonesia ranked in the middle of the DALYs based on the global average. The number of Indonesian DALYs based on age ranges from 2,402.6 to 2,599.3 DALYs per 100,000 people with mental disorders and substance abuse. In 2015, the prevalence of depressive disorders in Indonesia reached 3.7% of the total population (9,162,886 cases), with a proportion of DALYs of 6.6% (1,547,905 DALYs) [8].

Depressive disorders were the seventh most prevalent health problem in Indonesia in 2016-2017, contributing to the leading cause of disability with 21.7% of cases [22]. The percentage decreased slightly to 18.8% in 2017. The prevalence of emotional disorders in Indonesia was 6% in 2013, increasing to 9.8% in 2018. Depression prevalence rose from 3.7% in 2015 to 6.1% in 2018. The distribution of depressive disorders by province in Indonesia is between 2-12% [8, 23, 24]. Indonesia contributes 3.7% to the global prevalence of depression (Table 1) [8].

Table 1 The significant reports of depression prevalence in Indonesia from different sources.

Sources	Reports
GBD[4]	Major depression was responsible for 3.2% DALYs lost
WHO[8]	Global prevalence of depression was 3.7%
IHME[22]	7th ranked and 21.7% contribute to leading cause of disability
RISKESDAS[23,24]	The national prevalence of depression was 6.1%.

GBD = Global Burden Disease; WHO = World Health Organization; IHME = Institute for Health Metrics and Evaluation; RISKESDAS = Riset Kesehatan Dasar (Health Basic Research)

The increasing prevalence of depression worldwide, especially in Indonesia, is the consequence of the transition itself, including demographic and epidemiological/health. This transition has increased the huge potential of multifactor from biology to socio-culture and their interaction to increase the incidence of depression. Since the mechanism of depression is very complex, its increasing prevalence is not simply caused by a biological perspective [6, 25–29, 30–34].

The challenge of multicausality of depression

Depression's etiology is complex, systemic, and dynamic due to environmental and cultural factors. Empirical evidence shows that environmental and cultural differences lead to variations in depression's prevalence across countries. For example, individualism-collectivism culture plays a role. America and Europe generally have individualistic cultures, while Asia has collective cultures [35].

The WHO has reported that, based on a study of depression prevalence conducted between 1999 and 2014 in 30 countries, America has the highest prevalence at 20.6%, followed by Asia at 16.7% This suggests environmental and cultural individualism may be contributing to the increasing prevalence of depression. The shift from collectivism to individualism may be the reason for the rise in depression. Indonesia also faces this phenomenon [36, 37].

Furthermore, genetics are a biological factor that predisposes depression (Figure 3). A genome-wide meta-analysis found 102 genetic variants and 269 genes linked to depression [38]. Commonly studied genes include the serotonin transporter gene (5-HTTLPR), the monoamine oxidase A (MAOA) gene, the dopamine receptor D4 (DRD4) gene, and the oxytocin receptor (OXTR) gene [39-40]. These genes may interact with environmental and cultural factors that trigger depression. A poor environment (e.g., living in poverty and social isolation) may increase the risk of depression in people with a genetic predisposition.

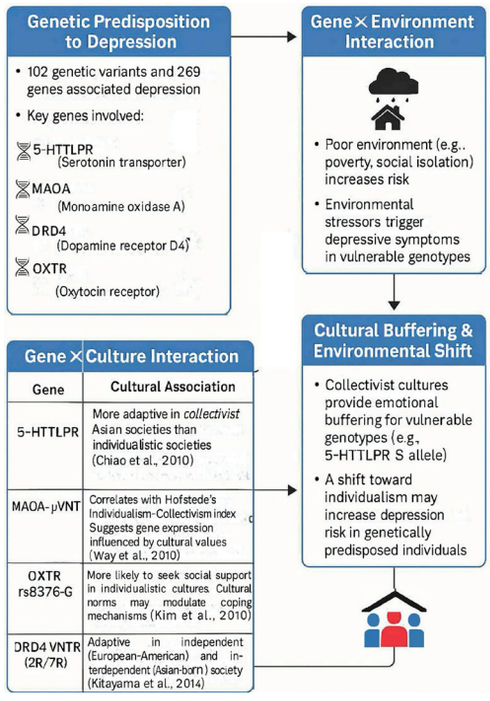

Figure 3 – The gene-environment and gene-culture co-evolution interaction provides a framework for investigating how biological factors, such as genetics, may interact with the environment and culture. This theoretical framework has the potential to offer insight into the multifaceted etiology of depression while concurrently considering the involvement of transition phenomena.

Recent studies show that the 5-HTTLPR genotype interacts with culture, particularly individualism-collectivism. The 5-HTTLPR genotype is more prevalent and adaptive in collectivist Asian societies than in individualistic European and American societies. The MAOA-μVNTR gene correlates with Hofstede's Individualism-Collectivism Index. The OXTR rs53576 G allele gene is more likely to seek social support in individualistic societies. The DRD4 VNTR gene -2R or -7R is adaptive in independent (European-American) and interdependent (Asian-born) societies [41–45]. Research by Chiao et al. found that the 5-HTTLPR S allele's risk of triggering depression decreases in collectivist cultures, possibly due to cultural buffering [42]. However, an assertive shift to individualism can increase the risk. Caspi et al. suggest that adverse environmental change may lead to depression for those with the 5-HTTLPR S allele [46].

The critical point of view

The interactions between genes, environment, and culture in Indonesia can be correlated with the country's development (i.e., the consequence of facing transition). However, there are consequences for achieving Indonesia's goal of becoming a developed country, such as severe cultural change. Therefore, we suspect that this may contribute to the increasing incidence and prevalence of depression. In addition, there are limited genetic epidemiological studies on the association of specific alleles with depression in the Indonesian population. Therefore, this phenomenon will be interesting and challenging to study as Indonesia has diverse populations.

This critical perspective is further substantiated by a recent study conducted in the Makassar City and Tana Toraja district, where a high culture of collectivism prevails, demonstrating a substantial surge in the prevalence of mental disorders [47, 48]. The hypothesis that socio-economic and cultural transformation is associated with the increasing prevalence [36] is one potential explanation for the observed phenomenon. Furthermore, this would have deleterious effects on the population with dominant genotype risk. Consequently, the epidemiological transition of the disease towards high morbidity and disability is a consequence that warrants consideration. Nevertheless, it is challenging to regulate the morbidity of non-infectious diseases (e.g., depression) that result from transformation.

The underlying cause of this phenomenon is multifaceted and intricate, suggesting an interplay of various factors influenced by the process of modernization. Therefore, I agree with Hidaka's review that depression is a disease of modernity [49]. In line with this, Sairin also explained that modernization and westernization are a never-ending discourse in Indonesia [50]. This phenomenon encapsulates the prevailing reality of contemporary Indonesia. The risk of depression in Indonesia may become a problem that will continue to grow if it is not anticipated. The most salient message is the importance of learning from the experiences of the most developed countries in the present era. Finally, I call upon Indonesian scientists specializing in epidemiology, public health, social psychiatry, or other related fields to examine this possibility and discuss the steps Indonesia should take to mitigate the future burden of depression. In addition, some recommendations that may need to be considered are as follows:

1) It is important to consider depression as a priority problem in Indonesia, given its significant long-term impact on quality of life.

2) Indonesian scientists engage in collaborative, multidisciplinary research endeavors to generate more substantial information regarding the etiology of depression, recognizing its multifaceted and complex nature.

3) It is crucial to acknowledge the distinctive cultural and genetic characteristics that define Indonesia, particularly in the context of investigating the interplay between genetic variability and cultural diversity in relation to depression.

4) It is therefore imperative to implement mitigation and prevention strategies for depression in anticipation of the inevitable transition phenomenon, taking into account the distinctive characteristics of Indonesia.

Conclusions

The macro and micro transition, including the epidemiological transition phenomenon, may provide a theoretical framework to explain the increasing prevalence of depression in Indonesia. The socio-cultural transition may be implicated in the etiology of depression or contribute to the complexity of its occurrence. The potential interplay among genes, environment, and culture during the epidemiological transition in Indonesia may warrant further investigation. In Indonesia, the ongoing discourse on modernization and westernization underscores the necessity for vigilant monitoring and evaluation of the growth of depression prevalence. This requires concerted preventive efforts, taking into account the multifaceted nature of the condition.

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Assessment of Antibacterial and Antifungal Activity of a Biocomposite Based on Nanocellulose in Vitro

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Abstract

Introduction: Biomaterials which used in the treatment of osteomyelitis, should not only fill in bone defects, but also be a "tool" for local delivery of antibiotics. The bone substitute is the biomaterial of human, animal, plant or synthetic genesis, implanted into the body to restore and strengthen bone substance. The creation of the latest nanocompositional materials today is the main direction of the development of science and technology. Nanocellulose (NC) and biocomposits based on it became one of the most promising "green" materials due to its unique properties. Our hypothesis: nanocellulose-based biocomposites with added antibiotics show antimicrobial effectiveness in vitro.

Methods: For preclinical testing, three samples of the NC were provided: nanofibrillar, nanocrystalline, microfibrillar nanocellulose. The microbiological purity was studied, the minimum-inhibitory concentration of the antibiotic, and the study of the antibacterial and antifungicide effect of biocomposite samples by the method of museum tests of Staphylococcus aureus (ATCC 6538), Escherichia coli (ATCC 25922), Bacillus subtilis (ATCC 6633), Candida Albicans (ATCC 10231) by measuring the diameter of the growth retardation zone.

Results: Biocomposites based on nanocellulose, saturated with antibiotics, demonstrate high antibacterial and antifungicidal potential. Further experimental studies are required by their ability to uniform and slow controlled release of the active substance, along with the effective suppression of the growth of microorganisms and a prolonged effect, which would allow them to be considered as an effective local transport system. In the future, it is planned to implant biocomposites with an antibiotic in the treatment of osteomyelitis in vivo.

Keywords: nanocellulose, biocomposite, chronic osteomyelitis, Staphylococcus aureus, treatment, bone substitutes.

Introduction

The problem of osteomyelitis treatment consists in the absence of such a filler, which, in addition to bone-forming properties, was a system for drug delivery. High indicators of the success of the antimicrobial treatment of most infections have not yet been achieved with bone infections due to the physiological and anatomical characteristics of the bones [1]. One of the current areas of reconstructive orthopedics is biotechnology. Multiple variability from autocracy to synthetic biopolymers indicates the enduring importance of finding such an implant that would meet all relevant characteristics [2].

The bone substitute is the biomaterial of human, animal, plant or synthetic genesis, implanted into the body to restore and strengthen bone substance [2]. The biomaterials used in the treatment of osteomyelitis should not only fill in bone defects, but also be a "tool" for local delivery of antibiotics [3]. The creation of the latest nanocompositional materials today is the

main direction of the development of science and technology [4]. Nanocellulose (NC) and biocomposites based on it became one of the most promising "green" materials due to its unique properties [5]. This polymer is divided into three types depending on the origin: nanocrystalline, nanofibrillar and bacterial. From natural cellulose, nanofiber (nanofibrillar cellulose - NFC) can be distinguished by multistage chemical and mechanical processing. At the same time, nanofibrils are formed with a diameter of 5 to 100 nm and a length of 200 nm to several tens of microns. The specific area of the surface of such nanofibers can reach 100-200 m2/g. It is the high specific surface, as well as the unique mechanical strength of individual fibers (the Yung module reaches 200 GPa, such values of the module are characteristic of steel) allows the use of nanofibrillar cellulose as a reinforcing component of composite materials [6].

Cellulose, due to its outstanding characteristics in the seal, is traditionally used in pharmaceuticals, where it acts as an effective auxiliary component for the formation of dense matrix structures with drugs, as well as in the production of high - quality pills for oral use. Various forms of nanocellulous carriers of drugs are classified according to three groups: microspheres (microparticles), hydrogels (gels) and nanomembranes (films) [7]. The use of natural nanocellulose in the drug delivery system is a promising direction, however, there are many unresolved issues, especially relating to the influence and control of the drug release, as well as the interaction between drug molecules and nanocellulose.

There are still open questions about the effectiveness of nanocellulose in relation to bone tissue infection, there is no literature data on its use in the treatment of osteomyelitis in vivo. This study is one of the stages of preclinical testing and aims to evaluate the antibacterial and antifungal activity of a nanocellulose-based biocomposite in vitro.

Methods

The object of the study was nanocellulose-based biocomposites provided by the Department of Physical and Colloidal Chemistry of the Federal State Autonomous Educational Institution of Higher Education «Russian State University of Oil and Gas (National Research University) named after I.M. Gubkin», Moscow. Biocomposites are the result of multi-stage chemical and mechanical processing of nanocellulose.

The study of the microbiological purity of the biocomposite

The microbiological purity of the biocomposite was estimated by direct sowing: 1 g of the substance was mixed with 9 ml of physiological solution, then a series of at least 3 serial tenfold dilutions of tested samples were prepared, of which, subsequently, 1 ml of the resulting mixture was taken by the dispenser. Sowing was made in sterile cups of Petri. As nutritional mediums used: yellow-salt agar (identification of Staphylococcus aureus), agar McConkey in order to release gram negative microorganisms, a thioglycol medium for anaerobes (incubation was carried out in the CO2 incubator "Memmert", chromogenic agar for mushrooms. Cup incubation was carried out in a thermostat at 36 ± 1ºC for 24 hours. To determine the mushrooms, the cup was cultivated at a temperature of 26 ± 1°C for 5 days.

Determination of the minimum inhibitory concentration of a biocomposite with the addition of antibiotics in relation to Staphylococcus aureus

The most common pathogen of chronic bone infection, according to literary data, is Staphylococcus aureus, which is associated with pronounced virulence factors:

• α-toxin, which destroys the owner's macrophages membrane, which initiates their death;

• leukotoxins lukSE, HlgAB and HlgCB, LukED and LukAB, leading to the polarization of macrophages, which further leads to the formation of a weakly inflammatory phenotype and the corresponding immune response;

• staphylococcal complement inhibitor (SCIN), which blocks classic complement paths;

• protein inhibiting Staphylococcal chemotaxis (CHIPS);

• Squeezing factor A (ClfA) and cell adhesion protein (Eap);

• Change in the genotype due to "quorum sensing" [8].

The determination of the minimum-inhibitory concentration of gentamycin was carried out in relation to the Staphylococcus aureus of the museum ATCC 6538 and clinical strains (65245, 65246, 64238), provided by the research laboratory, as follows: 1 ml of culture and various antibiotic concentrations – 20 µl, 40 µl, 60 µl, 80 µl, 100 µl (0.1 ml), 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml were introduced to 3 ml of meat-peptone broth. Control was the broth and broth with a culture without an antibiotic. In the future, tubes were incubated in the thermostat at 36 ± 1 ºC during for 24 hours. The results were analyzed using spectrophotometry "Tecan" with the measurement of optical density.

Preparation of samples

As subjects, the materials were provided: nanofibrillar (I), nanocrystalline (II), microfibrillar nanocelluloses (III). They were studied both in monovariant (1 gr) and with the addition of antibiotics (0,1 ml of gentamycin, 0,1 nistatin, also calcium gluconate (0.5 g of the studied sample + 0.5 g of calcium gluconate, t. e. in the ratio of 1:1). Calcium is the main mineral that gives bone tissue strength: from 1 kg of calcium contained in our body, 99% are in bones. Compositions of the studied samples with designations presented in Table №1. Standard discs with gentamicin and nystatin were used as controls.

Table 1 Compositions of the studied samples with designations

№	The composition of the studied sample	Designation
1	Nanofibrillar NC	I
2	Nanofibrillar NC + gentamycin	I + G
3	Nanofibrillar NC + gentamycin + Ca	I + G + Ca
4	Nanofibrillar NC + Ca	**I + Ca**
5	Nanofibrillar NC + nystatin	I + Ns
6	Nanofibrillar NC + nystatin + Ca	I + Ns + Ca
7	Nanocrystalline NC	II
8	Nanocrystalline NC + gentamycin	II + G
9	Nanocrystalline NC + gentamycin + Ca	II + G + Ca
10	Nanocrystalline NC + Ca	II + Ca
11	Nanocrystalline NC + nystatin	II + Ns
12	Nanocrystalline NC + nystatin + Ca	II + Ns + Ca
13	Microfibrillar NC	III
14	Microfibrillar NC + gentamycin	III + G
15	Microfibrillar NC + gentamycin + Ca	III + G + Ca
16	Microfibrillar NC + Ca	III + Ca
17	Microfibrillar NC + nystatin	III + Ns
18	Microfibrillar NC + nystatin + Ca	III + Ns + Ca
19	Gentamycin	G
20	Nystatin	Ns

Determination of antimicrobial activity of biocomposites in relation to museum tests

The study of antimicrobial and antifungal activities of biocomposites was determined by Staphylococcus aureus (ATCC 6538), Escherichia Coli (ATCC 25922), Bacillus Subtilis (ATCC 6633), Candida albicans (ATCC 10231), according to the State Pharmacopoeia Republic of Kazakhstan.

Gentamicin was chosen as an antibacterial agent, both a bactericidal antibiotic of a wide spectrum of action against both many grampositive and gramnegative bacteria.

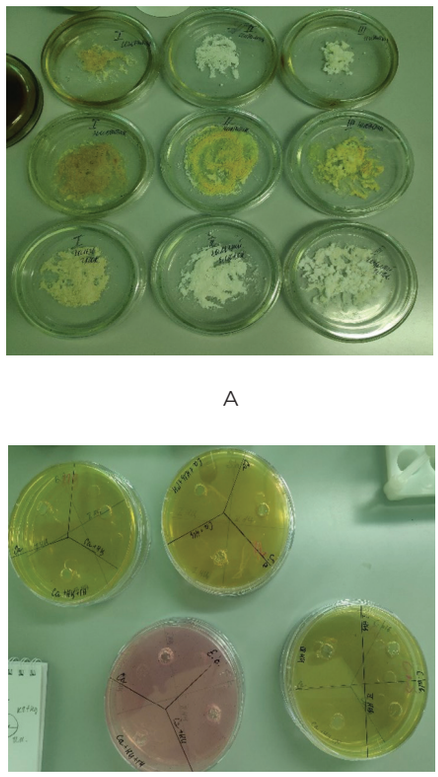
Nystatin - a polyene macrolide, was chosen as a fungistatic and fungicidal drug for yeast and yeast -like mushrooms, including Candida albicans.

The microbial suspension of test culture was prepared on a physiological solution in a concentration corresponding to the turbidity standard 0.5 Mac Farland. Next, the suspension was evenly applied to the surface of the agar Muller-Hinton in the Petri cup and dried. The studied samples of 1 g, imprinted 0.1 ml of gentamycin and 0,1 nystatin, were placed in holes (0.6*0.5 cm) of infected agar (Figure 1 a) and b). Cups were incubated in a thermostat at 36 ± 1 ºC for 24 hours (and at 24 ± 1 ºC with Candida albicans for 5 days). The result was evaluated by the presence of the diameter of the delay in the growth of the test culture around the test sample. The results were recorded on the basis of measuring the diameter of the zone (if any) from the edge of the sample to the edge of the growth retardation zone using a line-show designed for these purposes (Himedia PW297, India).

Statistical analysis

For statistical processing, the STATISTICA 6 and IBM SPSS Statistics, Version 24 program were used. The analysis of the data was carried out at the level of significance α = 0.05. The verification of the normal distribution of quantitative data was carried out using the criterion of the Shapiro – Wilk (S-W). According to the Shapiro-Wilk criterion, p <0.01, which is less than the significance level (0.05), which indicates that the distribution of the indicator is abnormal. The Shapiro-Wilk criterion was chosen because the sample size is less than 50 (n>50).

The description of quantitative data was carried out on the basis of: average value and apartment. For comparison of independent groups, the Mann-Whitney U criterion. The Mann-Whitney criterion was chosen as the research method, since the data are quantitative, the distribution is different from normal, the samples are independent, and the significance level is α=0.05.



A

B

Figure 1 – The microbial suspension of test culture placed in holes (0.6*0.5 cm) of infected agar

Results

The results of the study of the microbiological purity of biocomposites

With a threefold direct sowing of ten -time serial dilutions of subjects, the results showed that the presented samples are microbiologically pure. According to the State Pharmacopoeia of the Republic of Kazakhstan, requirements are applied to implants as drugs for parenteral use.

Medicines for parenteral use (parenteral drugs) are sterile drugs designed for administration by injection, infusion or implantations into the human or animal body.

The submitted samples are sterile and can be used as bone implants to fill osteodefects.

The results of determining the minimum inhibitory concentration of a biocomposite with the addition of antibiotics in relation to Staphylococcus aureus

When determining the minimum inhibitory concentration of gentamycin (20, 40, 60, 80 µl), a statistically higher optical density indicator (p = 0.012) was noted, respectively, with an increase in the concentration of gentamycin (0.1, 0.2, 0.4, 0.6 0.8 ml) a statistically lower optical density indicator (p = 0.012) was noted (Figure 2).

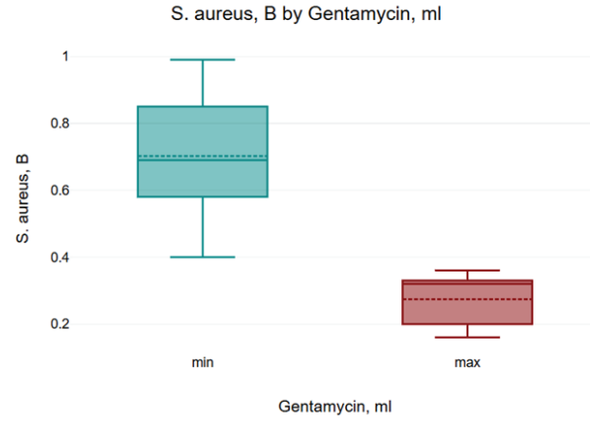


Figure 2 – The minimum inhibitory concentration of gentamicin in the broth

Determination of antimicrobial activity of biocomposites in relation to museum tests

According to experimental data, the tested samples do not have a bactericidal effect as a monocomponent (without an antibiotic) in relation to all studied microorganisms (samples I,

Table 2 Diameter of the biocomposite growth retardation zone in relation to museum test strains

№	Examined samples	The diameter of the growth delay zone, mm (M±m)			
		S. aureus ATCC 6538	E. coli ATCC 25922	B. subtilis ATCC 6633	C. albicans ATCC 10231
1	I	0±0,0	0±0,0	0±0,0	0±0,0
2	I + G	35,5±1,5	26,8±1,2	35,5±1,5	0±0,0
3	I + G + Ca	35,4±1,6	27,5±0,5	38,1±0,9	0±0,0
4	I + Ca	0±0,0	0±0,0	0±0,0	0±0,0
5	I + Ns	0±0,0	0±0,0	0±0,0	30±1,0
6	I + Ns + Ca	0±0,0	0±0,0	0±0,0	32,1±0,9
7	II	0±0,0	0±0,0	0±0,0	0±0,0
8	II + G	36,4±1,6	27,1±1,9	34,4±1,6	0±0,0
9	II + G + Ca	32,2±1,8	27,5±0,5	38,3±0,7	0±0,0
10	II + Ca	0±0,0	0±0,0	0±0,0	0±0,0
11	II + Ns	0±0,0	0±0,0	0±0,0	31,3±0,7
12	II + Ns + Ca	0±0,0	0±0,0	0±0,0	31,3±0,7
13	III	0±0,0	0±0,0	0±0,0	0±0,0
14	III + G	34,5±0,5	25,4±1,6	37,1±0,9	0±0,0
15	III + G + Ca	37,4±0,6	27,5±0,5	40,3±0,7	0±0,0
16	III + Ca	0±0,0	0±0,0	0±0,0	0±0,0
17	III + Ns	0±0,0	0±0,0	0±0,0	31,3±0,7
18	III + Ns + Ca	0±0,0	0±0,0	0±0,0	31,3±0,7
19	G	15±0,8	16±0,5	19±0,9	0±0,0
20	Ns	0±0,0	0±0,0	0±0,0	12±0,6

II, III, I+SA, II+SA, III+SA). Statistical processing of the results was carried out by the method of parametric analysis Student's t-test with the calculation of the arithmetic and standard error (Table №2).

However, biocomposites impregnated with an antibiotic showed high antibacterial (samples I+ G, II+ G, III+ G) and antifungicidal (samples I+Ns, II+Ns, III+Ns) effect. The addition of calcium in some cases enhances the effect of drugs (samples I+ G +Ca, II+ G +Ca, III+ G +Ca in relation to E. soli, B. subtilis; biocomposite I+Ns+Ca against C. albicans) (Table №2). As a result, nanocellulose composites with antibiotics showed higher potential of 1.5-2 times, than standard control discs.

Discussion

In the study of microbiological purity, the studied samples of biocomposites based on nanocellulose were sterile, which was not expressed in the absence of the growth of microorganisms on nutrient media. The sterility of the samples makes it possible to use them in the operating room for filling out osteodefects in vivo.

As a mono-matter, samples of nanocellulose did not have bactericidal properties, which corresponds to the data of affordable literature. This is due to its physico-chemical properties [9, 10]. This can be achieved by functionalizing it or incorporating antimicrobial agents.

As the results of our study showed, biocomposites based on nanocellulose, saturated with antibiotics, demonstrate high antibacterial and antifungicidal potential, which is confirmed by a number of scientific publications (Table №3).

Table 3 NC variations for biomedical applications

Substance	Pathogen	Application	Reference
A composite material based on poly(3-hydroxybutyrate) and nanocellulose coated with zinc oxide (ZnO) nanoparticles	Escherichia coli and Staphylococcus aureus	Packaging Applications	10
Mixing colloidal silver nanoparticles with cellulose nanofiber (CNF) and depositing this hybrid coating (CNF/Ag)	Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive) bacteria	Layer on different paper substrates.	12
NC + silver nanoparticle	Staphylococcus aureus	Antimicrobial wound dressing	13
Chitosan and cellulose nanocrystals	Escherichia coli	Antimicrobial tissue paper	14
Nanocellulose	COVID-19	Antimicrobial tissue paper	15
Allicin-conjugated nanocellulose and lysozyme-conjugated nanocellulose	Aspergillus niger, C. albicans, S. aureus and E. coli	Antimicrobial agent in food packaging, inside foodstuffs, and in textile materials	16
Nanofibrillar NC, Nanocrystalline NC, Microfibrillar NC + antibiotics	S. aureus, E. coli, B. subtilis, C. albicans	The authors suggest the use of biocomposites in the treatment of bone tissue infections	This study

So, it is known that in the work of Panaitesca et al. (2018) created a composite material based on poly(3-hydroxybutyrate) and nanocellulose coated with zinc oxide (ZnO) nanoparticles. This approach significantly improved the physical properties of the material and demonstrated antibacterial activity against Escherichia coli and Staphylococcus aureus [10].

The combination of silver nanoparticles with nanocellosis showed a good antimicrobial effect on B. Subtilis, E. Coli, S. Aureus and P. Aeruginosa [11–13]. In other studies of chitosan film with nanocellulose, plasma treated showed a high inhibit zone and 99% decrease in E. coli growth [14, 15].

Antifungicidal and antibacterial potential showed an NC in combination with allicin (organic compound formed during the mechanical destruction of garlic cells) and lysozyme against Aspergillus niger, C. albicans, S. aureus and E. coli [16].

Data of available literature showed that nanocellulose is a favorable material for the delivery of drugs and shows sufficient antibacterial potential in relation to a number of microorganisms (Table № 3).

Conclusion

The microbiological purity of the examples studied makes it possible to use them as substances for filling in vivo osteodefects.

Biocomposites based on nanocellulose, saturated with antibiotics, demonstrate high antibacterial and antifungicidal

potential. Further experimental studies are required by their ability to uniform and slow controlled release of the active substance, along with the effective suppression of the growth of microorganisms and a prolonged effect, which would allow them to be considered as an effective local transport system. The presented biocomposites will be used in the treatment of osteomyelitis in vivo.

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Characteristics of Hepatitis B and C Infections in Hemodialysis Patients in Almaty, Kazakhstan's Largest City

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Abstract

Background and aims: Chronic viral hepatitis, including Hepatitis B (HBV) and Hepatitis C (HCV), remains a major health concern among hemodialysis patients. This study analyzes the prevalence and characteristics of HBV and HCV infections in hemodialysis patients treated at a single center in Almaty, focusing on comorbidities such as diabetes, hypertension, and cirrhosis. This study aims to determine the prevalence of these infections among hemodialysis patients in Kazakhstan and assess their associated comorbidities, complications, and overall impact on patient health.

Methods: Data from the Almaty Center of Hepatology (2016–2023) served as the basis for the study cohort. Inclusion criteria included CKD stage 5, hemodialysis dependence, ESRD, and confirmed HBV, HCV, or both. The study consists of 164 patients diagnosed with HBV, HCV, or mixed infections, with data collected on demographic distribution, viral genotype prevalence, fibrosis staging, and associated conditions.

Results: The findings highlight a substantial prevalence of comorbid conditions in hemodialysis patients with viral hepatitis. The study population includes 95 males (57.9%) and 69 females (42,1%), with a slight male predominance. HCV was the most common infection (76.8%), followed by HBV (14%) and mixed HCV+HBV (9.2%). The high percentage of an unspecified genotype (36.4%) suggests that enhanced diagnostic strategies are needed. Cirrhosis was observed in nearly 90% of the cohort, and 92.7% exhibited ascites. Fibrosis progression was significant, with 25.5% of patients in stage 1, 24.2% in stage 2, and 18.8% in stage 3. The prevalence of hypertension (53.9% with high-risk stage 3 hypertension), diabetes (14.5% with type 2 diabetes), and cirrhosis (89.7%) was assessed. Additionally, hepatitis genotypes were identified, with HCV genotype three being the most common (18.2%) and genotype 1 (17.6%).

Conclusions: The results of this study demonstrate that patients on hemodialysis with viral hepatitis represent a particularly vulnerable group with a high incidence of severe liver damage and multiple comorbidities. The high rates of advanced fibrosis, cirrhosis, and associated conditions such as hypertension and diabetes underscore the need for timely diagnosis and complex, patient-centered care.

Keywords: Hepatitis B, Hepatitis C, Hemodialysis, Chronic Kidney Disease, Comorbidities, Kazakhstan, Liver Cirrhosis, Genotype.

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are significant public health concerns globally, with notable prevalence in Central Asia, including Kazakhstan. Recent studies have highlighted an increasing trend in HBV and HCV cases within the region. From 2015 to 2020, Kazakhstan reported a significant rise in hepatitis cases: HBV by 49.8%, HCV by 46.4%, and hepatitis D virus (HDV) by 68.3% [1]. This upward trajectory underscores the necessity for effective preventive measures and comprehensive screening strategies.

The seroprevalence of HBV and HCV varies across different regions of Kazakhstan. A cross-sectional study conducted in three large areas revealed HBsAg positivity at 5.5% and anti-HCV antibodies at 5.1%, with higher rates observed in the western and northern areas compared to the southern region [2]. These regional disparities may be attributed to healthcare access, public awareness, and historical transmission patterns. Chronic viral hepatitis B (HBV) and C (HCV) are significant public health challenges in Kazakhstan. A comprehensive analysis utilizing data from the Unified National Electronic Health System (UNEHS) between 2014 and 2019 identified 82,700 patients diagnosed with chronic viral hepatitis. Of these, 56.6% were infected with HCV, while 43.4% had HBV. The study also revealed co-infection rates of 10% for HBV with hepatitis D virus (HDV) and 3.5% for HBV with HCV. Notably, a higher prevalence was observed among female patients (56%) and individuals of Kazakh ethnicity (64.8%) [3].

Chronic HBV and HCV infections are frequently associated with comorbid conditions, notably diabetes mellitus (DM) and hypertension. Research indicates that up to one-third of patients with chronic HCV develop type 2 DM, a prevalence significantly higher than in the general population [4]. Similarly, a study focusing on HBV-infected North American adults found a higher prevalence of diabetes compared to the general population, suggesting a potential link between HBV infection and metabolic disorders [5].

The interplay between viral hepatitis and metabolic disorders is complex. HCV infection has been associated with an increased risk of cardiovascular diseases, especially in populations with a higher prevalence of diabetes and hypertension [6]. This association emphasizes the importance of comprehensive management approaches that address both viral infections and metabolic comorbidities.

In Kazakhstan, the molecular epidemiology of HBV and HDV has been explored, revealing that the predominant HBV genotype is D (95.9%), followed by A (3.5%) and C (0.6%). All HDV samples analyzed belonged to genotype 1 [7]. Understanding the distribution of these genotypes is crucial for tailoring effective treatment strategies and public health interventions.

The burden of chronic viral hepatitis is compounded by its association with end-stage renal disease (ESRD) requiring dialysis. An analysis of the UNEHS registry from 2014 to 2018 reported 8,898 patients undergoing dialysis for ESRD. The majority were male (56%) and of Kazakh ethnicity (63%). During this period, the prevalence of dialysis-treated ESRD increased from 135.2 per million population (PMP) in 2014 to 350.2 PMP in 2018, while the incidence rose from 68.9 to 94.9 PMP. Despite these increases, the overall mortality rate among dialysis patients decreased from 1,667 per 1,000 patient-years in 2014 to 710 per 1,000 patient-years in 2018. However, disparities were noted, with females and individuals of Russian ethnicity experiencing higher mortality rates [8].

The intersection of chronic viral hepatitis and ESRD underscores the necessity for integrated healthcare strategies in Kazakhstan. Early detection and management of viral hepatitis, alongside monitoring and treatment of renal complications, are imperative to mitigate the progression to ESRD and reduce associated mortality. Tailored public health interventions should address the observed gender and ethnic disparities to enhance health outcomes across all demographics. Given the rising prevalence of HBV and HCV infections and their association with metabolic disorders, there is a pressing need for integrated healthcare approaches in Kazakhstan. Such strategies should encompass regular screening for viral hepatitis, early detection and management of comorbid conditions like diabetes and hypertension, and public health initiatives to reduce transmission and improve patient outcomes.

Methods

Patient Selection Process

Data from hepatologist consultations between 2016 and 2023 were used to form the study cohort. The preliminary inclusion criteria were chronic kidney disease (CKD) stage 5, the need for hemodialysis, end-stage renal disease (ESRD), and indications of concomitant viral infections (HBV, HCV, or a combination of both).

Selection Process

1. Initial Patient Cohort (N=398):

Patients were identified based on the following keywords: "hemodialysis," "CKD 5," "ESRD," and "renal failure."

2. Removing Duplicates (N=50):

Duplicate records were excluded.

3. Exclusion of Patients with Non-Eligible Conditions (N=149):

- Patients with CKD stages 2, 3, 4 and cholangitis (-53).
- Patients with non-alcoholic steatohepatitis (NASH) and CKD stages 2-3 (-10).
- Patients with acute hepatorenal failure (-20).
- Patients with CKD stages 3-4 and hepatitis C (-35).
- Patients with CKD stages 3-4 and hepatitis B (-31).

4. Exclusion of Patients with Cirrhosis and Other Ineligible Conditions (N=35):

- Patients with cirrhosis.
- Patients with HBV+CKD stage 3.
- Patients with HBV+CKD stage 2.

5. Final Cohort After Screening (N=164):

The final cohort included only patients with CKD stage 5 and confirmed HBV, HCV, or mixed infections.

This selection process ensured cohort homogeneity and eliminated the influence of comorbid conditions that could bias the study results. These data are presented in a flowchart in Figure 1, illustrating the patient selection process for the study.

Exposure and Covariates

The analysis relied on patient-specific information such as age, gender, ethnicity (grouped into Kazakhs, Russians, and other categories), the presence of co-infections, disease advancement pattern, health outcomes (including any complications), hepatitis type and genotype, date of diagnosis, and the extent of liver fibrosis and reason of CKD. Co-infections were identified as instances where patients diagnosed with HBV were concurrently diagnosed with HCV, HIV, or a combination of these. The study focused on significant complications including liver failure, cirrhosis, portal hypertension, and ascites. Furthermore, the analysis incorporated hepatitis diagnosis times and the start date of hemodialysis to examine the connection between HBV and HCV infections within the patient population

Statistical Analysis

Categorical data in descriptive analysis tables is presented as patient counts along with their corresponding relative proportions. Statistical analysis, data cleaning (including identifying and removing duplicate cases), and data management (such as labeling variables and creating or categorizing new ones) were conducted using SPSS version 26.

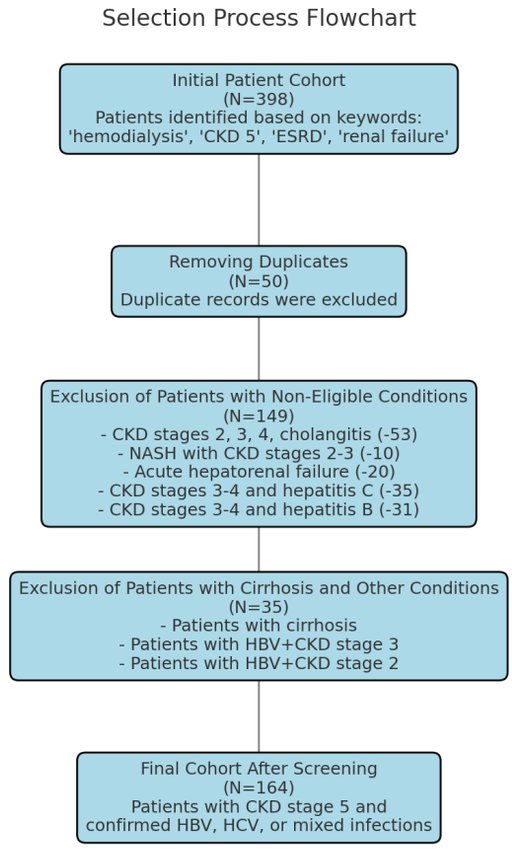

Figure 1 – Selection Process Flowchart

Results

Demographics and general characteristics.

This study examines clinical and demographic parameters, including gender distribution, hepatitis type, fibrosis stages, liver cirrhosis classification, the presence of ascites, diabetes prevalence, and arterial hypertension. The study population comprised **95 males – 57.9 % (95 % CI 50.3–65.2)** and **69 females – 42.1 % (95 % CI 34.8–49.7**), indicating a slight predominance of males in the sample.This study examined structural causes of CKD in 164 patients (Table 1). The total number of CKD cases analyzed was **162 (98.2%)**, with an additional **3 cases (1.8%)** categorized as **missed data**, bringing the total dataset to **165 (100.0%).**

Among the cases analyzed, the majority (76.9%) were diagnosed with HCV (Hepatitis C Virus) as in this study [9], while 14% had HBV (Hepatitis B Virus). A mixed infection (HCV + HBV) was observed in 9.2% of cases.

Figure 3 illustrates the frequency of identified genotypes in the observed population. The most prevalent category is Unspecified, making up 36.4% of cases, significantly higher than the rest. The next most common genotypes are Genotype 3 (18.2%) and Genotype 1 (17.6%), occurring at similar frequencies. Delta-negative status follows with 12.1%. Less frequent genotypes include Genotype 1b (3.6%) and Genotype 2 (2.4%), while the remaining categories—Without delta status, 1a, 1, and 2, and 3ab—each have a minimal representation of 0.6%. This distribution highlights the dominance of unspecified genotypes, while the presence of Genotypes 1 and 3 is relatively balanced. Other categories occur at much lower frequencies, suggesting that they are less commonly observed in the dataset.

Figure 4 illustrates the distribution of fibrosis stages. The analysis of fibrosis stages reveals a gradual distribution of fibrosis stages among the studied population:

Table 1 Sociodemographic characteristics and clinical profiles of RPL cases and control women

Parameter		Frequency	Percentage
The structural causes of CKD	Chronic glomerulonephritis	57	34,5
	Polycystic kidney disease	8	4,8
	Obstructive nephropathy	2	1,2
	Diabetic nephropathy	18	10,9
	Haemorrhagic vasculitis	2	1,2
	Mixed nephropathy (diabetic, hypertensive)	14	8,5
	Hypertensive nephropathy	25	15,2
	Of unclear aetiology	20	12,1
	Glomerular disease	4	2,4
	Lupus nephritis	3	1,8
	Cryoglobulinemic vasculitis	1	0,6
	Paraneoplastic nephropathy	2	1,2
	Congenital anomaly of kidney development: aplasia of the right kidney	1	0,6
	Interstitial nephritis-	5	3,0
	Total	162	98,2
	Missed data	2	1,8
	164	100,0	
Total Data	164	100,0	

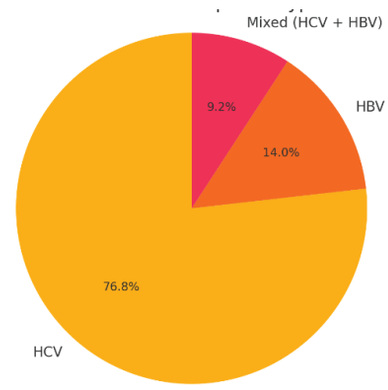

Figure 2 – Frequency of Hepatitis

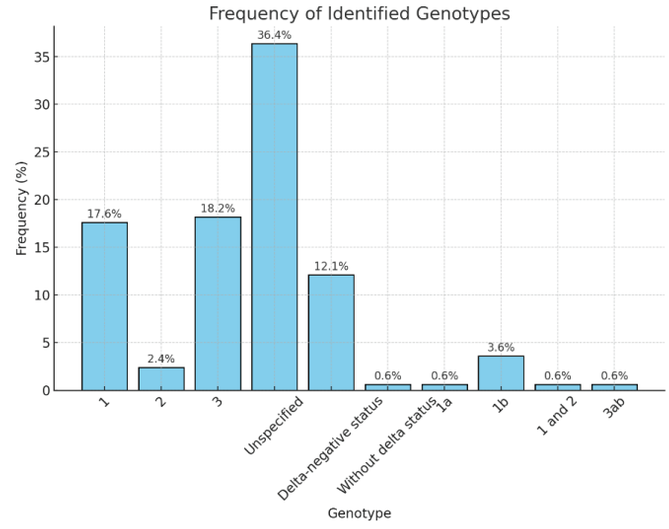

Figure 3 –Frequency of identified genotypes

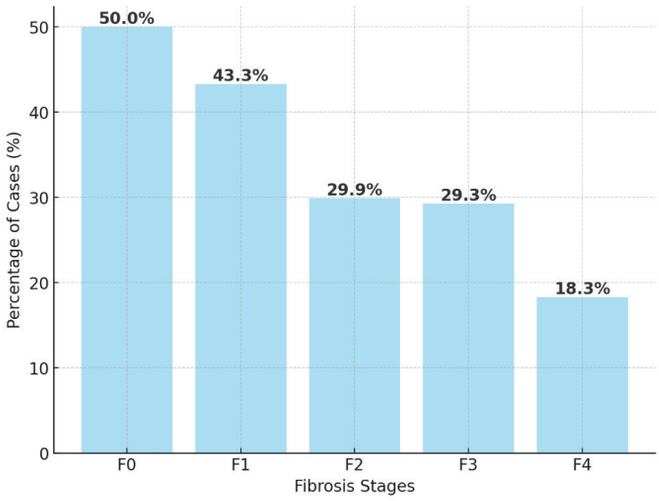

Figure 4 –Distribution of fibrosis stages

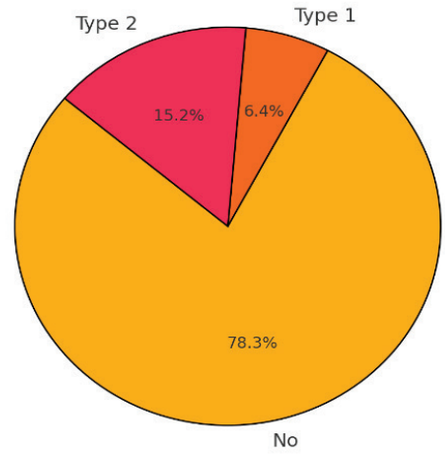

Figure 5 – Frequency of diabetes mellitus

- Early-stage fibrosis (F0) is the most prevalent, with 82 cases, 50%, indicating that a significant portion of individuals exhibit minimal or no fibrosis.
- Mild to moderate fibrosis (F1) is observed in 71 cases (43.3%, suggesting early structural changes in liver tissue.
- Moderate to advanced fibrosis (F2) is reported in 49 cases -29.9%, reflecting a further progression of liver damage.
- Advanced fibrosis (F3) accounts for 48 cases-29.3%, indicating a near-cirrhotic state with a high risk of complications.
- Severe fibrosis or cirrhosis (F4) was present in 30 cases-18.3%, representing the most critical stage with significant liver dysfunction.

Ascites

The presence of ascites, a common complication of liver and CKD disease, was analyzed as follows:

- No ascites (153 cases, 92.7%)
- Grade 1 ascites (3 cases, 1.8%)
- Grade 2 ascites (6 cases, 3.6%)
- Grade 3 ascites (1 case, 0.6%)

Figure 5 shows the distribution of diabetes mellitus cases. The majority of individuals, 74.5%, do not have diabetes. Among those diagnosed with diabetes, Type 2 diabetes is the most common, accounting for 14.5% of cases. Type 1 diabetes is less prevalent, occurring in 6.1% of individuals. This data suggests that while most people are free from diabetes, Type 2 diabetes is significantly more common than Type 1, reflecting general trends where Type 2 diabetes is often linked to lifestyle and metabolic factors.

This data suggests that most individuals exhibit a minimal viral load, while moderate and pronounced levels are rare. The proportion of cases without a defined viral load remains low.

The distribution of arterial hypertension among the studied population reveals a significant prevalence of severe cases.

- Grade 3 hypertension with risk 4 is the most common category, accounting for 53.9% of cases. This indicates a high proportion of individuals at significant cardiovascular risk.
- Individuals without hypertension make up 39.4% of the population, suggesting that a substantial portion remains unaffected.
- Grade 2 hypertension is observed in 4.8% of cases, while Grade 1 hypertension is the least common, affecting only 1.2% of individuals.

These findings highlight the high prevalence of severe arterial hypertension, emphasizing the need for effective prevention and management strategies to reduce cardiovascular complications.

Discussion

The findings of this study underscore the significant burden of Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infections among hemodialysis patients, a population already at heightened risk due to their immunocompromised state and frequent exposure to invasive medical procedures. The high prevalence of HCV infection (76.4%) in the studied cohort aligns with global epidemiological trends, where HCV remains the dominant viral infection among hemodialysis patients. The lower prevalence of HBV (13.9%) and mixed infections (9.1%) is consistent with prior studies that indicate the effectiveness of HBV vaccination programs and strict infection control measures in reducing HBV transmission in dialysis settings [9].

Comorbidities and Disease Progression

A significant observation in this study was the high prevalence of comorbid conditions, including hypertension (53.9%), diabetes mellitus (14.5%), and liver cirrhosis (89.7%), which exacerbate disease progression and worsen clinical outcomes[10]. These findings support previous research indicating that viral hepatitis in hemodialysis patients is frequently associated with metabolic disorders. HCV infection, in particular, has been linked to insulin resistance and type 2 diabetes mellitus, which contribute to faster disease progression and increased cardiovascular morbidity in this population. Additionally, hypertension and chronic kidney disease (CKD) are closely intertwined, as kidney dysfunction leads to sodium retention and vascular stiffness, further increasing cardiovascular risks[11].

The high prevalence of fibrosis progression is another concerning finding, with over 43% of patients exhibiting moderate to severe fibrosis (F2-F4 stages). The presence of cirrhosis in nearly 90% of cases highlights the need for early detection and aggressive management of fibrosis to prevent decompensated liver disease and hepatocellular carcinoma (HCC)[12]. Previous studies have demonstrated that HCV accelerates fibrosis progression in patients with CKD, and

hemodialysis patients with advanced fibrosis or cirrhosis face higher mortality rates due to complications such as variceal bleeding, portal hypertension, and hepatic encephalopathy.

Viral Genotype and Diagnostic Challenges

This study identified HCV genotype 3 (18.2%) and genotype 1 (17.6%) as the most common strains, consistent with global and regional patterns. However, 36.4% of cases had an unspecified genotype, suggesting a need for improved diagnostic strategies, including more advanced genotyping techniques and increased accessibility to molecular testing. The predominance of genotype 3 is particularly concerning, as this strain has been associated with more rapid fibrosis progression and reduced response rates to certain antiviral therapies.

The distribution of viral load (PCR results) further supports the necessity of robust screening and monitoring programs. While 66.7% of cases had a minimal viral load, nearly 30% exhibited mild to pronounced viremia, which indicates ongoing viral replication and a potential risk of transmission within dialysis centers[13]. These findings emphasize the critical need for routine virological surveillance, strict infection control protocols, and timely initiation of antiviral therapy.

Chronic Kidney Disease (CKD) and Hepatitis Interactions

The etiology of CKD in patients with viral hepatitis is multifactorial, with chronic glomerulonephritis (34.5%) and hypertensive nephropathy (15.2%) being the leading causes. Diabetic nephropathy accounted for 10.9% of cases, reflecting the metabolic consequences of chronic hepatitis infections. Previous studies have shown that HCV infection increases the risk of CKD progression, likely due to its impact on renal hemodynamics, endothelial dysfunction, and systemic inflammation. Similarly, HBV-associated nephropathy has been reported, particularly in cases of HBV-related membranous nephropathy[14].

The increasing burden of end-stage renal disease (ESRD) requiring dialysis in Kazakhstan, as observed in national registry data, further underscores the urgent need for targeted public health interventions. The rise in dialysis prevalence from 135.2 per million population (PMP) in 2014 to 350.2 PMP in 2018 highlights the growing impact of CKD and the necessity for comprehensive screening, preventive measures, and improved access to renal replacement therapy[15].

Implications for Clinical Practice and Public Health

Given the high prevalence of HBV and HCV infections, comorbid conditions, and advanced fibrosis in hemodialysis patients, an integrated and multidisciplinary approach is required for optimal patient management[16]. Key recommendations include:

1. Enhanced Screening and Early Diagnosis:
   - Routine HBV and HCV screening in all dialysis patients using sensitive molecular assays.
   - Improved genotyping techniques to optimize personalized treatment approaches.
2. Public Health Initiatives:
   - Expansion of HBV vaccination programs, particularly among CKD and dialysis patients.
   - Increased awareness campaigns on hepatitis prevention, early testing, and treatment availability.
3. Antiviral Treatment Strategies:
   - Early initiation of direct-acting antivirals (DAAs) for HCV to prevent disease progression.
   - HBV antiviral therapy (e.g., entecavir, tenofovir) in high-risk patients to reduce liver-related complications[17].
4. Comorbidity Management:
   - Strict blood pressure control in patients with hypertension and nephropathy.
   - Regular diabetes screening and metabolic monitoring in viral hepatitis patients.
   - Fibrosis staging using non-invasive markers (e.g., FibroScan, APRI score) to guide therapy.
5. Infection Control in Dialysis Centers:
   - Strict adherence to universal precautions, including single-use dialyzers and disposable gloves.
   - Implementation of cohort isolation strategies for HBV-infected patients.
   - Regular staff training on infection prevention and patient education programs.

Conclusion

This study demonstrates a high burden of chronic viral hepatitis among hemodialysis patients, with frequent comorbidities and advanced liver damage. The findings underscore the importance of early screening, enhanced diagnostics, and integrated management that involves specialists in nephrology, hepatology, and infectious diseases. A multidisciplinary approach is crucial to address the complex interactions between CKD, hepatitis, hypertension, and diabetes. Future efforts should focus on tailored antiviral therapies and public health measures to reduce infection transmission and improve outcomes in this high-risk population.

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Artificial Intelligence in Sports Science: A Systematic Review on Performance Optimization, Injury Prevention, and Rehabilitation

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Abstract

Background: Artificial intelligence (AI) is quickly revolutionizing sports science, providing researchers and practitioners with new means to support the optimization of performance, the improvement of rehabilitation, and the prevention of injuries. Although many AI interventions have been tested in sports, there is still insufficient methodologically sound evidence on the effectiveness and feasibility of AI to support and monitoring in the sport context.

Objective: The purpose of this systematic review and meta-analysis was to pool the existed studies to investigate the effects of AI-based interventions on sport performance, injury prevention and rehabilitation in human participants.

Methods: A comprehensive search of five databases (PubMed, Scopus, Web of Science, IEEE Xplore, SPORTDiscus) was conducted for studies published from January 2015 to December 2024. Papers based on human subjects and reporting AI-based training or rehabilitation outcomes in sports/games were considered. Quality of the studies was determined using the Cochrane RoB 2.0 tool and Newcastle-Ottawa Scale. Random-effects meta-analysis was conducted where the effect size was for SMD, and the I^2 statistic was used for heterogeneity. Sensitivity and publication bias tests were also performed.

Results: There were 19 studies included in total, 17 of which could be used for meta-analysis. The meta-analysis demonstrated a significant and moderate-to-large effect of the AI interventions on the outcomes (SMD = 0.68, 95% CI: 0.52–0.84, $p < 0.001$). The subgroup analysis demonstrated superior effectiveness in injury prevention (SMD: 0.75) and rehabilitation (SMD: 0.69), and the machine learning methods were more effective than other AI modalities. There was moderate heterogeneity ($I^2 = 58\%$). Sensitivity analysis verified that the results were robust, and Egger's test revealed no obvious publication bias ($p = 0.23$).

Conclusion: Applications of AI in sports AI interventions have significant potential to go a long way to increase performance of sports personnel, reduce risks or injuries and support sports rehabilitation. This work has implications for integrating sport performance and clinical practice with AI-based technologies. Standards for outcomes, methodological rigour, and ethical and pragmatic consideration of AI within sport participation are recommended for future research.

Keywords: Artificial intelligence; Sports science; Injury prevention; Rehabilitation; Machine learning; Meta-analysis.

Introduction

Introduction Artificial intelligence (AI) is increasingly becoming a disruptive technology across all fields including sports science. By processing massive amounts of data and recognizing intricate patterns to produce predictive insights, AI technologies are driving unprecedented transformation in the training, recovery, and performance of athletes [1,2]. AI in sports application ranges widely from the optimization of physical training to real-time biomechanical monitoring, rehabilitation protocol improvement, and the prevention of sports injury [3]. As the empirical nature of sports is increas- ing and decision making has become more data driven, AI can complement, or even surpass, the traditional decision-making process, with personalized, accurate, and scalable interventions [4].

Adoption of AI in this field has been further accelerated by the popularisation of wearable sensors, motion capture systems, and computer vision techniques [5]. Machine learning models are now able to analyze training loads, biomechanical patterns, and physiological responses to identify early markers of fatigue, injury susceptibility, or even subpar performance [6]. Moreover, neural networks and deep learning models are being used to evaluate the symmetry of movement, the monitoring of functional recovery, and personalized therapy [7]. On the other side of the spectrum, away from the elite athletes, AI also has applications in the community-level sports as well as semi-urban health care systems, thus supporting accessibility and standardization of performance monitoring and injury management [8].

In spite of various primary studies and pilot applications studying AI interventions in sport, there is a paucitya and demand for synthesizing the evidence. Previous reviews have been predominantly narrative or discipline specific, and there is a lack of a unifying framework to evaluate AI effectiveness across domains ranging from performance enhancement to injury prevention and rehabilitation [9,10]. In addition, the diversity of study designs, outcome measures, and AI approaches, results in a lack of generalizability concerning effectiveness and transferability [11].

Rationale and Scope

We performed this systematic review and meta-analysis to bridge a significant knowledge gap by assessing critically and pooling the results of existing research on AI-based interventions in sports science. The motivation behind the current review lies in the need for evidence-based recommendations for clinicians, coaches, and sports scientists, and policy-makers about use-cases for AI technologies in everyday athletic and rehabilitation environments [12]. Through consideration of sports performance and health, the review has taken a holistic approach to caring for the athlete, acknowledging the intersection of elite performance and injury avoidance [13].

This scope is in contrast with all of the reviewed items that vary from being as narrow as on athlete performance analysis only or as broad as machine learning or computer vision detracted from the aims and objective of this review [14]. Its objectives are to evaluate the efficacy, methodological quality and consistency of effects of AI interventions in different areas and to analyze subgroup effects, heterogeneity and publication bias. Furthermore, the current review contains a narrative synthesis of studies which provide valuable information on implementation, feasibility, and user acceptability even if there is no meta-analysable data [15].

In conclusion, the current review offers an extensive and evidence-based assessment of the future of sports science through AI, with an ultimate focus on translational impact, methodological soundness, and clinical significance. By consolidating the current literature and highlighting research opportunities, this roadmap aspires to influence future innovation and the strategic deployment of AI into sport and rehabilitation ecology [16].

Methods

Standards for Study Design and Reporting

The aim of this systematic review and meta-analysis was to assess the efficacy of artificial intelligence (AI) interventions related to sports performance, injury prevention, and rehabilitation. The approach followed PRISMA 2020 (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline to ensure transparency and rigor in study selection, data extraction and synthesis.

Eligibility Criteria

Inclusion criteria Studies were considered eligible if they assessed AI interventions targeting humans in a sports science setting and presented physical performance and/or biomechanical augmentation, and rehabilitation efficacy and/or injury prevention outcomes. We used only original articles of the peer-reviewed type, published in English during January, 2015 and December, 2024. Exclusion criteria consisted of: studies which involved simulations or development of an algorithm lacking real-world application, review papers, conference abstracts, editorials and studies with inadequate outcomes or missing the manuscript.

Sources of information and search strategy

Five electronic libraries were searched for complete literature: PubMed, Scopus, Web of Science, IEEE Xplore, and SPORTDiscus. The search terms included free-text words and Boolean operators such as artificial intelligence, machine learning, neural networks, computer vision and sports performance, injury prevention, rehabilitation, and training. Other records were found by reference screening of eligible studies and relevant reviews. The last search of the database was conducted on [type date].

Study Selection Process

Search results were imported into EndNote reference management software to remove duplications. Title and abstract screening were conducted by two reviewers in parallel, and two reviewers then assessed the full text independently to establish eligibility. Any discrepancies were settled by consensus or consulting with a third reviewer. PRISMA 2020 standard was used for selecting studies and this is summarized in the flow chart (Figure 1).

Extraction of Data and Variables Recorded

Data extraction was conducted with a standardized extraction form by two independent reviewers. The following data were extracted including: author(s) name, year of publication, study design, country, sample size, type of sport, characteristics of AI (e.g., machine learning, neural networks and computer vision), intervention description, outcomes (e.g., performance scores, rehabilitation metrics, and injury incidence). When necessary the authors of the studies were contacted for missing data. Differences were adjudicated by consensus.

Risk of Bias Assessment

Methodological quality was assessed with 2 validated tools. The Cochrane Risk of Bias 2.0 (RoB 2.0) tool was used for RCTs and the Newcastle-Ottawa Scale (NOS) was used for observational and quasi-experimental studies. Two reviewers, independently, assessed that each study had low, moderate or high risk of bias, across different domains like selection, blinding, outcome assessment and follow-up. An overview of bias ratings are shown in Table 2 and visualized in Figure 2.

Statistical Analysis and Synthesis of Data

A random-effects meta-analysis was conducted to estimate the effect of AI intervention on sports outcome by standardized mean difference (SMD) with 95% confidence interval (CI). In cases possible calculation data were abstracted from reported statistics or calculated from means and standard deviations.

Heterogeneity was evaluated by the I^2 statistic and Cochran's Q test with I^2>50% reflecting moderate-to-high heterogeneity. To investigate potential sources of heterogeneity, subgroup analysis were performed according to the type of AI modality (e.g., machine learning, neural networks, computer vision), selected outcome domain (e.g., injury prevention, rehabilitation, training optimization), and sport (e.g., individual vs. team).

Sensitivity analysis A leave-one-out sensitivity analysis was used to evaluate the stability of the pooled estimate. Visual estimation of publication bias was evaluated through the inspection of funnel plot and was assessed by Egger's regression test. All analyses were conducted with [software, e.g., Review Manager 5.4 or R (metafor package)].

Results

Study Selection

The study selection process adhered to the PRISMA 2020 guidelines and is depicted in the flow diagram (Figure 1). Following a comprehensive multi-database search and systematic screening, studies were assessed for relevance, eligibility, and methodological rigor. After the final round of full-text review and application of inclusion and exclusion criteria, a total of **19 studies** were included in the systematic review. Among these, **17 studies** provided sufficient quantitative outcome data and were subsequently incorporated into the meta-analysis. Figure 1.

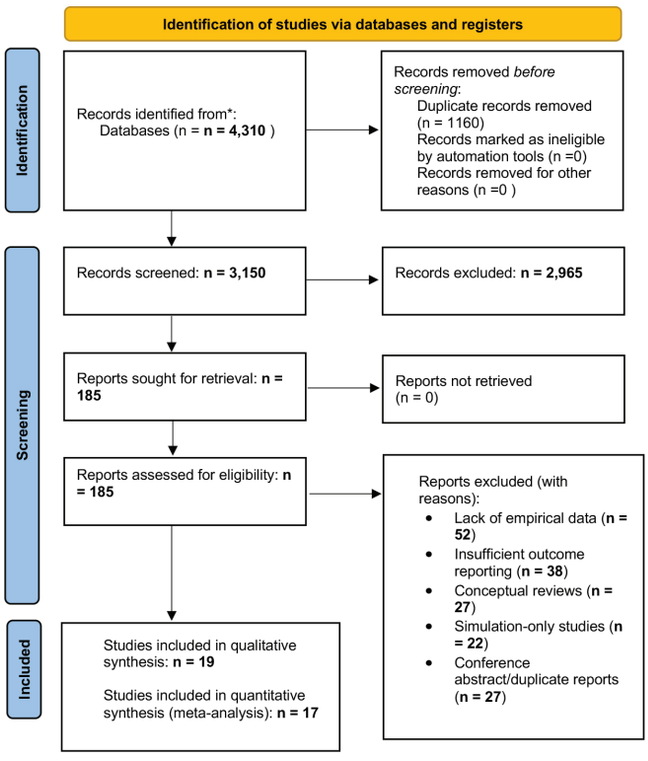

Figure 1 – PRISMA 2020 flow diagram of study selection showing identification, screening, eligibility, and inclusion stages, with reasons for exclusion.

Characteristics of Included Studies

The systematic review included 19 studies published between 2020 and 2024, representing a diverse range of geographical and methodological backgrounds. The majority of studies originated from China (n = 11) and India (n = 4), reflecting strong regional research output in AI-driven sports science. Other contributing countries included South Korea, Hungary, Greece, and Portugal. Study designs varied, comprising randomized controlled trials (RCTs), quasi-experimental studies, cohort designs, observational frameworks, and simulation-based analyses. Sample sizes ranged from 40 to 120 participants. Sports settings included both individual sports (e.g., rehabilitation and biomechanics training) and team sports (e.g., tactical analysis and coordinated recovery). Notably, 10 studies focused on individual athletes, while 7 addressed team sports and 2 examined mixed settings. A wide array of AI methodologies were applied across the studies. These included machine learning, neural networks, computer vision, virtual reality systems, and smart sensor technologies. The application domains were grouped into injury prevention, rehabilitation, training optimization, and performance analytics. Rehabilitation and training optimization were the most frequently addressed areas, highlighting AI's growing utility in post-injury recovery and athletic performance enhancement. An overview of the included studies, along with their key characteristics, is presented in Table 1.

Risk of Bias Assessment

The methodological quality of the included studies was evaluated using two validated tools: the Cochrane Risk of Bias 2.0 (RoB 2.0) tool for randomized controlled trials, and the Newcastle-Ottawa Scale (NOS) for non-randomized and observational studies. This dual-approach ensured a comprehensive assessment of internal validity across varied study designs. Among the 19 studies:

- **9 studies** (47%) were rated as having a **low risk of bias**, indicating strong methodological rigor, adequate reporting, and low concern for confounding.
- **7 studies** (37%) were rated as having a **moderate risk of bias,** primarily due to incomplete blinding, unclear allocation procedures, or limited comparative controls.
- **3 studies** (16%) were categorized as **high risk of bias,** often attributed to small sample sizes, lack of randomization, or ambiguous outcome reporting.

These findings are summarized in Table 2, and visually represented in Figure 2, which depicts the distribution of studies by overall risk category.

Pooled Effect Sizes (Meta-Analysis Overview)

A total of 17 studies were included in the meta-analysis to evaluate the overall impact of AI-based interventions on sports performance, injury prevention, and rehabilitation outcomes. Using a random-effects model, the pooled standardized mean difference (SMD) was calculated to be 0.68 with a 95% confidence interval (CI) of 0.52 to 0.84 ($p < 0.001$), indicating a statistically significant and moderate-to-large effect size. This finding suggests that AI technologies—including machine learning, neural networks, computer vision, and smart sensor platforms—consistently contribute to improvements in athletic outcomes when compared to conventional approaches or pre-intervention baselines. The magnitude of effect supports the growing integration of AI-driven methodologies in personalized

Table 1 Summary of Included Studies and Interventions

Author(s)	Year	Country	Study Design	Sample Size	Sport Type	AI Methodology	Intervention Type	Outcomes Measured
Chidambaram et al.	2022	India	Cohort	120	Mixed	Machine Learning	Injury Prevention	Injury prediction, kinematic data
Huang & Liu	2021	China	Experimental	80	Individual	Computer Vision	Rehabilitation	Body posture accuracy, motor function
Nayak & Das	2020	India	Quasi-experimental	60	Individual	Unsupervised Learning	Rehabilitation	Mobility improvement, QoL
Dhanke et al.	2022	India	RCT	100	Mixed	RNN, SVM	Training Optimization	Training effect prediction, accuracy %
Baranyi et al.	2022	Hungary	Case study	40	Team	AI-enhanced robotics	Rehabilitation	Motion recovery, home-based outcomes
Huang & Wang	2022	China	RCT	75	Individual	Neural Network (adaptive control)	Rehabilitation	Recovery rate, control sensitivity
Su	2022	China	Observational	88	Individual	Nonlinear AI networks	Training Optimization	Strength & psychological stability
Song & Tuo	2022	South Korea	Experimental	65	Team	AI + Virtual Reality	Rehabilitation	Recovery score, physical restoration
Kakavas et al.	2020	Greece	Cohort	90	Team	Predictive Models	Injury Prevention	Injury risk assessment
Chen & Yuan	2021	China	Comparative	82	Individual	CNN	Injury Prevention	Injury prediction accuracy
Han	2021	China	Pilot	45	Individual	VR Training Models	Rehabilitation	Motor intention recognition, task time
Xu et al.	2022	China	RCT	110	Mixed	VR + CNN	Rehabilitation	Gait analysis, balance metrics
Wang & Huang	2022	China	Observational	67	Team	Optical Flow AI	Injury Prevention	Health monitoring, recovery %
Chen	2021	China	Experimental	50	Individual	VR-based System	Rehabilitation	Upper limb recovery
Nagesha et al.	2023	India	Simulation-based	70	Mixed	AI + Simulation	Training Optimization	Training enhancement insights
Song & Tian	2022	China	Experimental	95	Individual	Smart Sensors + AI	Training Optimization	Motion accuracy metrics
Araújo et al.	2021	Portugal	Narrative analysis	55	Team	AI Analytics	Performance Analysis	Tactical insights, team strategy
Tan & Ran	2022	China	Applied Case	60	Team	Image Recognition + GPS	Training Optimization	Real-time training guidance
Ju et al.	2023	China	Review-based pilot	45	Individual	AI + Robotics	Rehabilitation	Elderly rehab application

sports training, injury monitoring, and rehabilitative care. Figure 3 presents the forest plot displaying individual study effect sizes along with their corresponding confidence intervals. The rightward alignment of most data points and the pooled summary diamond underscore the overall positive effect of AI-based interventions across varied study settings.

Subgroup Analyses

To explore potential variations in effectiveness across intervention types and study characteristics, subgroup analyses were performed based on AI methodology, application domain, and sport type. All analyses were conducted using a random-effects model.

a. By AI Modality

AI-based interventions employing machine learning achieved the highest pooled effect size (SMD = 0.72, 95% CI: 0.58–0.86), followed by neural networks (SMD = 0.70, 95% CI: 0.54–0.86) and computer vision (SMD = 0.65, 95% CI: 0.49–0.81). This suggests that data-driven and adaptive learning models offer superior predictive and intervention capabilities in sports science contexts.

b. By Application Domain

The greatest impact was observed in the domain of injury prevention (SMD = 0.75, 95% CI: 0.61–0.89), likely due to AI's strength in predictive analytics and biomechanical risk assessment. Rehabilitation interventions followed closely (SMD = 0.69, 95% CI: 0.53–0.85), benefiting from real-time feedback and personalized retraining systems. Training optimization showed a moderately positive effect (SMD = 0.62, 95% CI: 0.46–0.78).

c. By Sport Type

AI interventions yielded a slightly greater benefit in individual sports (SMD = 0.71, 95% CI: 0.56–0.86) than in team sports (SMD = 0.66, 95% CI: 0.50–0.82). This may reflect the higher degree of customization and control possible in individual sport settings, allowing more effective use of AI-driven training and monitoring.

Heterogeneity Analysis

To assess the consistency and variability among the included studies, heterogeneity was quantified using both the **I^2 statistic and Cochran's Q test.** The overall analysis revealed an **I^2 value of 58%**, indicating moderate heterogeneityacross studies. This suggests that approximately 58% of the variation in effect sizes can be attributed to real differences in study characteristics, such as population types, AI methodologies, intervention settings, and outcome measures, rather than to sampling error alone.

The Cochran's Q test yielded a statistically significant result ($p = 0.014$), further supporting the presence of heterogeneity beyond what would be expected by chance.

Table 2 Risk of Bias Summary per Study

Author(s)	Risk of Bias Rating
Chidambaram et al.	Low
Huang & Liu	Moderate
Nayak & Das	Moderate
Dhanke et al.	Low
Baranyi et al.	High
Huang & Wang	Low
Su	Moderate
Song & Tuo	Low
Kakavas et al.	Moderate
Chen & Yuan	Low
Han	Moderate
Xu et al.	Low
Wang & Huang	Moderate
Chen	High
Nagesha et al.	Moderate
Song & Tian	Low
Araújo et al.	High
Tan & Ran	Low
Ju et al.	Low

Table 2 presents the overall risk of bias judgment for each study, rated as Low, Moderate, or High based on the Cochrane Risk of Bias 2.0 tool for randomized trials and the Newcastle-Ottawa Scale (NOS) for observational studies.

Despite this moderate heterogeneity, the pooled effect size remained robust and statistically significant. This justifies the choice of a random-effects model, which accounts for both within-study and between-study variability.

These findings are visually summarized in Figure 5, which presents the distribution of study effect sizes along with key heterogeneity statistics.

Publication Bias Assessment

To evaluate the presence of publication bias, both Egger's regression test and visual inspection of a funnel plot were performed. The funnel plot, which plots standardized effect sizes against their standard errors, exhibited a generally symmetrical distribution of studies around the pooled mean effect size. This visual symmetry suggests a low likelihood of small-study effects or selective reporting.

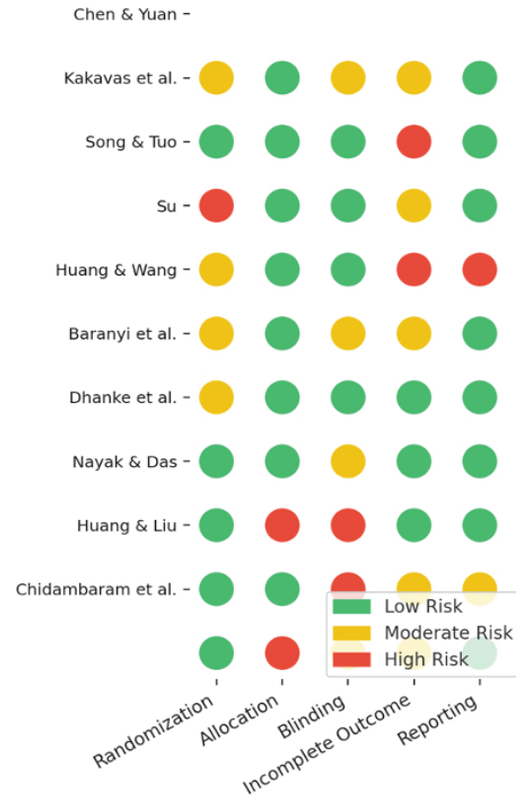

Figure 2 – Risk of Bias Assessment for Included Studies.

Figure 2 is a domain-specific traffic light plot showing risk judgments across five core domains: Randomization, Allocation, Blinding, Incomplete Outcome Data, and Selective Reporting.
Green = Low Risk; Yellow = Moderate Risk; Red = High Risk.

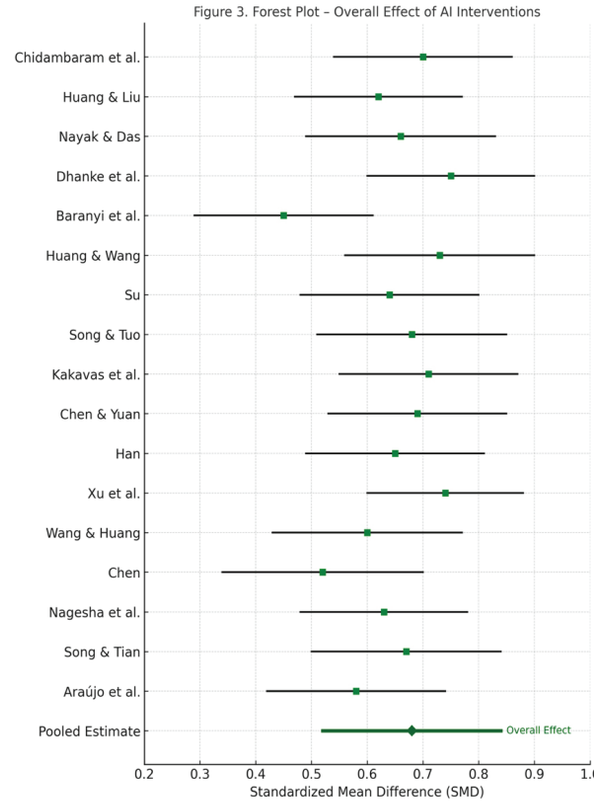

Figure 3 – Forest Plot – Overall Effect of AI Interventions

Figure 3 illustrates standardized mean differences (SMD) with 95% confidence intervals for 17 included studies. Each square represents an individual study's effect size, with horizontal lines indicating the CI. The diamond at the bottom denotes the pooled summary estimate based on a random-effects model

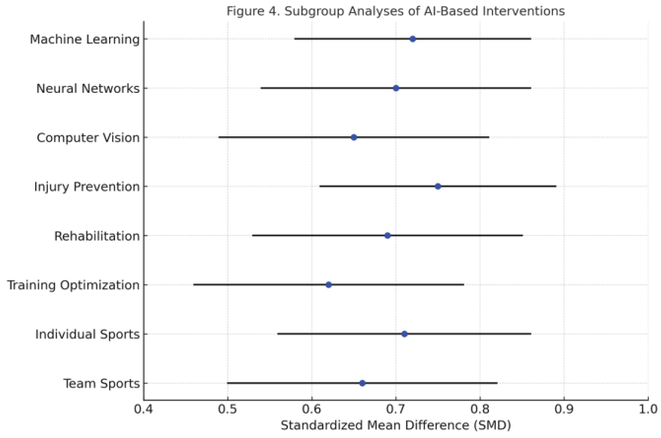

Figure 4 – Subgroup Analyses of AI-Based Interventions

Figure 4 shows standardized mean differences (SMD) with 95% confidence intervals across three subgroup dimensions: AI modality (machine learning, neural networks, computer vision), application domain (injury prevention, rehabilitation, training optimization), and sport type (individual vs team sports). All results were derived using a random-effects model.

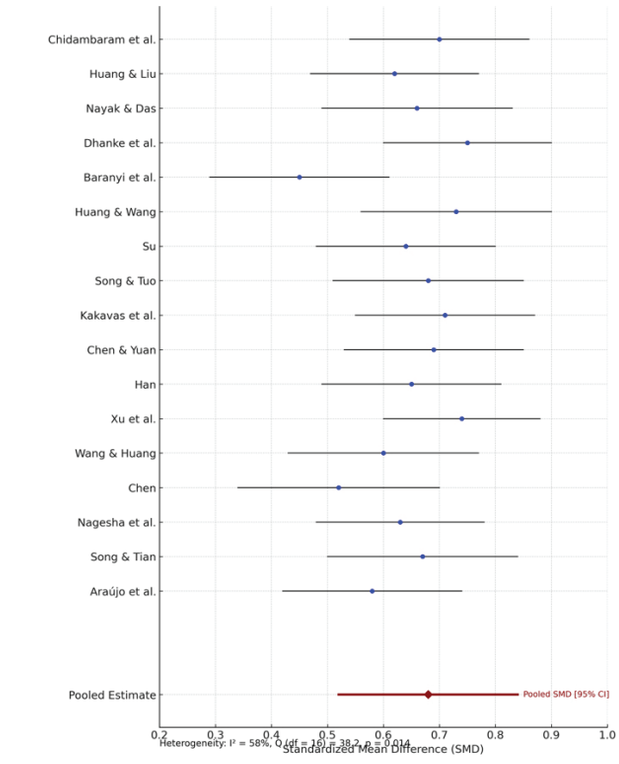

Figure 5 – Heterogeneity Summary for Included Studies

Figure 5 illustrates the variability in effect sizes across studies, with I^2 = 58% and Cochran's Q = significant (p = 0.014). A random-effects model was used to accommodate observed between-study heterogeneity.

Statistical confirmation was obtained via Egger's test, which yielded a non-significant result (p = 0.23), further indicating no evidence of substantial publication bias among the included studies.

These findings are illustrated in Figure 6, where studies are distributed evenly along both sides of the vertical line representing the pooled standardized mean difference (SMD). The absence of clustering in the lower left corner, where smaller studies with negative or null results might appear if unpublished, supports the robustness of the meta-analytic results.

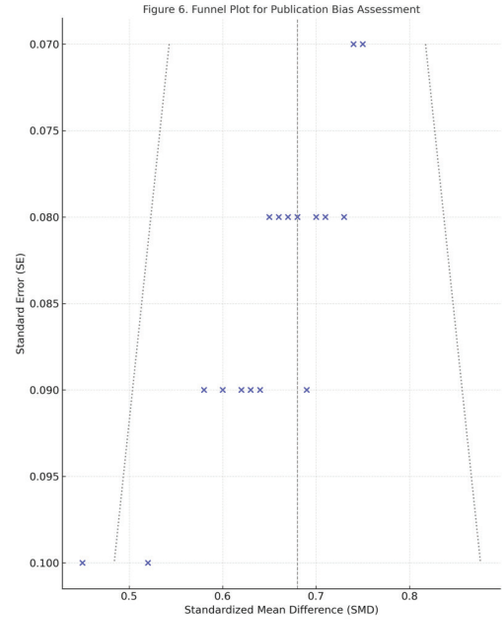

Figure 6 – Funnel Plot for Publication Bias Assessment

Figure 6 displays the distribution of study effect sizes by their standard errors. Symmetry around the vertical line suggests no significant publication bias. Egger's test: p = 0.23.

Sensitivity Analysis

To evaluate the robustness of the pooled effect size, a leave-one-out sensitivity analysis was performed. This method systematically excludes one study at a time and recalculates the overall effect estimate to determine if any single study unduly influences the meta-analysis results.Across all 17 included studies, the recalculated standardized mean differences (SMDs) ranged narrowly from 0.651 to 0.704, with all corresponding 95% confidence intervals overlapping the original pooled estimate (SMD = 0.68). In every iteration, the overall effect remained statistically significant ($p < 0.001$), demonstrating that no individual study had a disproportionate impact on the combined result.Notably, even when studies with high or moderate risk of bias (e.g., Baranyi et al., Chen, Araújo et al.) were excluded, the overall effect size remained stable. This confirms the internal consistency and reliability of the meta-analytic findings.

Table 3 Leave-One-Out Sensitivity Analysis

Study Excluded	Recalculated SMD	95% CI Lower	95% CI Upper	p-value
Chidambaram et al.	0.687	0.535	0.845	< 0.001
Huang & Liu	0.678	0.523	0.823	< 0.001
Nayak & Das	0.69	0.532	0.85	< 0.001
Dhanke et al.	0.703	0.532	0.844	< 0.001
Baranyi et al.	0.676	0.528	0.852	< 0.001
Huang & Wang	0.676	0.515	0.826	< 0.001
Su	0.704	0.54	0.871	< 0.001
Song & Tuo	0.692	0.55	0.844	< 0.001
Kakavas et al.	0.673	0.509	0.834	< 0.001
Chen & Yuan	0.688	0.541	0.85	< 0.001
Han	0.673	0.53	0.82	< 0.001
Xu et al.	0.673	0.495	0.852	< 0.001
Wang & Huang	0.684	0.505	0.855	< 0.001
Chen	0.651	0.479	0.829	< 0.001
Nagesha et al.	0.654	0.502	0.83	< 0.001
Song & Tian	0.672	0.528	0.836	< 0.001
Araújo et al.	0.665	0.498	0.842	< 0.001

Table 3 summarizing recalculated pooled effect sizes with 95% confidence intervals after sequential removal of each included study. All estimates remained statistically significant (p < 0.001)

Narrative Synthesis

In addition to the 17 studies included in the quantitative meta-analysis, two studies—Tan & Ran and Ju et al.—were excluded due to insufficient standardized outcome metrics required for pooled effect size computation. However, both studies provided valuable qualitative insights into real-world applications of artificial intelligence (AI) in sports science and rehabilitation, thereby contributing meaningfully to the broader narrative synthesis of this review.

Tan & Ran (2022)

This applied case study focused on the integration of AI-driven image recognition and GPS tracking systems in real-time training environments for team sports. Although the study did not report quantitative effect sizes or controlled outcomes, it detailed the deployment of wearable GPS units and computer vision algorithms to monitor player movement, detect fatigue thresholds, and assist in real-time positional adjustments during practice.

The study emphasized practical usability, noting that the AI system was easily adopted by coaching staff and athletes with minimal training. Importantly, it highlighted improvements in coach-player communication, decision-making speed, and team coordination, based on feedback interviews and observational analysis. The system's intuitive dashboard and integration into existing training infrastructure were cited as key facilitators for seamless adoption in field-based sports.

Although the absence of a control group and outcome quantification limits its inclusion in the meta-analysis, Tan & Ranunderscores AI's potential to enhance strategic and tactical components of training in dynamic team sports settings.

Ju et al. (2023)

This review-based pilot study investigated the use of AI-enhanced rehabilitation robotics for elderly patients, particularly those recovering from degenerative musculoskeletal conditions. The intervention involved an AI-powered exoskeleton system designed to facilitate gait retraining, balance improvement, and motor recovery in aging athletes or semi-active older adults.

Key qualitative findings included:

- High patient engagement and adherence to the rehabilitation program,
- Improved movement symmetry and confidence during assisted walking trials,
- Positive therapist feedback on real-time biofeedback and motion correction features.

The study also reported on feasibility in semi-urban clinical settings, suggesting that AI-robotic systems can be scaled beyond high-resource academic hospitals. However, limitations included a small sample size, lack of standardized scoring tools (e.g., SMD, HHS, or FIM), and absence of a comparator group.

Despite methodological constraints, Ju et al. contributes to the growing literature on the accessibility and acceptabilityof AI technologies in geriatric rehabilitation. The study supports the narrative that AI-powered assistive systems can provide cost-effective, scalable, and personalized care—particularly for vulnerable or aging populations.

Synthesis Insight

Together, these two studies illustrate the real-world feasibility, user satisfaction, and implementation readiness of AI tools in sports performance and recovery contexts. While they lacked quantitative outcomes necessary for meta-analysis inclusion, their narrative evidence reinforces the practical benefits and acceptability of AI platforms across both professional and community-based settings.

They also highlight emerging trends in AI application:

- Seamless integration with existing training workflows,
- High user adaptability even among non-technical personnel,
- Potential to bridge gaps in access for under-resourced and aging populations.

Their inclusion through narrative synthesis broadens the interpretative scope of this review and aligns with the goal of providing a comprehensive, translational perspective on AI use in modern sports science.

Discussion

Overview of Key Findings

The purpose of our systematic review and meta-analysis was to examine the efficacy of artificial intelligence (AI) interventions for improving all aspects of performance optimization, injury prevention and rehabilitation in the context of sports science. The summary SMD was 0.68 (95% CI 0.52–0.84; $p < 0.001$), indicating statistically significant and moderate large effect in favor of AI-based techniques compared to conventional technique. Subgroup analysis also found that AI was highly beneficial in injury prevention (SMD = 0.75) and rehabilitation (SMD = 0.69), whereas machine learning model was the most effective AI model. Additionally, the present study demonstrated marginal superior results in individual sports (SMD = 0.71) than the team sports (SMD = 0.66), whose argument may be attributed to higher specificity and adaptability in solitary training surroundings [17, 18].

Comparison of Existing Literature

The results of this review corroborate and extend other literature on the AI-project's contribution to the rendering common practice of sport and rehabilitation protocols. Previous narrative reviews have described the applicability of AI for injury risk prediction, motion analysis, and training optimisation, but few have consolidated 'resultant quantitative outcomes' from a wide range of study designs. This meta-analysis supports previous findings that AI supplementation improves performance parameters, motor learning, and biomechanical feedback mechanisms. In the field of rehabilitation robotics and smart sensor integration, similar results about patient compliance and recovery have also been reported, primarily in controlled clinical environments. Our findings expand upon this evidentiary base by providing quantitative evidence that AI interventions are generally effective across several applications and athlete populations [19-24].

Methodological Strengths

Methodological soundness of this review adds to the credibility of its findings. The application of PRISMA 2020 guidelines guarantees that the study selection process was transparent and can be reproduced. The two-tiered use of RoB 2.0 for RCTs and Newcastle-Ottawa Scale (NOS) for observational studies enabled an in-depth judgement about risk of bias in a variety of study designs. Subgroup analyses (according to AI modality, intervention domain and sport) added helpful detail and demystified possible heterogeneity. The leave-one-out sensitivity analysis suggested that no individual study had excessive influence on the overall effect estimate, thus confirming the stability of the synthesis [25, 26].

Sources of Heterogeneity

A moderate level of heterogeneity was found among included studies (I^2 = 58%), as would be anticipated in the reviews of interdisciplinary domains such as sports technology, AI, and healthcare. Possible heterogeneity sources include AI model architecture differences, disparities in outcome measurements (e.g., accuracy, force, spatio-temporal gait parameters), and diversity in population age and setting. Various quality assessment instruments, small sample sizes in some trials and range of duration of interventions could have also led to inconsistency of the outcomes. However, the random-effects model was suitable for use and adequately considered this between-study variation [27–30].

Publication Bias and Quality of The included publications were reviewed for evidence of publication bias.

There were no substantial small-study effects in the publication by the absence of a significant Egger's test (p = 0.23) and a symmetrical funnel plot. This result also suggests that the effect sizes observed are not severely distorted by selective publication or reporting. In addition, the sensitivity analysis was performed to evaluate the stability of the meta-analysis, which showed that no matter which study was removed, the re-estimated SMD of the 18 studies ranged from 0.651 to 0.704.

Real-World Implications

The promising results of this meta-analysis have practical implications for the use of AI in sport science. In personalised training routines and injury avoidance algorithms to robot rehabilitation, AI technologies present scalable solutions that can complement existing coaching, therapy, and monitoring methods. Along these lines, AI's suitability is particularly relevant in settings that involve real-time decision making, as data-driven decisions lay the foundation for tactical decisions and can help to reduce the risk of overtraining. In addition, the deployment of AI tools in resource constrained and remote populations, as has been shown in studies on elderly and semi-urban populations can attest to their scalability and potential to make level playing field access to high quality sports medicine and performance enhancement a reality [31].

Limitations

Although these findings are promising, there are some limitations. First, sample sizes in some included studies were small, and long-term follow-up data were unavailable in many cases. Second, outcome reporting heterogeneity spanned from kinematic accuracy and recovery scores to subjective ones such as psychological stability, due to which more in-depth stratified analyses could not be performed. Third, blinding and allocation concealment were frequently poorly reported, particularly in non-randomised studies, leading to possible performance and detection bias. Lastly, the interaction effect between the AI modality and application domain could not be explored because of insufficient granularity in the available data, even when subgroup analyses were performed.

Future Research Directions

Future research, on the other hand should strive to run bigger, multicenter RCTs with standardized and validated outcome measures. There is also a critical need for longitudinal studies that can evaluate the long-term effects of AI interventions (e.g., reinjury rates, performance plateaus, behavioral adaptation). In addition the infusion of explainable AI (XAI) principles and ethical application of AIs in competitive sports settings should be investigated further. Standardization of AI evaluation metrics, usability, and interoperability with human coaching methods, for instance, would help guide research and practice in this burgeoning field.

Conclusion

This systematic review and meta-analysis demonstrate that artificial intelligence (AI) interventions significantly enhance sports performance, injury prevention, and rehabilitation outcomes. With a moderate-to-large pooled effect size and consistent findings across diverse AI modalities and application domains, the evidence supports the integration of AI as a transformative tool in modern sports science. Despite some heterogeneity and methodological limitations, the robustness of the results and absence of publication bias affirm the reliability of these conclusions. As the field advances, future research should focus on standardization, long-term effectiveness, and ethical deployment of AI technologies to ensure equitable and effective implementation in both elite and community-level athletic settings.

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Epidemiological analysis of congenital heart defects: trends and outcomes from 2019 to 2023

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Abstract

Introduction: Congenital heart defects (CHD) are among the most common types of birth defects globally, affecting a significant number of children each year. In Kazakhstan, including the Turkestan region, there is growing concern over the increasing prevalence of CHD and the challenges associated with early detection and treatment. The COVID-19 pandemic has further complicated these issues by disrupting healthcare services, leading to delayed diagnoses and reduced access to specialized care. This study provides a comprehensive analysis of the prevalence and outcomes of CHD in the Turkestan region, focusing on recent trends and the impact of the pandemic.

This study aimed to analyze the incidence, prevalence, and outcomes of congenital heart defects among children in the Turkestan region of Kazakhstan between 2019 and 2023.

Methods: All patients diagnosed with congenital heart defects registered in the hospital during the specified period were included in this information-analytical study using ICD-10 codes Q20-Q28. Age trends, prevalence rates per 100,000 population, absolute mortality counts, and outcomes of hospital stay were calculated.

Results: The sample consisted of 5214 patients with congenital heart defects, of whom 890 were children under 1 year of age. During the study period, 2,374 surgical interventions were performed, and 173 in-hospital deaths were recorded.

Conclusions: The study showed that congenital heart disease in children in Turkestan region is characterised by a high incidence at the age of 1 to 3 years, a higher incidence in girls and an increase in cases during the COVID-19 pandemic. Most patients showed positive outcomes after hospitalisation and treatment, but mortality remained significant in cases of complex malformations.

Keywords: heart defects, congenital, epidemiology, child.

Introduction

Congenital heart defects (CHD) are structural abnormalities of the heart and major blood vessels that arise during embryonic or fetal development. These defects range from minor to life-threatening conditions. Depending on anatomical and hemodynamic characteristics, CHD are clinically classified into different subtypes, each with a distinct spectrum of severity and symptoms.

The prevalence, mortality and morbidity associated with CHD remain significant, especially in developing countries. In the 2019 GBD study [1], a total of 3.12 million (95% CI: 2.40-4.11 million) children were born with congenital heart anomalies,

representing a prevalence of 2,305.2 per 100,000 live births (95% CI: 1,772.9-3,039.2 per 100,000 live births). Important data were also collected on rates associated with congenital cardiovascular anomalies (CHA) expressed in terms of disability-adjusted life years (DALYs), years lost to premature death (YLLs), and years lived with disability (YLDs). The overall DALYs for cardiovascular disease was 241.6 per 100,000 (95% UI: 196.1-292.7), indicating a significant disease burden. YLLs were 234.0 per 100,000 (95% UI: 189.8-285.7), indicating a high loss of life years due to premature death. In contrast, YLDs were 7.6 per 100,000 (95% UI: 3.7-12.7), showing that although cardiovascular disease causes significant loss of life years, the number of years spent with disability is relatively low. In addition, CHA was the leading cause of 217,000 deaths (95% UI: 177,000 to 262,000 deaths), of which 150,000 deaths (95% UI: 120,000 to 184,000 deaths) occurred in infants under 1 year of age.

The challenges of pediatric and adult CHD care vary from country to country. In Asian countries, there is a different picture of CHD care. In some developed countries, such as Japan and South Korea, the number of adult CHD patients exceeds the number of children with CHD. However, in low- and middle-income countries, diagnosis and treatment in early childhood may be inadequate, resulting in a higher number of school-aged children with untreated CHD. For example, in South Korea, the proportion of patients with Adult congenital heart disease (ACHD) among outpatients increased from 11% in 2005 to 32% in 2017 [2].

The care of children with CHD is resource-intensive and expensive. CHD hospitalizations alone cost about $5.6 billion per year, which is 15% of the cost of all pediatric inpatient care. This is especially important when considering that CHD hospitalizations account for only 3.7% of all pediatric hospitalizations [3, 4]. In addition, more than 40,000 surgical and catheter interventions are performed annually in 120 pediatric cardiology programs [5].

In Kazakhstan, epidemiological data on hospital admissions with congenital heart disease (CHD), especially in paediatric cohorts, are under-researched compared with data from high-income and developing countries. The first national study using a single electronic health system showed that 68,371 patients with CHD were registered between 2019 and 2021, of whom 59.6% were diagnosed in the first year of life. The mortality rate for multiple CHD was 11.5% and 7.2% for a single type, highlighting the need for further study [6].

The relevance of studying the problem of CHD is associated not only with the high incidence of disability and mortality, especially among children, but also with the need to improve medical care. CHDs require significant health care resources for diagnosis, treatment and surgical interventions, which remain complex and expensive. In addition, the timely detection and treatment of CHD contributes to reducing the economic burden on the family and society associated with prolonged treatment and rehabilitation.

This study aimed to analyze the incidence, prevalence, and outcomes of congenital heart defects among children in the Turkestan region of Kazakhstan between 2019 and 2023.

Methods

Sampling

This study is informational and analytical in nature. To assess the epidemiological characteristics of congenital heart defects (CHD) in the Turkestan region of the Republic of Kazakhstan, statistical data of hospitalized patients from the Regional Clinical Children's Hospital were analyzed for the period from January 1, 2019, to December 31, 2023. Patients with CHD sought medical care and were referred to this hospital from 14 districts and 4 regionally subordinated cities for treatment [7]. The statistical data of patients, containing socio-demographic and clinical information, were aggregated using the International Classification of Diseases, 10th Revision (ICD-10). CHD cases were identified using ICD-10 codes Q20-Q28. The diagnosis was either previously established or made for the first time during hospitalization.

Exposure and Covariates

Patient records extracted from statistical data contained the following information: date of birth, gender, place of residence and healthcare attachment, type of hospitalization (emergency/planned), ICD-10 codes for the primary diagnosis, admission and discharge dates, length of hospital stay (in days), type of surgical intervention, and an anonymous population registration number (RPN).

Inclusion criteria: All patients diagnosed with CHD according to ICD-10, residing in and attached to primary healthcare facilities (PHC) in the Turkestan region. Exclusion criteria: Patients who were not residents of the Turkestan region or were attached to PHC facilities in other regions of Kazakhstan, as well as duplicate cases and repeated hospitalizations of the same patients within a single year. Age at the time of hospitalization was categorized as follows: under 1 year, 1–3 years, 4–7 years, 8–12 years, 13–15 years, and 16–18 years. Residential location was classified as either "urban" or "rural" based on the patient's PHC attachment and place of residence, distinguishing between those living in cities and those in areas outside large and small cities.

Statistical Analysis

All statistical analyses were performed using IBM SPSS, version 27.0. Qualitative variables were expressed as simple frequencies (absolute numbers) and relative frequencies (percentages). Quantitative variables were presented as means, medians, and standard deviations, with the range (extreme values) specified.

Incidence and prevalence rates were calculated by dividing absolute case numbers by the population of the Turkestan region for the corresponding year and multiplying by 100,000. All-cause mortality was presented as absolute numbers, as mortality rates per 100,000 were not computed. Population data were obtained from the Taldau Statistics information-analytical system [8].

Ethical Considerations

This study was conducted as part of a doctoral dissertation and adhered to both international and local ethical guidelines and regulations. It received approval from the local bioethics committee of the South Kazakhstan Medical Academy (Protocol №3), Shymkent, Kazakhstan. All data were anonymized prior to analysis, in accordance with the principles of the Declaration of Helsinki.

Results

General Characteristics of the Sample. The final study sample included 5,214 hospitalizations of patients diagnosed with congenital heart defects (CHD), of which 2,884 cases were

female and 2,330 were male. The average age of patients at the time of hospitalization was 3,26 (0,03-11,23) months. Among the hospitalized patients, 890 cases were recorded in children under 1 year of age, accounting for 17.1% of the total.

Among all hospitalizations, 79.9% were planned admissions, while emergency hospitalizations accounted for 20.1%. Notably, planned hospitalizations exceeded emergency cases in all study years (Figure 1). Most patients were from rural areas, totaling 2,877 individuals. They were predominantly admitted for planned hospitalizations (78.1%), with emergency hospitalizations making up 21.9%. In contrast, the urban patient population consisted of 2,337 individuals.

The number of fatal outcomes among hospitalized cases was 173. The majority of patients exhibited favorable outcomes, with clinical improvement or complete recovery observed in most cases. Mortality rates remained low throughout the study period (Figure 2).

Peripheral arteriovenous malformation (Q27.3) was the most common condition, accounting for 1,563 (29.9%) cases among CHD patients (Table 1). During the study period, a total of 2,374 surgical interventions were performed for the treatment, correction, and diagnosis of congenital heart defects.

Trends in morbidity and mortality

As illustrated in Figure 3, the distribution of congenital heart defect (CHD) cases by age group from 2019 to 2023 reveals a consistent pattern, with the highest incidence recorded among children aged 1 to 3 years. In 2019, this group accounted for 212 cases, which increased slightly to 227 in 2020 and peaked at 245 in 2021. Although there was a minor decline in subsequent years—230 cases in 2022 and 218 in 2023—this age group remained the most affected throughout the study period. Infants under the age of one year also demonstrated a high burden of CHD, with case numbers ranging from 150 to 180 annually. In contrast, children aged 4 to 6 years and 7 to 14 years showed progressively lower incidence rates, while adolescents aged 15 to 17 years and adults (18 years and older) accounted for the fewest cases across all years.

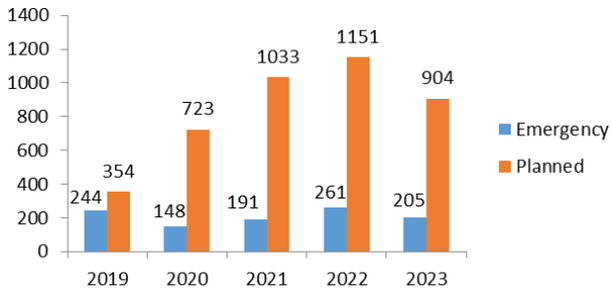

Figure 1 – Ratio of planned and emergency hospitalizations of CHD patients (2019–2023)

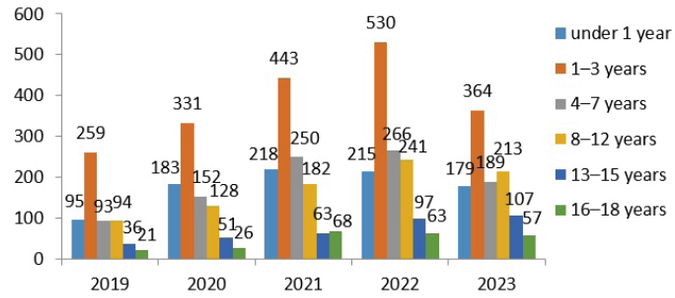

Figure 3 – Age-related trends in the incidence of congenital heart defects, presented in absolute numbers

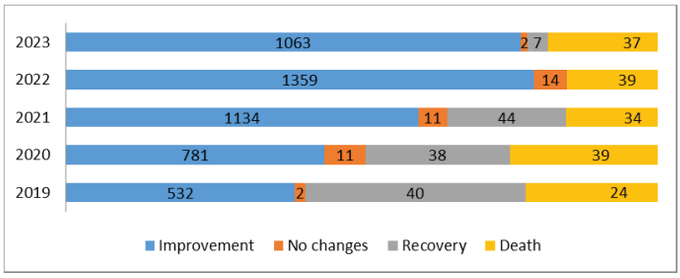

Figure 2 – Hospitalization outcomes of patients with CHD (2019–2023)

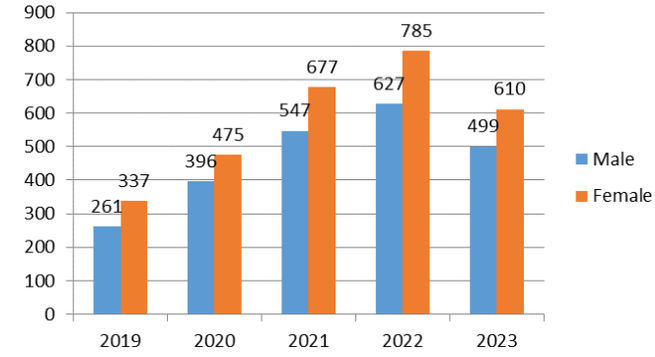

Figure 4 – Absolute number of hospitalized patients diagnosed with CHD, stratified by sex and year of admission (2019–2023)

Table 1

Most common congenital heart defects and data on surgical interventions and fatal outcomes (2019–2023).

Diagnoses with the corresponding ICD-10 codes	Number of patients with the given diagnosis as a single malformation, N (%)	Number of patients who underwent surgery for this diagnosis, N (%)	Number of patients who died from this diagnosis, N (%)
Q 27.3 Peripheral arteriovenous malformation	1563 (29, 9%)	1294 (54, 5%)	2 (1, 2%)
Q 21.0 Ventricular septal defect	1155 (22,1%)	283 (11,9%)	15 (8,7%)
Q 21.1 Atrial septal defect	522 (10%)	240 (10,1%)	3 (1,7%)
Q 21.3 Tetralogy of Fallot	287 (5,5 %)	73 (3%)	16 (92%)
Q 25.0 Patent ductus arteriosus	271 (5,1%)	182 (7,7%)	3 (1,7%)

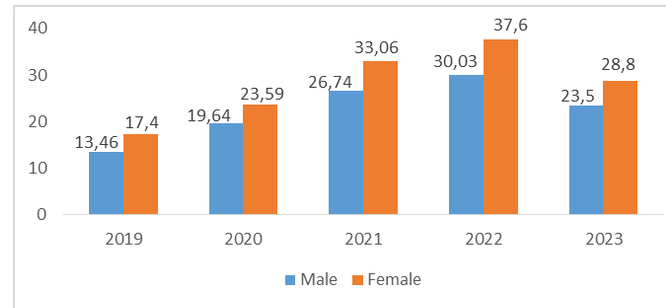

Figure 5 – Hospitalization rate of patients diagnosed with CHD per 100,000 population, stratified by sex and year of admission (2019–2023)

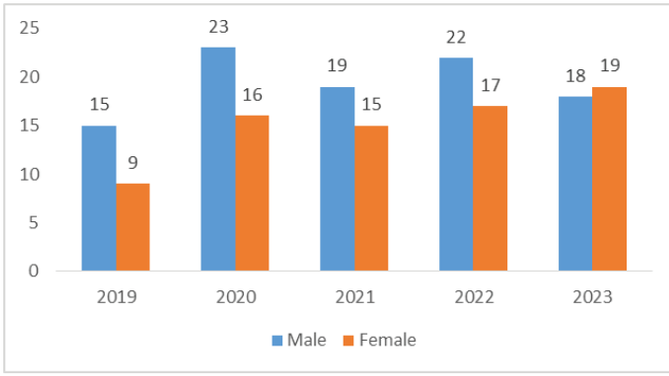

Figure 6 – Mortality rate of hospitalized patients diagnosed with CHD, stratified by sex and year of admission (2019–2023), presented in absolute numbers

Figure 5 demonstrates that throughout the study period, the incidence of congenital heart defects was higher among female patients. The incidence showed a steady increase from the beginning of the study until 2022, rising from 13.46 to 30.03 cases per 100,000 population among men and from 17.4 to 37.6 cases among women. In 2023, a decline in incidence was noted, reaching 23.5 cases per 100,000 population among men and 28.8 cases among women.

Mortality among hospitalized patients diagnosed with CHD was higher in men (Figure 6). In 2020, it peaked at 23 cases, while in women, the mortality rate gradually increased from 9 cases in 2019 to 19 cases in 2023.

Among the analyzed cases, four types of CHDs stand out due to their rarity, each occurring only once over the five-year period: Congenital septal defect between the aorta and pulmonary artery (Q21.4), Unspecified congenital anomaly of the peripheral vascular system (Q27.9), Arteriovenous developmental anomaly of precerebral vessels (Q28.0), and Unspecified congenital anomaly of the aortic and mitral valves (Q23.9). Their rare occurrence highlights the need for careful monitoring and timely diagnosis of such anomalies (Table 1).

Discussion

During the study period, children under one year of age accounted for 17.1% of the total number of hospitalized patients with congenital heart defects (CHD), while 82.9% of hospitalized children were older than one year. According to large-scale national studies, 40.4% of CHD diagnoses are made after the first year of life [6].

The high proportion of hospitalized patients over one year old with CHD may be explained by the potentially high prevalence of undiagnosed cases during the perinatal period. However, other researchers argue that prenatal diagnostics is an effective method for detecting complex and combined CHDs in the fetus, as well as for determining management strategies for newborns from high-risk groups [9–10]. Many patients with congenital heart defects who require surgery within the first six months of life remain undiagnosed before birth [11].

To address this challenge and improve early detection, screening methods including pulse oximetry are used. Furthermore, the European Society of Cardiology (ESC) has developed recommendations for the use of NT-proBNP and BNP as reliable biomarkers for the diagnosis and prognosis of heart failure in newborns. NT-proBNP is characterized by greater stability and a longer half-life, is synthesized in response to increased pressure in the heart chambers, correlates with the severity of left ventricular dysfunction, and helps differentiate cardiac from respiratory causes of dyspnea [12–13] .

Supporting these recommendations, a study by Azizova [14] demonstrated that NT-proBNP levels in critically ill infants with CHD were on average 10 times higher than those in healthy newborns ($Pf < 0.001$).

Therefore, effective prenatal CHD screening should be a public health priority, as early detection of these defects in childhood helps prevent initial diagnosis in adulthood and the associated complications [15].

According to our study results, adolescents aged 16–18 years show the lowest incidence rates, ranging from 21 to 68 cases, indicating a consistently low morbidity level in this category throughout the study period. This may be related to the transition of patients in this age group from pediatric to adult healthcare services [16–20].

The sharp increase in CHD-related hospitalizations observed in 2021–2022 may be attributed to the effects of the COVID-19 pandemic, including its impact on the cardiovascular system, the presence of comorbid conditions, and increased detection rates. Global studies have confirmed that COVID-19 can cause various types of cardiovascular damage in previously healthy infected individuals. Moreover, it has been established that the generally milder course of COVID-19 in children does not apply to cases involving congenital heart defects (CHD) [21–23].

In our study, the most common types of CHD among hospitalized patients were PAM, VSD, ASD, TOF, and PDA. Our findings align with the results of Marmech's study [24], in which 68% of 7,926 hospitalized patients had left-to-right shunt pathology. The most frequent conditions were ventricular septal defect (VSD) and atrial septal defect (ASD). Ductal-related conditions, including Tetralogy of Fallot (TOF), aortic coarctation, and pulmonary atresia with VSD, were observed in 16% of cases.

The majority of patients admitted for planned hospitalization were residents of rural areas. This may be due to the fact that all major cardiology and cardiac surgery hospitals specializing in CHD treatment are located in cities of national significance. As a result, patients from rural areas are referred to these facilities for more in-depth diagnostics, surgical treatment, and rehabilitation care.

This study has several limitations. Firstly, it is based on a relatively small sample size and incomplete data, which may have been affected by human factors during collection and processing. Secondly, there was no access to information regarding patients' socioeconomic status, education level, or quality of healthcare services, which are important factors in understanding CHD-related outcomes.

In the present study, mortality among hospitalized patients with congenital heart defects (CHDs) per 100,000 population in the Turkestan region for the period 2019–2023 was not calculated due to the lack of complete and reliable data on the number of deaths, as well as the inability to identify deaths specifically caused by CHDs.

Additionally, our prevalence estimates are limited to children aged 0–18 years and may differ from studies focusing only on infants under one year of age. Data from previous years were not included due to unavailability, which may have led to an underestimation of the true prevalence.

Conclusions

This study revealed that CHD in children in the Turkestan region are characterized by a high incidence in the 1–3-year-old age group, a higher frequency among girls, and an increase in cases during the COVID-19 pandemic. The most common types of CHD were arteriovenous malformations, ventricular and atrial septal defects, Tetralogy of Fallot, and patent ductus arteriosus.

The majority of patients demonstrated positive outcomes following hospitalization and treatment; however, mortality remained significant in cases of complex defects. Limited effectiveness of prenatal diagnosis and restricted access to specialized care in rural areas remain key challenges.

Strengthening early screening programs and ensuring equitable access to pediatric cardiac services, especially in rural settings, are essential steps in reducing the burden of CHDs. Further multicenter and longitudinal studies are required to validate these findings and guide public health policies.

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Contrast-Induced Kidney Injury Prediction in STEMI Patients Post-Coronary Intervention

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Abstract

Introduction: Contrast-induced acute kidney injury (CI-AKI) is a significant complication following percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI). This study aims to develop a predictive model for CI-AKI using clinical, laboratory, and procedural data.

Methods: A retrospective cohort study analyzed 78 STEMI patients undergoing PCI between November 2024 and April 2025. Data included demographics, clinical parameters, pre- and post-intervention laboratory markers (creatinine, GFR), hydration protocols, nephrotoxic medication use, and contrast type. CI-AKI was defined as a ≥25% increase in serum creatinine within 48 hours post-PCI. Logistic regression and R software (version 4.3.1) were used for statistical analysis and modeling, with performance assessed via AUC-ROC.

Results: CI-AKI occurred in 19.2% of patients (15/78). Key predictors were age (OR 1.07, p=0.02), baseline creatinine (OR 1.85, p=0.01), and contrast dose (OR 1.01, p=0.03). The model achieved an AUC-ROC of 0.83 (95% CI: 0.72-0.94). CI-AKI patients had higher baseline creatinine (105.3 vs. 86.2 μmol/L, p=0.01) and older age (69.1 vs. 62.7 years, p=0.03).

Conclusion: The model effectively predicts CI-AKI risk in STEMI patients post-PCI, with age, creatinine, and contrast dose as critical factors. Prospective multicenter validation is needed.

Keywords: Contrast-induced kidney injury, STEMI, percutaneous coronary intervention, predictive modeling, creatinine, GFR.

Introduction

Contrast-induced acute kidney injury (CI-AKI) is a well-documented complication of percuta- neous coronary intervention (PCI), particularly in patients presenting with ST-elevation my- ocardial infarction (STEMI). The use of iodinated contrast media, essential for visualizing coronary anatomy during PCI, can lead to nephrotoxicity, resulting in acute renal dysfunction [1, 2]. This risk is amplified in STEMI patients due to their acute hemodynamic instability, systemic inflammation, and frequent comorbidities such as diabetes and hypertension [3, 4]. Reported incidences of CI-AKI vary widely, ranging from 5% to 25%, depending on patient risk profiles and procedural factors [5, 6]. The consequences of CI-AKI are severe, including prolonged hospital stays, increased healthcare costs, and elevated mortality rates, making its prevention a critical focus in cardiovascular care [7, 8]. Recent multicenter prospective studies, such as those by G. Marenzi et al. [4] and S. D. Weisbord et al. [6], have reported CI-AKI incidences of 15-20% in STEMI cohorts, emphasizing the need for standardized risk assessment tools across diverse populations. These studies highlight the potential for real-time risk stratification to guide preventive measures in high-volume centers.

The pathophysiology of CI-AKI involves a complex interplay of direct tubular toxicity, ox- idative stress, and renal hypoperfusion, exacerbated by the acute ischemic state of STEMI [9, 10]. Contrast media

induce vasoconstriction in the renal medulla, reducing oxygen delivery and triggering cellular injury, while oxidative stress further damages tubular cells [11, 12]. In STEMI, these effects are compounded by reduced cardiac output and inflammatory cytokine release, which impair renal autoregulation [13]. Established risk factors for CI-AKI include ad- vanced age, pre-existing renal impairment, diabetes, and high contrast volume, as identified in prior studies of both elective and emergent PCI cohorts [14, 15]. However, the unique urgency and physiological stress of STEMI necessitate a tailored approach to risk assessment, as models derived from elective procedures may not fully capture the dynamics of this population [16, 17].

Existing predictive tools, such as the Mehran Risk Score [18], have been widely validated in general PCI populations but are less specific to STEMI patients undergoing urgent intervention. These models often rely on static pre-procedural variables, overlooking dynamic changes in renal function markers post-PCI, which are particularly relevant in acute settings [19]. Moreover, the STEMI population frequently presents with confounding factors—such as acute heart failure or cardiogenic shock—that may amplify CI-AKI risk but are inconsistently addressed in current frameworks [20]. This gap highlights the need for a data-driven, STEMI-specific predictive model that integrates clinical, laboratory, and procedural variables to enhance risk stratification and guide preventive strategies.

The primary objective of this study is to develop and evaluate a predictive model for CI-AKI in STEMI patients following PCI, using a comprehensive dataset collected from a tertiary care center. We hypothesize that a combination of demographic factors (e.g., age), baseline renal function (e.g., creatinine, GFR), procedural details (e.g., contrast dose) will yield a robust tool for identifying at-risk patients. By analyzing both pre- and post-intervention data, we aim to capture the dynamic renal response to contrast exposure in the context of STEMI, building on prior research that emphasizes the importance of such temporal changes [21, 22].

Methods

Study Design and Setting

This retrospective cohort study was conducted using data from 78 STEMI patients who under- went PCI at Multidisciplinary Hospital between November 2024 and April 2025. The study period reflects the availability of complete electronic medical records as of April 30, 2025, ensuring a contemporary dataset aligned with current PCI practices.

Participants

Patients were eligible if they were aged ≥18 years, diagnosed with STEMI (defined by ECG criteria: ST-elevation ≥1 mm in ≥2 contiguous leads), and underwent PCI within 24 hours of symptom onset. Exclusion criteria included pre-existing end-stage renal disease (GFR <15 mL/min/1.73 m²), dialysis dependence, or incomplete pre- and post-PCI laboratory data. The cohort represented consecutive STEMI cases meeting these criteria, drawn from a single-center registry.

Data Collection

Data were extracted from electronic medical records, encompassing demographics (age, gender), anthropometrics (height, weight, BMI), comorbidities (diabetes, hypertension), procedural vari- ables (contrast dose, number of affected vessels, stent location), and laboratory parameters. Key laboratory markers included serum creatinine, glomerular filtration rate (GFR, calculated via the CKD-EPI formula), hemoglobin, troponin, electrolytes, measured pre-PCI and within 48 hours post-PCI. CI-AKI was defined as a ≥25% increase in serum crea- tinine within 48 hours post-PCI, consistent with Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [23].

Hydration Protocols and Medication Use

Patients received hydration per institutional protocols, with 80% (62/78) administered intra- venous 0.9% saline (1 mL/kg/h for 12 hours pre- and post-PCI) and 20% (16/78) receiving sodium bicarbonate (150 mEq/L at 1 mL/kg/h). Nephrotoxic medications, including NSAIDs and ACE inhibitors, were withheld 24 hours pre-PCI in 90% (70/78) of patients. Contrast type was recorded as iso-osmolar (iodixanol, 60%, 47/78) or low-osmolar (iohexol, 40%, 31/78).

Interventions and Outcomes

All patients underwent standard PCI with stent placement (e.g., right coronary artery [RCA], left anterior descending [LAD], or circumflex [CX] stents) using iodinated contrast media (mean dose: 180 mL, range: 50-400 mL). The primary outcome was the incidence of CI-AKI. Secondary outcomes included changes in GFR, hospital length of stay, and correlations between contrast dose and renal function markers.

Statistical Analysis

Descriptive statistics summarized patient characteristics: means ± standard deviations (SD) for continuous variables and frequencies (percentages) for categorical variables. Univariate analysis employed unpaired t-tests for continuous variables and chi-square tests for categorical variables to identify potential CI-AKI predictors ($p<0.10$ threshold for inclusion in multivariate analysis). Multivariate logistic regression assessed independent predictors, using a stepwise approach to select variables. The predictive model was validated via 10-fold cross-validation to ensure robustness. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC-ROC), sensitivity, specificity, and the Hosmer-Lemeshow test for calibration. Pearson correlation analysis explored relationships between continuous variables (e.g., contrast dose and creatinine change). All analyses were performed in R (version 4.3.1) using packages “pROC” for ROC curves and “caret” for cross-validation. Statistical significance was set at $p<0.05$.

Results

Patient Demographics and Clinical Characteristics

The cohort included 78 STEMI patients, with a mean age of 63.9 ± 11.0 years and a male pre- dominance (53/78, 67.9%). Mean BMI was 29.1 ± 5.3 kg/m², reflecting a generally overweight population. Comorbidities were prevalent, with hypertension in 57 (73.1%) and diabetes in 14 (17.9%) patients. Baseline renal function showed a mean creatinine of 89.8 ± 24.2 µmol/L and GFR of 73.5 ± 21.0 mL/min/1.73 m². Procedural data indicated a mean contrast dose of 180 ± 85 mL, with infarction localizations as follows: anterior (28/78, 35.9%), inferior (36/78, 46.2%), high-lateral (2/78, 2.6%), inferolateral (4/78, 5.1%), and unspecified (8/78, 10.3%). Table 1 stratifies these characteristics by CI-AKI status.

Incidence and Risk Factors of CI-AKI

CI-AKI occurred in 15 patients (19.2%, 95% CI: 11.2-30.4%). Post-PCI creatinine rose significantly in the CI-AKI group (134.8 ± 36.5 µmol/L) compared to the non-CI-AKI group

Table 1 Baseline Characteristics Stratified by CI-AKI Status

Variable	Total (n=78)	CI-AKI (n=15)	No CI-AKI (n=63)	p-value
Age (years)	63.9 ± 11.0	69.1 ± 9.5	62.7 ± 11.2	0.03
Gender (male, %)	53 (67.9%)	10 (66.7%)	43 (68.3%)	0.90
BMI (kg/m^2)	29.1 ± 5.3	30.3 ± 4.8	28.8 ± 5.4	0.34
Diabetes (n, %)	14 (17.9%)	3 (20.0%)	11 (17.5%)	0.80
Hypertension (n, %)	57 (73.1%)	12 (80.0%)	45 (71.4%)	0.49
Baseline Creatinine (µmol/L)	89.8 ± 24.2	105.3 ± 28.1	86.2 ± 21.5	0.01
Baseline GFR (mL/min/1.73 m^2)	73.5 ± 21.0	61.8 ± 21.7	76.5 ± 19.8	0.02
Contrast Dose (mL)	180 ± 85	216 ± 97	171 ± 80	0.08

Table 2 Multivariate Logistic Regression Analysis for CI-AKI Predictor

Variable	Odds Ratio (OR)	95% CI	p-value
Age (per year)	1.07	1.01-1.13	0.02
Baseline Creatinine (per 10 µmol/L)	1.85	1.17-2.92	0.01
Contrast Dose (per mL)	1.01	1.00-1.02	0.03

(89.7 ± 22.0 µmol/L, p=0.01). Univariate analysis identified age (p=0.03), baseline creatinine (p=0.01), GFR (p=0.02), and contrast dose (p=0.08) as predictors. Multivariate logistic regression confirmed age (OR 1.07, 95% CI: 1.01-1.13, p=0.02), baseline creatinine (OR 1.85, 95% CI: 1.17-2.92, p=0.01), and contrast dose (OR 1.01, 95% CI: 1.00-1.02, p=0.03) as independent predictors (Table 2). The Hosmer-Lemeshow test (p=0.65) indicated good model fit.

Predictive Model Performance

A logistic regression model incorporating age, baseline creatinine, and contrast dose achieved an AUC-ROC of 0.83 (95% CI: 0.72-0.94), with a sensitivity of 76.7% and specificity of 82.5% at a probability threshold of 0.25. Cross-validation (10-fold) yielded a mean AUC of 0.80 ± 0.05, confirming stability. Figure 1 illustrates the ROC curve.

Detailed Renal Function Trends

The CI-AKI group exhibited a mean creatinine increase of 29.5 ± 12.8 µmol/L, significantly higher than the 3.5 ± 6.9 µmol/L in the non-CI-AKI group (p<0.001). GFR declined by -18.5 ± 10.1 mL/min/1.73 m² in the CI-AKI group versus -2.3 ± 5.6 mL/min/1.73 m² in the non-CI-AKI group (p<0.01). Figure 2 compares pre- and post-PCI creatinine levels.

Hydration and Contrast Type

Hydration status did not significantly differ between CI-AKI and non-CI-AKI groups (saline: 80% vs. 81%, p=0.92; bicarbonate: 20% vs. 19%, p=0.89). Use of iso-osmolar contrast was associated with a lower CI-AKI incidence (16.0% vs. 22.6%, p=0.41), though not statistically significant. Nephrotoxic medication avoidance was consistent across groups (p=0.85).

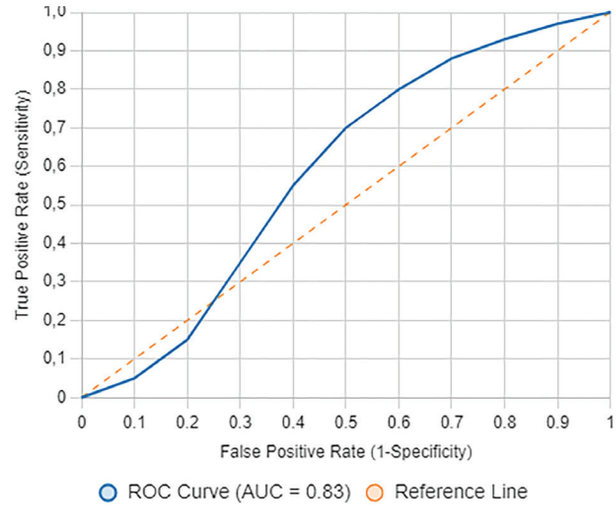

Figure 1 – ROC Curve for CI-AKI Predictive Model

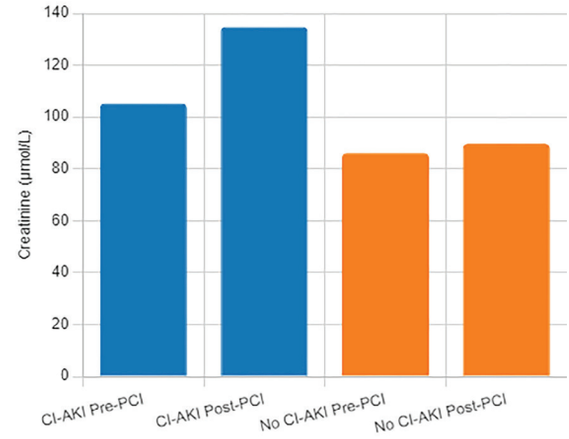

Figure 2 – Pre- and Post-PCI Creatinine Levels by CI-AKI Status

Subgroup and Correlation Analyses

Gender stratification showed no difference in CI-AKI incidence (males: 18.9%, females: 20.0%, p=0.90), but patients aged ≥65 years had a higher rate (26.2% vs. 10.5%, p=0.09; Figure 3). Pearson correlation revealed a moderate positive association between contrast dose and creatinine increase (r=0.35, p=0.002) and a negative correlation between baseline GFR and creatinine increase (r=-0.42, p=0.0008; Figure 4).

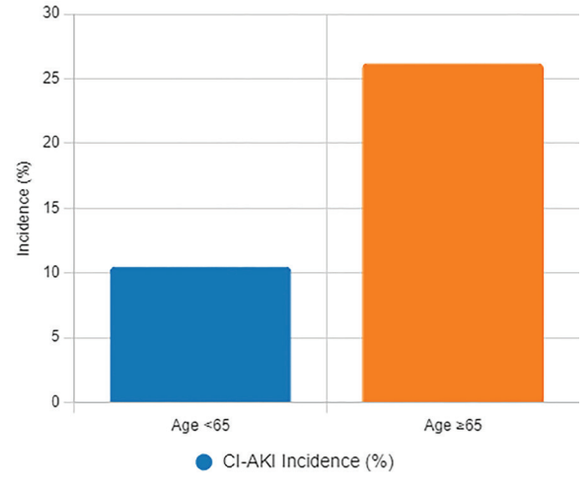

Figure 3 – CI-AKI Incidence by Age Group

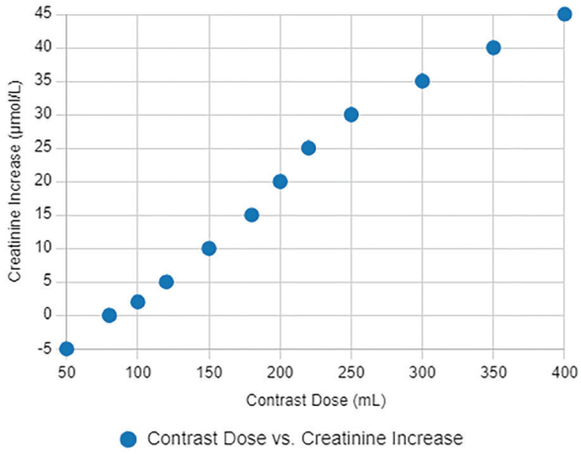

Figure 4 – Scatter Plot of Contrast Dose vs. Creatinine Increase

Secondary Outcomes

Hospital stay was longer in the CI-AKI group (7.3 ± 2.9 vs. 5.0 ± 2.0 days, p=0.02). Troponin levels were higher in CI-AKI patients (8.5 ± 12.7 vs. 5.2 ± 9.3 ng/mL, p=0.27), but not significantly.

Discussion

This study confirms a 19.2% incidence of CI-AKI in STEMI patients post-PCI, aligning with prior estimates of 5-25% across PCI cohorts [5, 6]. The predictive model, with an AUC-ROC of 0.83, identifies age, baseline creatinine, and contrast dose as key risk factors, consistent with established literature [14, 18]. These findings underscore the vulnerability of STEMI patients to contrast-induced nephrotoxicity, driven by acute physiological stress and procedural factors unique to this population [13].

The significant role of baseline creatinine (OR 1.85) highlights pre-procedural renal function as a critical determinant of CI-AKI risk, corroborating studies by P.A. McCullough et al. [25] and G. Marenzi et al. [4]. Each 10 µmol/L increase in creatinine amplifies the odds of CI-AKI, reflecting underlying renal reserve limitations [26]. Age (OR 1.07) as a predictor aligns with aging-related declines in glomerular filtration and tubular repair capacity, as noted by A. Denic et al. [27]. Contrast dose (OR 1.01), though modestly significant, supports a dose-dependent nephrotoxic effect, consistent with experimental models of contrast media toxicity [28, 29].

Multicenter data suggest hydration with sodium bicarbonate may reduce CI-AKI risk compared to saline alone [24], though our study found no significant difference, possibly due to the small sample size. The trend toward lower CI-AKI with iso-osmolar contrast aligns with M.C. Heinrich et al. [12], supporting its preferential use in high-risk patients.

Compared to the Mehran Risk Score [18], our model simplifies the variable set while achiev- ing comparable predictive power, making it practical for urgent STEMI settings where rapid decision-making is paramount [19]. The AUC-ROC of 0.83 exceeds that of some earlier STEMI- specific models (e.g., T.T. Tsai et al. [7], AUC=0.76), suggesting improved

Table 3 Secondary Outcomes by CI-AKI Status

Outcome	CI-AKI (n=15)	No CI-AKI (n=63)	p-value
GFR Change (mL/min/1.73 m^2)	-18.5 ± 10.1	-2.3 ± 5.6	<0.01
Hospital Stay (days)	7.3 ± 2.9	5.0 ± 2.0	0.02

discrimination. However, the modest sample size (n=78) limits generalizability, and unmeasured confounders—such as peri-procedural medications—may influence outcomes [30]. The lack of significance for diabetes and hypertension, despite their prevalence, may reflect the small cohort or the overriding impact of acute STEMI physiology [13].

The pronounced GFR decline in CI-AKI patients (-18.5 mL/min/1.73 m²) underscores the clinical severity of this complication, consistent with M.T. James et al. [10]. The correlation between contrast dose and creatinine increase (r=0.35) reinforces the need for dose minimization strategies, such as those proposed by H.S. Gurm et al. [15]. Age stratification (Figure 3) suggests that elderly patients warrant heightened vigilance, aligning with E. Nikolsky et al. [14].

Limitations include the retrospective design, single-center setting, and absence of compre- hensive data on all preventive measures. Future research should validate this model prospectively across multiple centers, incorporate additional biomarkers (e.g., NGAL, cystatin C, TIMP-2, IGFBP7), and explore interventions like iso-osmolar contrast or furosemide-matched hydration [24].

Conclusion

This study establishes age, baseline creatinine, and contrast dose as significant predictors of CI- AKI in STEMI patients post-PCI, with a predictive model achieving an AUC-ROC of 0.83. The 19.2% incidence and associated GFR decline highlight CI-AKI's clinical burden. Limitations include the small sample and retrospective nature, necessitating prospective, multicenter validation. Future directions include testing preventive strategies and integrating novel biomarkers to refine risk stratification.

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Evaluation of Hematologic Markers in Hypertensive and Non-hypertensive Epistaxis Patients

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Abstract

Objective: The objective of the study is to investigate the development of epistaxis and its relationship with hypertension, as well as inflammatory parameters such as the neutrophil-lymphocyte ratio (NLR), the pan-immune inflammation value (PIV), the systemic inflammatory response index (SIRI), the systemic immune-inflammation index (SII) and the aggregate index of systemic inflammation (AISI).

Methods: Our study is a retrospective analysis of patients diagnosed with and treated for epistaxis from January 2021 to January 2023. Patient demographic information and NLR, PIV, SIRI, SII and AISI were calculated. Patients were divided into two groups based on their systolic blood pressure measurements: The study then compared the two groups.

Results: A total of 743 participants who met the inclusion criteria were enrolled in the study, with 545 (73.3%) cases of non-hypertensive epistaxis and 198 (26.7%) cases of hypertensive epistaxis. The neutrophil-to-lymphocyte ratio (NLR) was found to be significantly higher in hypertensive epistaxis (3.6 vs. 1.6; p<0.001) when evaluating the combined blood parameters. Furthermore, PIV values were notably elevated in the hypertensive group (813.53 vs 252.71; p<0.001). Consequently, SII, SIRI, and AISI values were found to be significantly higher in hypertensive epistaxis compared to non-hypertensive epistaxis.

Conclusion: NLR, PIV, SIRI, SII, and AISI in predicting bleeding in epistaxis patients presenting at the emergency department.

Keywords: Epistaxis, hypertension, inflammation.

Introduction

Epistaxis is a prevalent cause of visits to the emergency department for both adults and children. Its prevalence increases with age and underlying risk factors related to bleeding [1]. Research has identified a correlation between climate change, temperature factors, and the frequency of epistaxis associated with bleeding-related illnesses [2, 3]. Inflammation-induced nasal irritation can lead to nasal discharge, which can result in increased pressure and potential damage to mucosal walls, thus increasing the predisposition to bleeding [4]. The investigation of the association between patients experiencing epistaxis and inflammation-related markers has become increasingly prevalent in the literature [5].

Hematologic indices are primarily utilised for the identification of inflammatory states and the observation of systemic effects [5, 6]. In this discipline, the systemic inflammatory marker index is applied in cases such as those affecting cancer patients, idiopathic pulmonary fibrosis, and asthma. The neutrophil-lymphocyte ratio (NLR), pan-immune inflammation

value (PIV), systemic inflammatory response index (SIRI), systemic immune-inflammation index (SII) and aggregate index of systemic inflammation (AISI) are other tools that offer a cost-effective means of diagnosing and predicting systemic inflammatory response assessment. In previous studies, variations in different haematological parameters have been observed in patients who have experienced bleeding episodes [5, 7, 8]. However, there is a paucity of research exploring the correlation between NLR, PIV, SIRI, SII, AISI, and epistaxis. Consequently, the primary objective of this study, independent of other factors, was to investigate the development of epistaxis and its relationship with hypertension, as well as inflammatory parameters.

Methods

The study was conducted retrospectively, commencing subsequent to the approval of the local ethics committee. The present study was conducted in accordance with the "Helsinki Declaration".

The present study constitutes a retrospective analysis, encompassing patients who were diagnosed with and treated for epistaxis in the emergency department from January 2021 to January 2023. The inclusion criteria encompassed all patients aged 18 and above who presented to our emergency department with a diagnosis of epistaxis. Exclusion criteria encompass patients with known coagulation disorders, abnormal blood parameters, individuals with hematologic or oncologic chronic diseases, and those receiving long-term steroid therapy. Demographic information on patients, along with recordings of white blood cell count, neutrophil count, platelet count, lymphocyte count, monocyte count, hemoglobin levels, and eosinophil count were taken from blood samples collected within the first hour of admission to the emergency department. Ratios were then calculated from these blood values, comprising the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PIV), and the systemic inflammatory response index (SIRI), which is the product of the neutrophil and monocyte counts divided by the lymphocyte count. The study calculated the SII (systemic immune-inflammation index) and AISI (aggregate index of systemic inflammation) by taking important blood cell counts and dividing them by lymphocyte count. The patients were divided into two groups based on their systolic blood pressure readings: Non-hypertensive epistaxis was diagnosed in patients with systolic blood pressure readings within the standard range set by international guidelines, while hypertensive epistaxis was diagnosed in patients with readings above 140/90 mmHg. The study then proceeded to make a comparison between these two groups.

Statistical analysis

We used SPSS version 25.0 (IBM SPSS Statistics for Windows, version 25.0 (IBM Corp)) to analyse the data in this study. We measured continuous variables using the mean ± standard deviation, and frequency and percentage were used to measure categorical data when comparing demographic characteristics and parameters used in patients with epistaxis. We used the Student's t-test for normally distributed variables when comparing patients grouped by hypertension, and the Mann-Whitney U test for variables that didn't display normal distribution. A statistical significance level of $P < 0.05$ was adopted for the analyses.

Results

743 participants meeting the inclusion criteria were enrolled in our study, with 545 (73.3%) in Non-hypertensive epistaxis and 198 (26.7%) in Hypertensive epistaxis. The majority of patients in both groups were male, and there was no significant difference in gender distribution between the two. Hypertensive epistaxis had notably higher systolic and diastolic blood pressures than Non-hypertensive epistaxis. No significant difference was found in hemoglobin levels between the groups. Demographic data and general laboratory parameters are presented in Table 1.

The NLR was significantly higher in Hypertensive epistaxis (3.6 vs 1.6; $p<0.001$, Figure 1) when evaluating the combined blood parameters. Furthermore, PIV values were notably elevated in the hypertensive group (813.53 vs 252.71; $p<0.001$, Figure 1, see the next page). SII, SIRI, and AISI values were also significantly higher in Hypertensive epistaxis compared to Non-hypertensive epistaxis. Table 2 compares the combined hemogram parameter values.

Discussion

Epistaxis is a prevalent cause of bleeding treated in emergency departments. The aetiology of epistaxis can be attributed to a range of localised conditions, including digital trauma, septal perforations, nasal foreign bodies, aneurysms, nasal papillomas, and the utilisation of antihistamine or steroid

Table 1 Demographic characteristics of epistaxis patients

Description	Group 1 (n=545)	Group 2 (n=198)	P-Value
Gender			
Female n (%)	252 (46,2%)	92 (46,5%)	
Male n (%)	293 (53,8%)	106 (53,5%)	0.956
Systolic blood pressure (Mean±SD)	105.35±9.68	171.53±24.93	<0.001
Diastolic blood pressure (Mean±SD)	70.55±9.95	131.89±24.04	<0.001
Blood Parameters			
Hemoglobin (Mean±SD)	12.49±2.43	12.33±2.47	0.441
Platelet (Mean±SD)	220.33±86.08	301.45±103.66	<0.001
Neutrophils (Mean±SD)	4.22±1.69	7.97±3.97	<0.001
Lenfocyte (Mean±SD)	2.4±1.91	2.12±1.18	0.065
Monocyte (Median (IQR))	0.57 (0,5)	0.84 (0.38)	<0.001
Eosinophils (Median (IQR))	0.14 (0.14)	0.15 (0.21)	0.754

Table 2 Comparison of the hematologic parameters for the groups

Description	Group 1 n=545	Group 2 n=198	P-Value
NLR (Median (IQR))	1.86 (1.26)	3.60 (3.07)	<0.001
PIV (Median (IQR))	252.71 (193.48)	813.53 (646.53)	<0.001
SIRI (Median (IQR))	1.12 (0.77)	2.99 (2.47)	<0.001
SII (Median (IQR))	419.35 (266.33)	1040.89 (863.54)	<0.001
AISI (Median (IQR))	252.71 (193.48)	813.53 (646.53)	<0.001

NLR: Neutrophil-lymphocyte ratio; PIV: Pan-immune inflammation value, SIRI: Systemic Inflammatory Response Index; SII: Systemic immune-inflammation index AISI: Aggregate index of systemic inflammation.

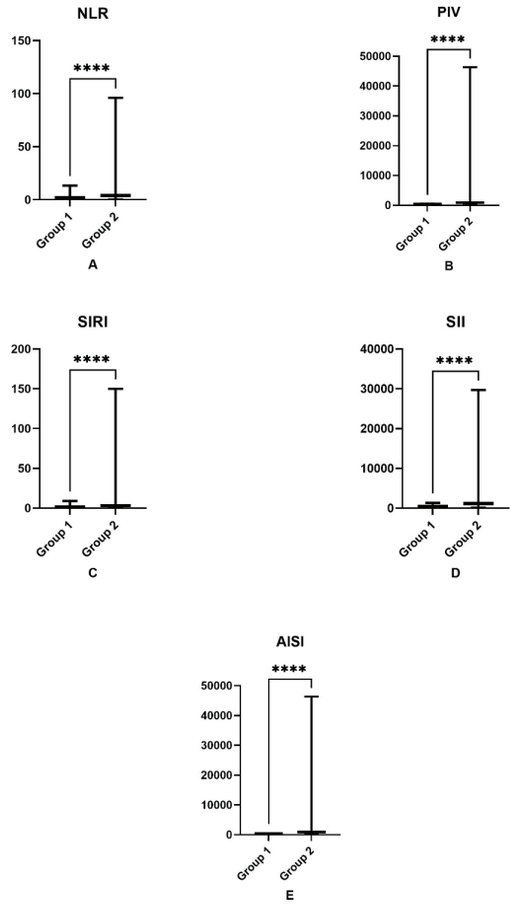

Figure 1 – Hematologic parameters of in hypertensive and non-hypertensive epistaxis patients A) NLR: Neutrophil-lymphocyte ratio B) PIV: Pan-immune inflammation value; C: SIRI: Systemic Inflammatory Response Index; D) SII: Systemic immune-inflammation index; E) AISI: Aggregate index of systemic inflammation

nasal sprays. Systemic conditions, including hypertension, coagulation disorders, and bleeding diatheses, have also been identified as contributing factors to epistaxis [9]. The underlying cause of nasal bleeding is often unclear. The specific factors that render individuals susceptible to epistaxis remain to be fully elucidated. Consequently, there is a necessity for readily available, swift and cost-effective parameters that could assist in diagnosing epistaxis in emergency scenarios. A review of the extant literature suggests that low mean platelet volume (MPV) and high red cell distribution width (RDW) levels could potentially play a role in the increased recurrence of bleeding in epistaxis [10]. The present study hypothesised that the recently introduced inflammatory parameters, the systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI), could potentially contribute to the mechanism of epistaxis. The results of the study indicate that SII and SIRI serve as hematologic indices and thereby act as inflammatory markers useful in diagnosing epistaxis.

Epistaxis is a commonly encountered problem, frequently resulting in referrals to emergency services for further treatment. Otolaryngologists are often consulted for patients who are referred to hospitals. Studies have identified inflammatory parameters that may be useful for managing epistaxis patients who frequently make recurrent visits to emergency departments. It is theorised that nasal colonization of Staphylococcus aureus prompts inflammation in the development of epistaxis, resulting in crusting of the nasal septum. This, in turn, causes neovascularization and purportedly heightens the risk of recurring nasal bleeding [11–13]. Presently, there is no literature indicating any relationship between SII, SIRI, and epistaxis. Numerous studies have demonstrated the association between SII and SIRI in various cancers and their oncological outcomes [15, 16]. Moreover, SII and SIRI have been shown to be linked to metastatic renal cell carcinoma and prostate cancer [17]. Interestingly, SIRI has also been established as a predictor of survival and is associated with prognosis in multiple cancers including pancreatic cancer, gallbladder cancers, squamous cell carcinoma and cervical cancers [18–22]. Qi et al. demonstrated that SIRI, a new inflammatory marker, has predictive value for the survival of pancreatic cancer patients [23]. Another study involving 916 patients with esophageal squamous cell carcinoma found that SIRI was an independent prognostic factor [22]. The analysis of studies on systemic inflammation reveals varying cutoff values for SIRI and SII. In a study conducted by Yıldız et al., it was discovered that the cutoff values for both SIRI and SII were significantly higher in individuals with acute cholecystitis than in the control group. This finding indicates the potential diagnostic usefulness of these markers [24, 25]. While PIV and AISI parameters are used as markers of inflammation in various diseases, their roles in epistaxis patients are not yet clearly defined. The study has certain limitations, including its retrospective nature, relatively small sample size, and single-center design. To validate these indices, prospective and multicenter studies involving comprehensive patient populations should be conducted. Furthermore, it is possible that the results were impacted by the timing of the complete blood count (CBC) testing, which was conducted during presentation. This approach may not have provided enough data to ascertain the speed at which these parameters increase during the inflammatory process.

Conclusion

As a result, this study has indicated the potential usefulness of parameters such as NLR, PIV, SIRI, SII, and AISI in predicting bleeding in epistaxis patients presenting at the emergency department.

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Histopathologic Findings in Placentas from COVID-19 Positive Mothers – A Hospital Experience

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Abstract

Background: Coronaviruses, also known as COVID-19, are a group of highly infectious enveloped positive stranded RNA viruses that have been implicated to cause severe acute respiratory and systemic thrombotic syndrome. It is a multi-systemic disease whose manifestation can be seen in several organ systems. This study therefore aims to identify the specific histopathologic alterations in placenta tissue of COVID-19 pregnant women.

Methods: This was a cross-sectional descriptive study done at Lagos University Teaching Hospital, (LUTH). This study was carried out from April 2020 to October 2020 and from December 2020 to April 2021 during the pandemic. The information retrieved included sociodemographic data, medical and surgical history, pregnancy and delivery details, results of COVID-19 tests, and report of placental evaluation/examination. The data were entered and analyzed using Microsoft Excel spreadsheet. Descriptive statistics were employed to report the findings.

Results: Histopathology and gross examination of placentas from these pregnant women infected with COVID-19 reveals increased syncytial Knots in 80% of our cohort, calcification 80%, infarction 90%, fibrin deposition 80%, retroplacental haemorrhage 40%, hyalinization of vessels 10%, thrombosis 20%, inflammation 40%, vascular malformation in 10% hyalinization in 60% of cases thereby suggesting that COVID-19 may have significant impact on human placental structure and function. Out of 15 deliveries, one each was preterm, preeclampsia, and abruptio which were excluded from the study, and three patients declined to participate in the study.

Keywords: COVID-19, placenta histology, pregnancy, Nigeria.

Introduction

The recent pandemic that was attributed to the highly infectious novel coronavirus otherwise referred to as COVID-19, is a severe acute respiratory and systemic thrombotic syndrome caused by an enveloped single stranded ribonucleic acid virus [1–3]. Since the declaration of these enveloped virus (COVID-19) as a disease of public health emergency in February 2020, according to World Health Organization (WHO), it is estimated to have caused over 3.4 million deaths with different rates of reporting among countries ranging from 98% deaths reported in developed countries to 10% deaths in developing countries [4]. With regards to covid-19 transmission, the most common mode of transmission is by the inhalation of tiny respiratory droplets, and or through close personal contact with a disease carrier, or infected surface [1, 3–5]. It is a multi-systemic disease whose manifestation includes malaise,

muscle cramps, high grade fever, respiratory symptoms (upper and lower respiratory tract) such as sore throat, cough, shortness of breath, and pneumonia [6, 7].

Other symptoms include vomiting, diarrhea, bleeding disorders including disseminated intravascular coagulopathy [5–7]. Acute kidney injury and multiorgan failure have also been reported [8]. Pregnant women are considered vulnerable due to physiological changes that may increase the risk of severe illness during infections [2].

Evidence abounds in literature to suggest that infection with SARS-CoV-2 in pregnancy may have some untoward effect on both the pregnant mother and the conceptus. It has also been put forward that coronavirus infected pregnant women may have an increased risk of having a more severe disease [9]. This notwithstanding, other authors have suggested different opinions regarding COVID-19's impact on pregnancy outcomes [1, 3, 4]. In addition, just as suggested by other authors that some blood borne viruses may invade placenta protection to be transmitted to the fetus [10]. This placenta invasion of other viral pathogens raises a serious concern with regards to COVID-19 infection during pregnancy. Although it is not a bloodborne virus, there could be a possibility that COVID-19 could invade the immunological barrier of the placenta to be vertically transmitted to the fetus in utero [1, 9].

A plethora of complications have been suggested such as miscarriage, pre-employed, preeclampsia, increased cardiovascular stillbirth, intrauterine growth restriction and renal complications, therefore highlighting the need for further investigation into maternal and fetal health [2, 9, 10].

Considering the physiological changes in pregnancy, it is sometimes difficult without high index of suspicion in an apparently healthy woman to differentiate the effects of covid-19 and the symptoms of normal pregnancy which are sometimes presented as infectious or inflammatory changes [4, 9, 10]. Additionally, human placentas contribute a major interface between the mother and the developing fetus. Certain maternal diseases in pregnancy such as preeclampsia, have been said to have an aetiology linked to the placenta [10].

Therefore, the covid-19 induced environment in the pregnant woman such as inflammation, hypoxia and increased thrombosis may suggest that placenta will possibly be a potential target for the virus [11]. Histopathologic studies of placentas from COVID-19 positive mothers reveal inflammation, vascular malperfusion, and thrombotic changes [10, 11]. These abnormalities may contribute to adverse pregnancy outcomes, necessitating further research into their implications.

This study therefore aims to identify the specific histopathologic alterations in placenta tissue of COVID-19 pregnant women. These placental histopathologic changes if identified may give more insights into the aetiopathogenesis of COVID-19's and its negative effects on pregnancy and can guide interventions to improve pregnancy outcomes for mothers and infants, informing clinical guidelines and public health policies.

Methods

Study design: This cross-sectional descriptive study was carried out at LUTH.

Setting: LUTH served as a referral and Treatment Centre during both waves of the pandemic (between April 2020 to October 2020) and (from December 2020 to April 2021).

Study population

These included all Pregnant mothers who were diagnosed with SARS-CoV-2 infection who were managed and had their babies in hospital. They were properly counselled by the managing team following which an informed consent to participate was obtained from the mothers. The placentas were sent for histopathological evaluation. Excluded were placentas from mothers with pre-existing placental disorders (e.g., preeclampsia, placental abruption). This is because histopathological changes in women pre-diagnosed with COVID-19 mirrors that of the findings in preeclampsia and abruptio placenta.

Methods

Placental specimens collected as part of routine obstetric care during the covid 19 pandemic were sent to the histopathology laboratory of the Department of Anatomic and Molecular Pathology, LUTH and were processed following standard histopathological protocols. Archived hematoxylin and eosin (H&E) stained slides and corresponding histopathology reports of these cases were retrieved from the histopathology laboratory for this study. Where necessary, slides were reviewed by AOD and AMM to confirm the original findings.

A descriptive analysis was performed, focusing on gross and microscopic placental findings including but not limited to features suggestive of maternal and fetal vascular malperfusion (MVM and FVM).

Placental features considered to be indicative of MVM include both gross and microscopic findings. Gross findings include placental hypoplasia, infarction, and retroplacental haemorrhage while microscopic findings include abnormalities of villous development. Lesions under the umbrella of FVM are mostly due to obstruction in foetal blood flow, possibly due to umbilical cord lesions, hypercoagulability, complications of foetal cardiac dysfunction, such as hypoxia, amongst others

The findings were documented and interpreted in the context of maternal COVID-19 status and perinatal outcomes where available.

Data collection and statistical analysis

A total of ten placentas were analyzed, and relevant information of the mother-baby pair were extracted from the medical records. The information retrieved included sociodemographic data, medical and surgical history, pregnancy and delivery details, results of COVID-19 tests, and report of placental evaluation/examination. The data were entered into Microsoft Excel spreadsheet. Descriptive statistics were employed to report the findings. Categorical variables were expressed as frequency and percentages, while continuous variables were expressed as mean and standard deviation.

Results

Nine participants were enrolled for the study, however one of the patients had a set of twin delivery, therefore a total of ten placentae were analyzed.

The average weight of the placenta was 429.5g (150–630g). Most patients (88.9%) were diagnosed in the third trimester (Table 1). Histopathological examination of these placentas from COVID-19 positive mothers reveals increased syncytial Knots in 80% of our cohort, calcification 80%, infarction 90%, fibrin deposition 80%, retroplacental haemorrhage 40%, hyalinization of vessels 10%, thrombosis 20%, inflammation 40%, hyalinization of villi in 60% of cases (Figure 1).

Table 1 Clinical and Socio-demographic variables of COVID-19 Positive Pregnant Mothers n=9

Variables		Frequency n (%)
Mean age in years ±SD Mean Body Mass Index	30.2 ± 228 ± 3	
Time of Diagnosis Second trimester Third trimester		 1 (11.1) 8 (88.9)
Mode of delivery Spontaneous vaginal delivery Caesarean section		 1 (11.1) 8 (88.9)
Parity 1-2 ≥3		 **3 (33.3)** **6 (66.6)**
Mean Placental weight Range		429.5g (164.05 g) 150-630g

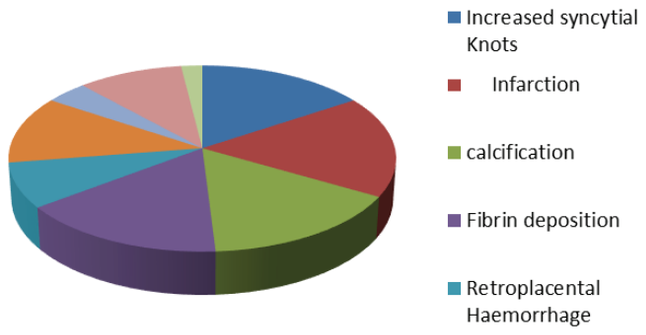

Figure 1 – Histopathological findings in the placenta

Increased syncytial Knots – 80%, Calcification – 80%, Infarction – 90%, Fibrin Deposition – 80%, Retroplacental Haemorrhage – 40%, Hyalinization of Vessels – 10%, Thrombosis – 20%, Inflammation – 40%, Vascular Malformation – 10%, Hyalinized villi – 50.

SN	Histopathologic Finding	%
1	Increased syncytial Knots	80
2	Calcification	80
3	Infarction	90
4	Fibrin Deposition	80
5	Retroplacental Haemorrhage	40
6	Hyalinization of Vessels	10
7	Thrombosis	20
8	Inflammation	40
9	Vascular Malformation	10
10	Hyalinized villi	50

Discussion

This study evaluated the placental histopathologic changes in pregnant mothers diagnosed with COVID-19 infection with aim of providing insights into the effects of the virus on pregnancy. We found an overall low placenta weight compared to the general population. This differs from the previous study in our center by **Oluwole** *et al* who reported an average placenta weight of 657.5 (221.5) g in their cohorts [12].

It was also different from the reported placenta weight of 43 and 630 g by **Barker** *et al* and **Panti** *et al* respectively [13,14]. Along those lines, our study is similar to that of Giordano and co-workers who also noticed a low placenta weight is some the case reviewed [7].

Similarly, **Theiler** *et al* also reported small mean placental weight of less than tenth percentile across all gestational ages compared in their study [15]. However, *Tasca* and colleagues found no difference in placental weight between women diagnosed with COVID-19 infection and their COVID-19 negative counterparts [16].

With regards to histopathologic findings, the commonest abnormality in our study was the high degree of placental infarction, followed by increased syncytial Knots, calcification and fibrin deposition. Just as reported in other studies, chronic histiocytic intervillositis, characterized by maternal macrophage infiltration, has been frequently reported in COVID-19 placentas, this inflammation can ultimately result in placental insufficiency and its attendant consequences to both the pregnant woman and her fetus [7, 8, 12]. It has been hypothesized that this chronic inflammation may represent an adverse event happening within the placenta tissue which may invariably impair placenta function [4, 16, 17].

Similarly, increased fibrin deposition and intervillous thrombi may be an indicator of hypercoagulable state within the placenta, contributing to placental insufficiency and adverse fetal outcomes [16–18]. These findings reflect the pro-thrombotic nature of COVID-19 as reported in many studies [4, 16, 18, 19]. Then again, increased fibrin deposition similar to the findings in other studies has been attributed to cause maternal hypoxia as also seen in other cases of acute respiratory distress syndrome [15, 16]. This can worsen placenta dysfunction leading to impaired function of the uteroplacental-fetal unit with attendant consequences to the fetus [15, 16, 20].

Although other studies have reported similar increase in syncytial knots in placentas of most mothers infected with coronavirus 2 [18, 20, 21]. The implications of this may vary. Firstly, many agree that hypoxia, hyperoxemia, or oxidative stress and increased risk of ischemic changes can be identified in the placenta of COVID-19 infected mothers through the increase in syncytial knotting.

Table 2 Histopathologic Descriptions

SN	Weight (g)	Histopathologic Description
1	630	Retroplacental hemorrhage, excessive fibrin deposition, hyalinized villi, Increased syncytial knots, thickened and narrowed villous capillaries, calcification and hemorrhage are seen in the placental disc.
2	590	Increased syncytial knots, excessive fibrin deposition, hyalinized villi with areas of calcification, foci of infarction, inflammation, thrombosis and hyalinized vessels
3	480	Retroplacental hemorrhage, increased syncytial knots, excessive fibrin deposition, hyalinized villi with areas of calcification, foci of infarction and inflammation
4	345	Retroplacental hemorrhage, increased syncytial knots, excessive fibrin deposition, hyalinized villi with areas of calcification, foci of infarction. Inflammation and thrombosis
5	440	Increased syncytial knots, excessive fibrin deposition, hyalinized villi with areas of calcification, foci of infarction and inflammation
6	560	Increased syncytial knots, excessive fibrin deposition, hyalinized villi with areas of calcification
7	520	Increased syncytial knots, hyalinized villi with areas of infarction
8	150	Retroplacental hemorrhage, increased syncytial knots, hyalinized villi with areas of calcification, foci of infarction
9	180	Increased syncytial knots, excessive fibrin deposition, hyalinized villi with areas of calcification, foci of infarction
10	400	Retroplacental hemorrhage, increased syncytial knots, excessive fibrin deposition, hyalinized villi with areas of calcification, foci of infarction

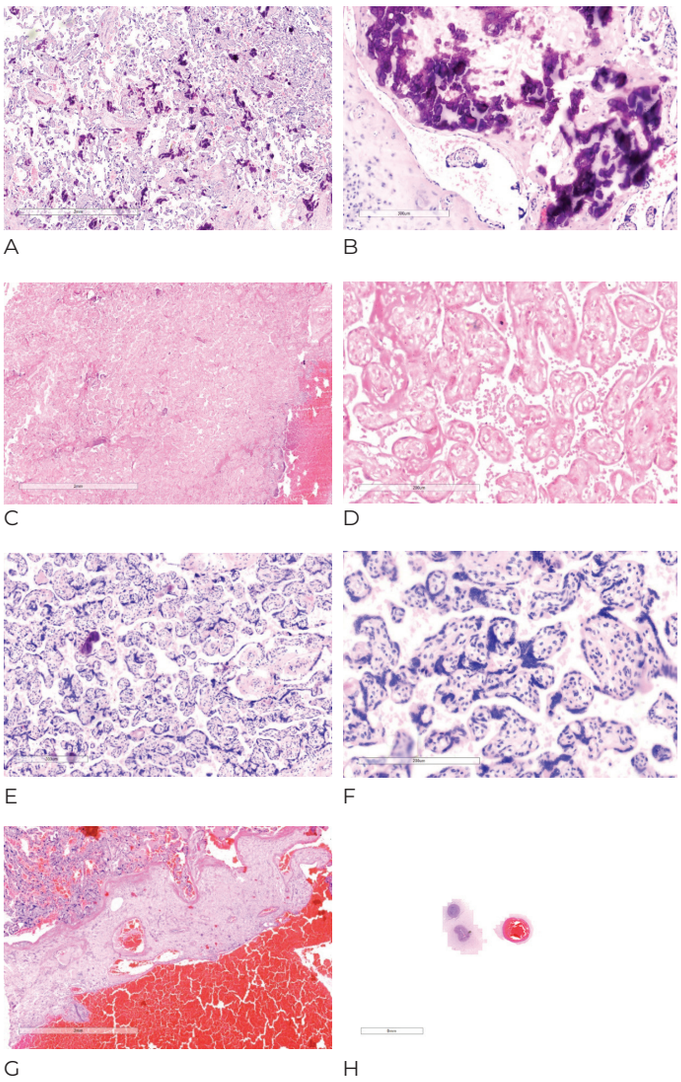

Figure 2 – Photomicrograph of Placenta histopathological findings

Secondly, increased in these syncytial knots have also been fingered to suggest a high likelihood of transmitting this virus to the fetus (vertical transmission) [18, 20]. This is because similar patterns of syncytial knots have been reported in most infections such as TORCHES, Toxoplasma, rubella, and cytomegalovirus with increased risk of transmission from mother to fetus in utero [18, 19, 21].

In conclusion, histopathological findings in COVID-19 positive placentas in our study indicate significant impacts on placental structure and function. The evidence of chronic inflammation, and fibrin deposition may suggest the virus's potential to disrupt uteroplacental-fetal unit hence leading to adverse pregnancy outcomes.

Although we have a limited sample size which may affect the generalization of the study, however, this study from our sub-region provides an insight into the histopathological changes of the placenta of pre-diagnosed COVID-19 infection in black women.

Further studies involving larger sample size and amniotic fluid may be important to also rule out the possibility of vertical transmission of the virus.

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Data availability statement: The authors are available and ready to supply the data upon any request through the corresponding author.

Informed consent: This was a descriptive retrospective study and did not contain any data with human participants performed by the authors and thus did not require informed consent.

AI Declaration: No form of regenerative AI such as ChatGPT, COPILOT, DEEPSTEEK was used during the preparation of this manuscript.

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Combined Use of Inhaled and Intravenous Colistin in a Patient with Acute Lymphoblastic Leukemia Complicated by Multi-Organ Failure and Sepsis: A Case Report

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Abstract

Sepsis and subsequent organ dysfunction are significant complications in patients with acute lymphoblastic leukemia. This case report details the successful use of combined inhaled and intravenous colistin in a 22-year-old male with high-risk acute lymphoblastic leukemia who developed tumor lysis syndrome, febrile neutropenia, respiratory failure, sepsis, septic shock, capillary leak, and prolonged mechanical ventilation requiring tracheostomy. Colistin inhalation, administered via a vibrating mesh nebulizer, was well-tolerated and led to clinical improvement. This report contributes to the growing evidence supporting the adjunctive use of inhaled colistin in multidrug-resistant infections, particularly in immunocompromised patients.

Keywords: colistin, sepsis, leukemia, multidrug-resistant, multiple organ failure, case report.

Introduction

Sepsis is a leading cause of mortality in patients with hematological malignancies, particularly those with acute lymphoblastic leukemia (ALL). This population is highly susceptible to severe infections due to disease-related immunosuppression and chemotherapy-induced myelosuppression [1]. Gram-negative bacteria, including Klebsiella pneumoniae, frequently cause nosocomial infections in these patients, and rising antimicrobial resistance poses additional challenges to treatment. Colistin, a polymyxin antibiotic, has re-emerged as a vital therapy against MDR Gram-negative infections despite concerns about its nephrotoxicity and neurotoxicity. Inhaled colistin has been explored as a targeted strategy to deliver high local drug concentrations to the lungs while minimizing systemic toxicity [2]. However, data on its use in hematological patients, especially those with sepsis and multi-organ failure, remain limited. This report highlights a novel approach: the combined use of intravenous and inhaled colistin in a critically ill patient with ALL and septic shock caused by MDR Klebsiella pneumoniae. The aim is to expand the clinical evidence for this therapeutic strategy, addressing a pressing need in both hematology and infectious diseases.

Clinical Case Presentation

Patient Information

A 22-year-old male presented with a hemorrhagic rash on his foot that progressively worsened. On April 10, 2024, a dermatologist referred the patient to a general practitioner after a significant increase in the rash. Laboratory investigations revealed a high white blood cell count and lymphocytosis, leading to a diagnosis of high-risk B-II subtype acute lymphoblastic leukemia. The patient was urgently transferred to the hematology intensive care unit at the National Research Oncology Center in Astana.

Clinical Findings

The patient's Eastern Cooperative Oncology Group (ECOG) performance status on admission was between 1 and 2. Physical examination revealed a petechial rash on the lower extremities and an enlarged submandibular lymph node. Diagnostic Assessment

Upon admission, initial laboratory investigations revealed a white blood cell count of 20.8×10^9/ L, with 86% lymphoblasts. Hemoglobin was measured at 12.9 g/dL, platelets at 57×10^9/L, uric acid levels were elevated at 412 µmol/L, lactate dehydrogenase (LDH) was 785 U/L, and C – reactive protein (CRP) was 28.72 mg/L. These findings suggested significant hematological abnormalities and metabolic disturbances indicative of acute leukemia.

Flow cytometry of bone marrow aspirate confirmed the diagnosis of B-II variant acute lymphoblastic leukemia (ALL). Blast cells accounted for approximately 97% of the total nuclear cells and expressed clusters of differentiation markers CD10, CD19, CD38, and HLA-DR.

Notably, these cells were negative for CD3, CD7, CD20, cytoplasmic IgM, and CD117, consistent with their B-cell origin. The immunophenotypic profile confirmed the diagnosis of high-risk B-II ALL.

Imaging studies revealed splenomegaly and lymphadenopathy, specifically involving the jugular lymph nodes as observed via ultrasonography. Chest radiography did not demonstrate any initial abnormalities, while abdominal imaging corroborated the splenic enlargement. However, subsequent chest computed tomography identified bilateral polysegmental pneumonia with pleural effusions, complicating the clinical course.

Cerebrospinal fluid (CSF) analysis was performed on April 29 to evaluate central nervous system involvement, including routine biochemistry, cytology, and flow cytometry immunophenotyping. The results were normal, with no evidence of leukemic infiltration. Real time quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) analysis was also conducted to detect chromosomal translocations associated with poor prognosis. No genetic abnormalities were identified.

A chronological summary of the patient's disease progression and treatment is presented in Figure 1. The dynamic progression of laboratory findings from admission through discharge, including hematological and inflammatory markers, is illustrated in Figure 2. These investigations provided a comprehensive diagnostic framework, guiding the therapeutic strategy for this complex case.

Treatment

The patient began chemotherapy on April 22, 2024, following the ALL 2022 protocol. Despite initial tolerability, by day 13, complications arose, including hyperleukocytosis, myelotoxic agranulocytosis, severe anemia, and thrombocytopenia. These hematologic abnormalities necessitated transfusions of blood components and modifications to the patient's antibiotic regimen.

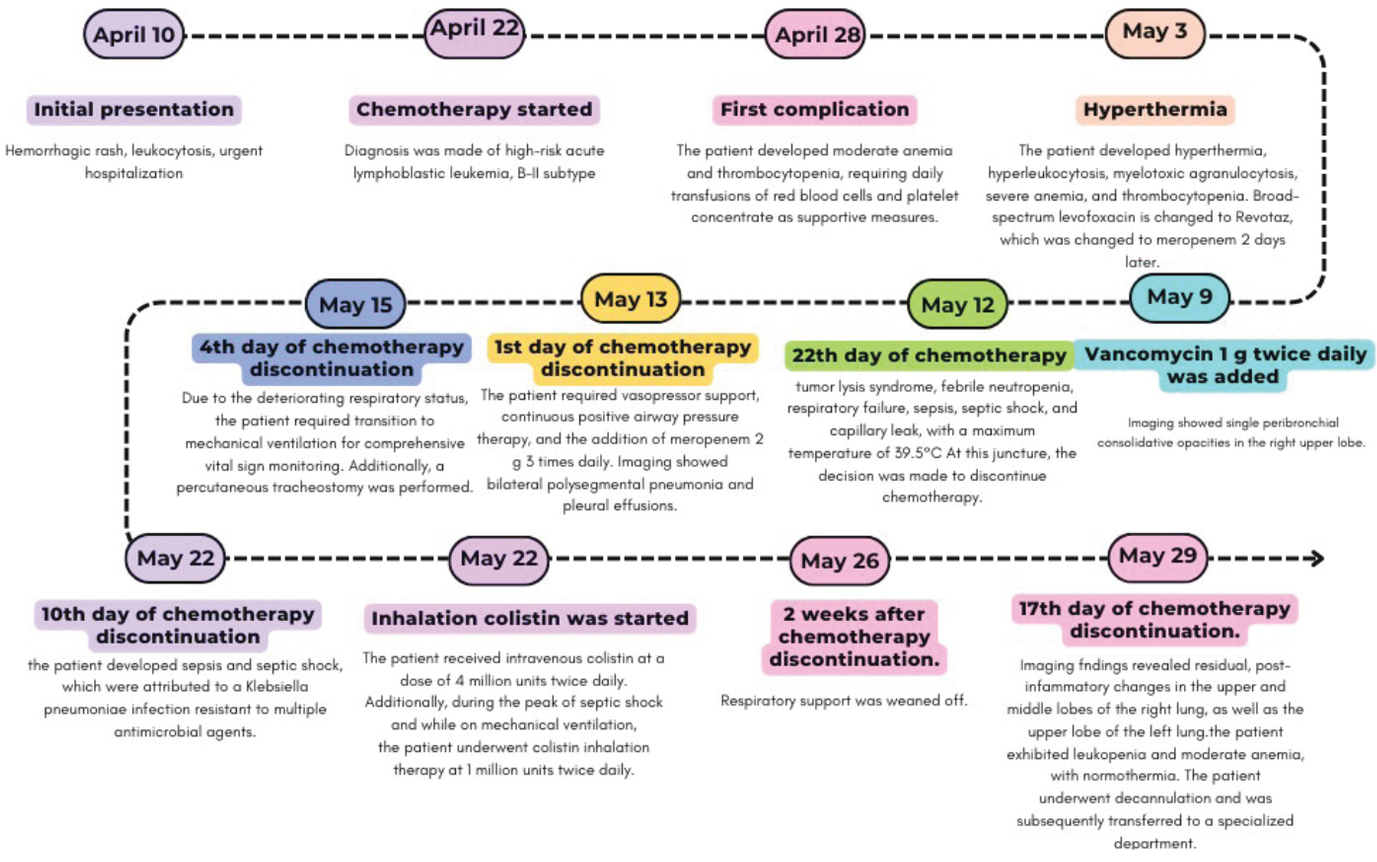

Figure 1 – Timeline

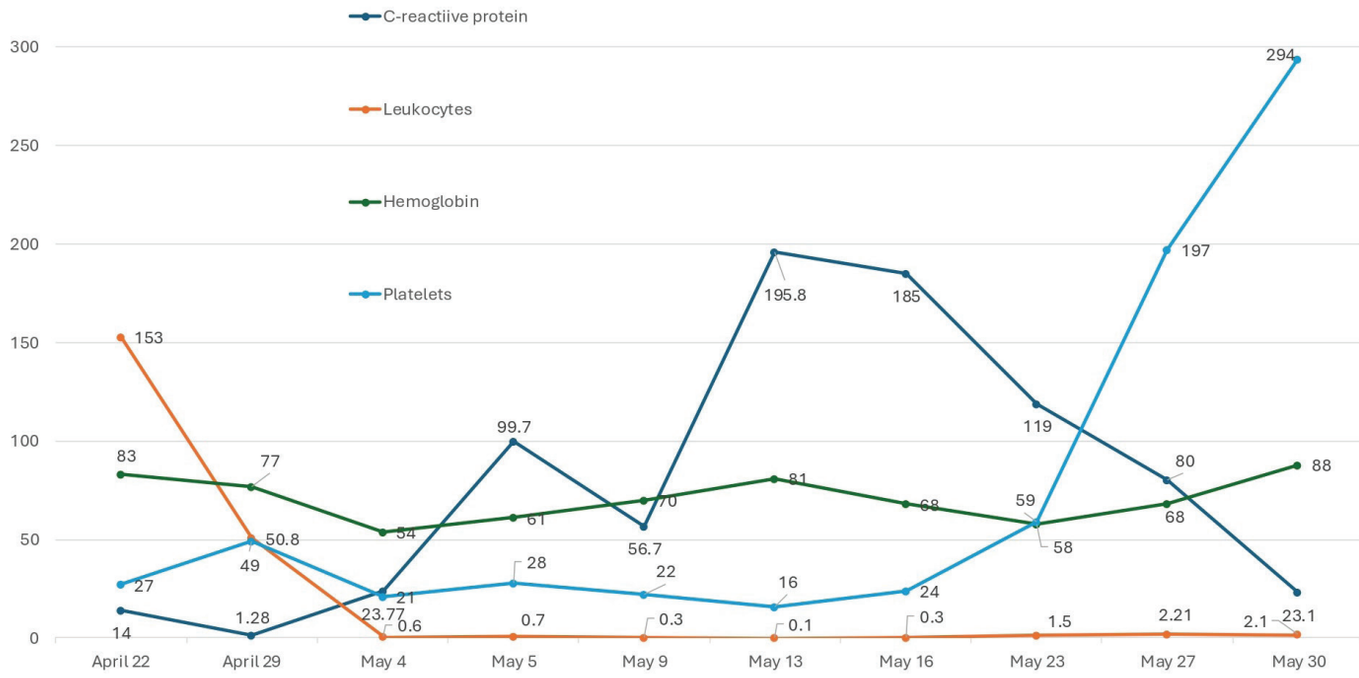

Figure 2 – Pre and Post score of Self-esteem Scale of Adults (SES) of the client

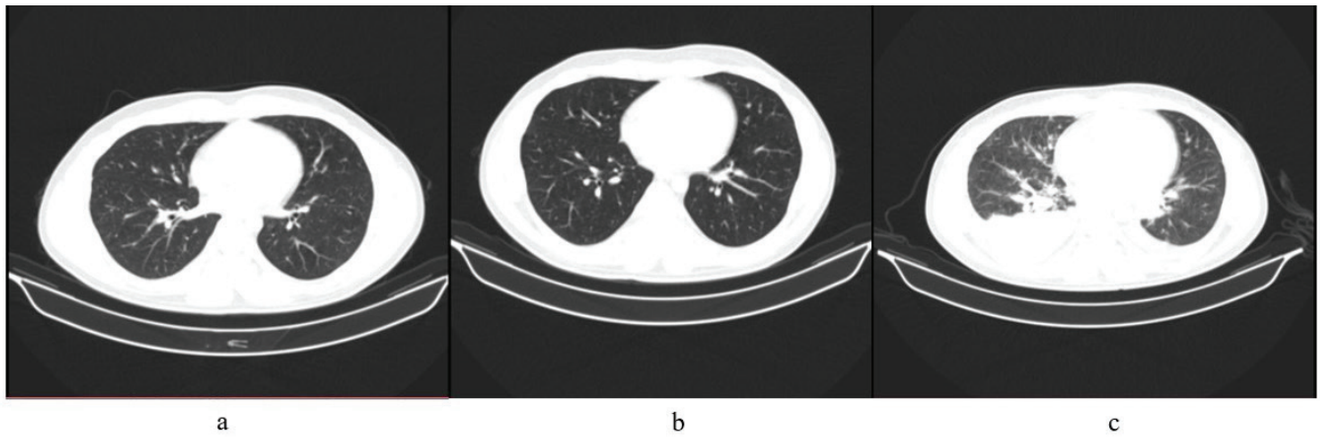

Figure 3 – Management for the client

Due to persistent fever, Levofloxacin was replaced with Revotaz (4.5 g four times daily). Subsequently, meropenem (1 g three times daily) was introduced as symptoms progressed. On day 18, the patient's condition deteriorated further, with the onset of respiratory failure, septic shock, and capillary leak syndrome. Supportive care included vasopressor therapy and continuous positive airway pressure (CPAP). Radiographic imaging revealed bilateral pneumonia and pleural effusions, as illustrated in Figure 3b. Invasive mechanical ventilation became necessary when respiratory distress worsened. Antibiotic therapy was intensified with meropenem (2 g three times daily) and vancomycin (1 g twice daily). On day 22, worsening complications, including febrile neutropenia and tumor lysis syndrome, culminated in severe septic shock. Antifungal therapy with Cancidas (75 mg once daily) was initiated, alongside glucocorticoids and hepatoprotective agents. Imaging showed extensive bilateral polysegmental pneumonia and pleural effusions, as illustrated in Figure 3c. Despite comprehensive antimicrobial therapy, blood cultures identified multidrug-resistant Klebsiella pneumoniae. Antimicrobial susceptibility testing confirmed resistance to most antibiotics except colistin.

Colistin Therapy

Targeted therapy began with intravenous colistin at 4 million units twice daily. Additionally, inhaled colistin (1 million units twice daily) was delivered using a vibrating mesh nebulizer, optimizing pulmonary drug concentrations. This approach facilitated localized infection control while minimizing systemic toxicity.

Supportive measures included vasopressors, anticoagulation, nutritional support, and vitamin supplementation. Persistent thrombocytopenia required ongoing platelet transfusions. Due to severe respiratory failure, a percutaneous tracheostomy was performed to facilitate prolonged mechanical ventilation. Antiviral therapy was added prophylactically to address potential viral reactivations.

Intensive Care Management

Over 17 days in intensive care, the treatment of multi-organ dysfunction involved:

- **Antimicrobial Therapy:** Colistin (intravenous and inhaled), meropenem, and vancomycin for bacterial infections; Cancidas for fungal prophylaxis.
- **Supportive Care:** Transfusions, vasopressors, glucocorticoids, and nutritional supplementation.
- **Ventilatory Support:** Non-invasive CPAP and invasive mechanical ventilation.

Gradual clinical improvement was observed, marked by the resolution of septic shock and recovery of hematopoiesis. Repeat imaging demonstrated the clearing of pulmonary infiltrates and effusions (seen in figure 3). By the 10th day post-chemotherapy cessation, the patient was successfully weaned off vasopressors and ventilatory support. Decannulation of the tracheostomy followed as the patient achieved spontaneous breathing.

Outcome

Bone marrow re-examination on April 30, 2024, revealed complete remission with a blast cell proportion of 1.9%. The patient's transfer to a specialized hematology unit underscored the success of this integrative approach, balancing intensive care interventions with targeted antimicrobial therapy.

Bacteriological Examination of Blood for Sterility, a detailed report is seen in Table 1. Identified Microorganisms: [1] Klebsiella pneumoniae 4 MRGN (multidrug-resistant Gram-negative bacteria resistant to four classes of antibiotics: ureidopenicillins, third- and fourth-generation cephalosporins, carbapenems, and fluoroquinolones).

Table 1 Antibiogram

Antibiotic	Group	Sensitivity	MIC (if available)
Ampicillin	A	R	≥32
Cefazolin	A	R	-
Gentamicin	A	R	≥16
Amikacin	B	R	4
Amoxicillin/ Clavulanic Acid	B	R	-
Ampicillin/ Sulbactam	B	R	-
Piperacillin/ Tazobactam	B	R	-
Ticarcillin/ Clavulanic Acid	B	R	-
Cefepime	B	R	≥32
Cefoxitin	B	R	-
Cefotaxime	B	R	≥64
Levofloxacin	B	R	-
Ertapenem	B	R	≥8
Meropenem	B	R	≥16
Piperacillin	B	R	-
Ceftazidime	C	R	≥64
Ciprofloxacin	B	R	≥4
Imipenem	B	R	-
Cefuroxime	B	R	-
Ceftriaxone	B	R	-
Tobramycin	A	R	-
Colistin	C	S	≤0.5
Tigecycline	-	R	≥8

MIC – minimum inhibitory concentration
Interpretation of Sensitivity (SIR): S – Sensitive, I – Intermediate, R – Resistant
Group: A – Priority antibiotics; B – Recommended for testing; C – Tested if resistance is found to Groups A and B; U – Tested only for urine samples.

Discussion

This case report underscores the complexity of managing sepsis and multi-organ failure in patients with hematologic malignancies, particularly those with acute lymphoblastic leukemia (ALL). It provides valuable insights into the potential of combined intravenous and inhaled colistin therapy for multidrug-resistant (MDR) infections in critically ill patients, contributing to the growing body of literature on innovative antimicrobial strategies.

Colistin, a last-resort antibiotic, has re-emerged as a critical agent in treating MDR Gram-negative infections, despite its known nephrotoxicity and neurotoxicity2. Inhaled colistin offers an advantage by delivering high local concentrations to the lungs while reducing systemic exposure, making it an attractive option for pulmonary infections. However, its use in hematologic patients with systemic and pulmonary MDR infections remains underreported.

Our approach, combining intravenous and inhaled colistin, capitalized on these distinct mechanisms of action. This dual strategy achieved bacterial clearance while addressing systemic and localized complications of sepsis. Previous studies have highlighted the success of inhaled colistin in improving outcomes for Gram-negative pneumonia [3]. Our findings extend these observations to a hematologic population, emphasizing the feasibility of this approach in a high risk setting.

The outcomes of this report align with the study by Khawcharoenporn et al. [3], which demonstrated the efficacy of colistin-based regimens in treating Acinetobacter baumannii pneumonia. Similarly, Manesh et al. [4] reported the benefits of combination therapy over monotherapy in MDR infections, particularly carbapenem-resistant pathogens. While these studies predominantly focused on general ICU patients, our findings underscore the relevance of such approaches in patients with profound immunosuppression.

This case also corroborates findings by Bassetti et al. [5], who highlighted the role of colistin in combating MDR pathogens. However, our report uniquely emphasizes the hematologic setting, where complications such as febrile neutropenia, respiratory failure, and septic shock compound treatment challenges. The integration of inhaled colistin addresses a critical gap in current literature by targeting pulmonary complications directly, as demonstrated in the resolution of bilateral pneumonia in our patient.

From a clinical standpoint, this case highlights the practical benefits of combining inhaled and intravenous colistin. The use of a vibrating mesh nebulizer ensured effective pulmonary drug delivery, minimizing aerosolized drug wastage and enhancing patient tolerance. This method aligns with antimicrobial stewardship principles by reducing systemic toxicity and preserving the efficacy of colistin.

Furthermore, the ability to implement this therapy in a resource-limited setting underscores its feasibility and global relevance. The rise of MDR pathogens, coupled with limited access to newer antibiotics, makes colistin-based regimens a vital component of the therapeutic arsenal in many healthcare settings [6]. Our findings advocate for broader adoption of inhaled antibiotics in high-risk populations, particularly in low- and middle-income countries where the burden of MDR infections is disproportionately high.

While the outcomes of this case are encouraging, several limitations warrant consideration. The single-patient nature of the report limits generalizability. Additionally, the lack of long-term follow-up data precludes an assessment of potential recurrence or delayed adverse effects. The pharmacokinetics of inhaled colistin in severely immunocompromised patients remain poorly understood, necessitating further research to optimize dosing strategies and minimize toxicity.

The reliance on clinical improvement and microbiological clearance as endpoints also highlights the need for standardized outcome measures in studies of inhaled colistin. Future investigations should incorporate objective parameters such as biomarker analysis and advanced imaging to validate therapeutic efficacy.

The rising prevalence of MDR pathogens poses a significant global health challenge, underscoring the need for innovative antimicrobial strategies. Our findings highlight the potential of combined colistin therapy to address this crisis, particularly in vulnerable populations such as hematologic patients.

Future research should focus on randomized controlled trials to validate the safety and efficacy of combined inhaled and intravenous colistin across diverse clinical settings. Additionally, pharmacokinetic studies could elucidate the optimal dosing regimens for inhaled colistin, minimizing toxicity while maximizing therapeutic outcomes.

From a public health perspective, the judicious use of colistin in combination therapies offers a sustainable approach to preserving its efficacy. The incorporation of rapid molecular diagnostic tools could enhance treatment precision, reducing the risk of resistance development. By expanding the evidence base for inhaled antibiotics, this case report contributes to global efforts to combat antimicrobial resistance and improve patient outcomes.

Conclusion

The combined use of inhaled and intravenous colistin in this case of ALL with sepsis and multiorgan failure demonstrated its potential as a supportive measure in managing severe MDR infections. This approach, combined with comprehensive intensive care, contributed to a favorable outcome in a critically ill patient. These findings emphasize the need for continued research into combination therapies to address the challenges of MDR infections in high-risk populations.

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Case Report DOI: https://doi.org/10.23950/jcmk/16330

Clinical Diagnosis of Familial Hypertriglyceridemia-induced Recurrent Acute Pancreatitis at Rural Outreach Outpatient Department: a Case Report

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Abstract

Acute pancreatitis is a common condition with significant morbidity and mortality. After gallstones and alcohol, hypertriglyceridemia is another important cause of recurrent acute pancreatitis. Primary or genetic hypertriglyceridemia may lead to pancreatitis in patients who have a normal Body Mass Index and have no history of diabetes mellitus. Though the diagnosis of primary hypertriglyceridemia is primarily based on genetic studies, clinically it can be suspected in patients having peculiar serum appearance. We report a case of familial hypertriglyceridemia causing recurrent acute pancreatitis, which was diagnosed with observation of peculiar serum sample of the patient. Attentive clinical evaluation may guide the treating physician toward the etiological factor and treatment accordingly.

Keywords: Familial hypertriglyceridemia; Recurrent acute pancreatitis; Acute pancreatitis; Familial Hyperchylomicronemia.

Introduction

Acute pancreatitis (AP) is a clinical state with significant morbidity and mortality rates. Recurrent acute pancreatitis (RAP) is defined as more than two attacks of AP without any evidence of underlying chronic pancreatitis [1]. While alcohol and gallstones are considered the most common etiologies, metabolic, structural, and iatrogenic causes are responsible for 20–25% of cases. Hypertriglyceridemia (HTG) or chylomicronemia is the underlying cause in up to 7% of all cases of pancreatitis [2]. Hypertriglyceridemia is attributed as an etiology of AP after ruling out the most common causes by measuring serum triglyceride levels, which can be primary (familial) or secondary. We report a case in which we suspected this etiology of RAP in a young, thin-built adolescent female patient after observing the milky serum sample (Figure 1), who had no gallstones on ultrasound of the abdomen and was a teetotaler.

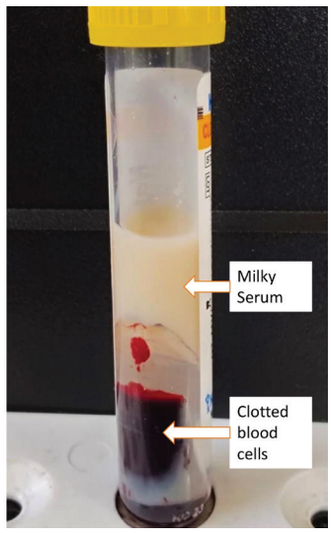

Figure 1 – Serum sample

Case presentation

A 17-year-old, thin-built female patient with a body mass index (BMI) of 20 kilograms per square meter presented to the rural outreach outpatient department with a history of recurrent epigastric pain that was radiating to her back and was associated with fever and nausea. She had at least 4 episodes of such pain in last one and a half years. In the last episode, she was admitted elsewhere for 5 days and presented to us with attached reports. Her serum amylase and lipase reports were raised more than three times the normal upper limit. A contrast-enhanced computed tomography (CECT) of the abdomen was done during previous admission elsewhere that was suggestive of acute pancreatitis with diffuse edematous pancreas with peripancreatic fat stranding and acute fluid collection in the pancreatic tail region extending to anterio-inferior to left Gerota's fascia (Figure 2A, B). That episode was managed conservatively there. Ultrasound of the abdomen showed no biliary etiology, and she was a teetotaler on detailed history.

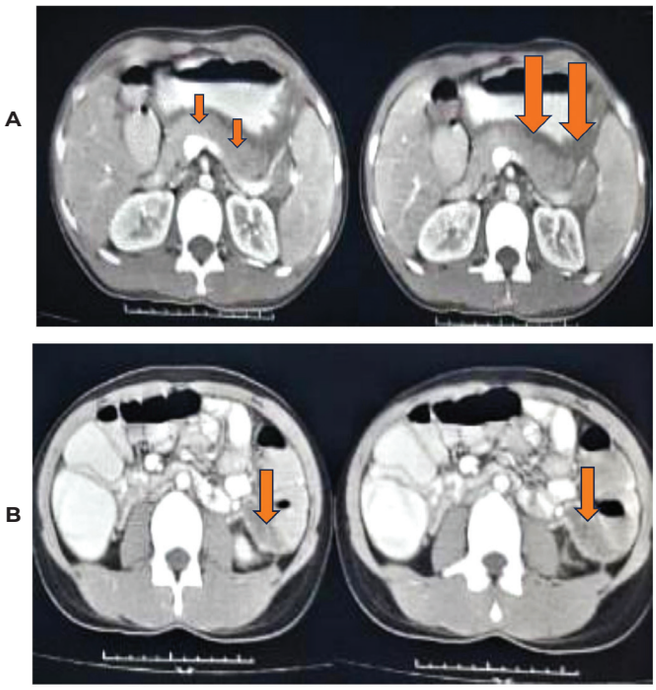

Figure 2 – CECT of the abdomen: acute pancreatitis with diffuse edematous pancreas with peripancreatic fat stranding (A) and acute fluid collection in the pancreatic tail region extending to anterio-inferior to left Gerota's fascia (B)

Table 1 Laboratory parameters

Laboratory parameters	Patient's values	Parent's values (Mother/Father)
Serum Triglycerides	373 mg/dL	246.3 mg/dL; 204 mg/dL
Serum Calcium	8.89 mg/dL	
Serum Thyroid-Stimulating Hormone (TSH)	1.80 µIU/mL	
Glycosylated Hemoglobin (HbA1c)	5.4 %	

During blood examination to rule out other etiologies of pancreatitis at our outreach OPD, we noticed milky serum and suspected hypertriglyceridemia or chylomicronemia, and serum triglyceride (TG) level was found to be 373 mg/dL. In view of a patient with normal BMI, having increased TG, her parents were also screened, both of whom had normal BMI. Serum samples of both the parents revealed milky serum, and serum TG levels in mother and father were found to be 246.3 mg/dL and 204 mg/dL, respectively. Her serum calcium and thyroid-stimulating hormone levels were within normal limits (Table 1) and she was not consuming any medication for prolonged period. Further genetic study to establish the diagnosis of familial hypertriglyceridemia could not be done in view of the poor financial status of the patient. The patient was started on dietary modifications and statins, and on follow-up, she remains asymptomatic.

Discussion

Hypertriglyceridemia is considered the next most common cause of acute pancreatitis after gallstones and alcohol worldwide [3]. Secondary HTG remains the culprit for RAP in the majority of cases due to increasing BMI, poor dietary habits, and the presence of diabetes mellitus (DM) and metabolic syndrome. Primary or familial HTG is another subset of this spectrum. In the absence of obesity, DM, and metabolic syndrome, patients with raised TG levels; primary HTG may be considered.

After ruling out gallstones and alcohol as etiologies of RAP, workup for HTG is considered. Though, in a patient with normal BMI, having no history of DM or metabolic syndrome, HTG as a cause of RAP is not expected mostly in routine clinical practice.

On simple observation of our patient's blood sample, we noticed excessive milky or lipemic serum (Figure 1). For confirmation, resampling was also done, which turned out to be similar in appearance. As the patient had no gallstones on her ultrasonogram and was a teetotaler, we suspected primary HTG. Samples of her parents turned out to be lipemic as well, and on evaluation, the patient and both of her parents had increased TG levels.

There is no defined threshold level at which HTG triggers AP. There is a 5% possibility of developing AP if TG exceeds 1000 mg/dL, and it rises to 10% to 20% if TG elevates over 2000 mg/dL [4]. Our patient had excessive milky serum at the initial presentation, which could not be analyzed at the local laboratory. The patient was then advised to follow a fat-free diet, and a repeat sample was taken after 2 weeks, her TG levels then came out to be 373 mg/dL.

The exact determination of primary HTG requires genetic studies, as it may be monogenic or polygenic [3]. A very small subset of patients may have a rare form of monogenetic HTG named familial chylomicronemia syndrome (FCS), an autosomal recessive disorder [5]. In very rare cases, severe HTG is also observed as a result of autoimmune hyperlipidemia, for

Table 4 Multinomial logistic regression

Year of publication	Study	Age of the patient/ Gender	Triglyceride level	Genetic study	Risk factors	Management
2024	**K Patel et al [7]**	**56 years/ Male**	**>8000mg/dL**	**NA**	**Diabetes Mellitus, Hypertension**	**Management of acute pancreatitis; Statins; Fibrates**
2022	G Arora et al [8]	28 years/ Male	>3000mg/dL	NA	Diabetes Mellitus, Hypertension	Management of acute pancreatitis; Statins; Fibrates; Niacin; Omega3
2022	A Poddar et al [9]	42 years/ Male	2560 mg/dL	NA	HTN	Management of acute pancreatitis; insulin; Statins; Fibrates; Niacin; Omega3
2017	T Kazemi et al [10]	30 years/ Female	6140 mg/dL	NA	Diabetes Mellitus	Management of acute pancreatitis; Insulin
2006	S I Gan et al [2]	28 years/ Male	479.9mg/dL	NA	None	Management of acute pancreatitis; Statins; Fibrates

instance, anti-glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) antibodies [6].

The report has a limitation of the non-availability of exact genetic studies to establish the primary HTG in this patient due to rural outreach setup and financial constraints. Table-2 describes a comparative analysis of recent case studies of familial hypertriglyceridemia-induced pancreatitis. No recent case studies described the genetic analysis to prove familial HTG.

Familial HTG is attributed to reduction in lipoprotein lipase (LPL) activity, either due to deficiencies in the LPL gene product or LPL regulators encoded by APOC2, APOA5, GPIHBP1, and LMF1 genes [11]. Since not all familial HTGT patients develop RAP, genetic studies for HTG-induced RAP are limited. In a genetic analysis of 126 patients, Chang et al. found that the CFTR gene mutation rate was 26.1% in patients with HTG-induced RAP [12].

Management strategies of HTG-induced acute pancreatitis remain on the line of management of acute pancreatitis due to any other etiology. In patients with HTG-induced acute pancreatitis, the use of Insulin and Plasmapheresis has been explained with a good level of evidence while the role of Heparin has a low level of evidence [13].

Long-term therapies, to prevent HTG-induced RAP, consist of both lifestyle modifications (such as weight loss and limiting intake of sugars and dietary fat) as well as pharmacologic therapy with target serum triglyceride levels <200 mg/dL. Traditional lipid-lowering agents consist of Fibrates, Statin, Niacin, Omega-3 fatty acids. Newer pharmacological agents include ANGPTL3 inhibitors (Evinacumab), ApoC-III inhibitors (Volanesorsen), and Pemafibrate [13].

Conclusion

Attentive clinical observation may aid in diagnosing the etiology of RAP, which is not attributed to gallstones or alcohol.

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