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EDITORIAL

Visualizing medicine: The case for implementing graphical abstracts in clinical reporting

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Abstract

Graphical abstracts (GAs) are emerging as a pivotal tool in medical literature, enhancing the dissemination and comprehension of complex clinical data through visual summaries. This editorial highlights the significant advantages of GAs, including improved clarity, increased reader engagement, and enhanced visibility of research findings. By transforming intricate scientific data into accessible visual formats, these abstracts facilitate quick and effective knowledge transfer, crucial in clinical decision-making and patient care. However, challenges such as potential data misrepresentation due to oversimplification, the skill gap in graphic design among researchers, and the lack of standardized creation guidelines pose barriers to their widespread adoption. Additionally, while software such as Adobe Illustrator, BioRender, and Canva are commonly employed to create these visuals, not all researchers may be proficient in their use. To address these issues, we recommend that academic journals establish clear guidelines and provide necessary design training to researchers. This proactive approach will ensure the creation of high-quality GAs, promote their standardization, and expand their use in clinical reporting, ultimately benefiting the medical community and improving healthcare outcomes.

Key Words: Graphical abstracts; Clinical data dissemination; Visual communication; Research impact; Academic publishing

Core Tip: Graphical abstracts significantly enhance the clarity and dissemination of complex clinical data in medical literature, offering both improved comprehension and increased reader engagement. Addressing challenges like data oversimplification and skill gaps in graphic design is crucial for their effective implementation and standardization.

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INTRODUCTION

Graphical abstracts (GAs) are increasingly recognized as a novel approach in medical literature, particularly for distilling and presenting complex clinical data and research in a visually compelling format[1,2]. These visual summaries distill essential points, making critical information immediately clear and more accessible to readers. This approach is particularly beneficial in clinical reporting, where the precision and speed of information delivery are crucial for sound decision-making and patient care[3-5]. The importance of visual tools in clinical communication is well-established.

GAs have gained significant popularity in the past two decades, emerging as a critical tool to enhance the accessibility and dissemination of scientific research[6,7]. They were initially more common in chemistry and biomedical journals but have now spread across multiple fields of science. The concept of GAs began taking off in the early 2000s, notably as more journals began to emphasize visual content to attract broader readerships, including those in social media. Chemistry journals, such as *Chemistry: A European Journal* and *Angewandte Chemie*, were among the first to adopt this format as early as the late 1990s[8]. Over time, GAs spread to other disciplines, including medicine, biology, and even social sciences[9]. GAs are especially prominent in fields that involve complex data or highly visual subject matter, such as chemistry, biology, medicine, and engineering[8,9]. Biomedical journals like *The Lancet* and *Journal of the American Chemical Society* use GAs extensively to make intricate research findings more accessible to non-experts[8]. Clinical research has also adopted a variant called the visual abstract, which presents study results in a table-like format[9].

Several leading journals have set clear policies regarding GAs. For example, Elsevier and Springer Nature journals often provide guidelines or mandates for GAs during submission. Journals like *PLoS One*, *Cell*, and *The Journal of Visualized Experiments* (*JoVE*) strongly encourage or require authors to submit GAs along with their manuscripts[9]. In contrast, some journals like *Nature* do not require GAs at submission but allow or encourage authors to add them at the acceptance stage[9,10]. Many journals see GAs as a valuable tool for promoting articles, particularly through social media and conferences[9]. The continued push towards visual media, accelerated by social media platforms, has made GA an essential part of modern research dissemination. They serve as an entry point for broader audiences, enhancing the visibility of articles and potentially boosting citation metrics[11]. Each journal has its unique specifications, so it is essential to consult journal-specific guidelines on aspects like file format, size, and resolution. GAs are now integral for researchers seeking to engage audiences beyond their immediate field[12,13].

Studies demonstrate that GAs significantly enhance comprehension and knowledge retention among readers. For instance, research has shown that visual summaries, particularly when shared on social media, increase engagement and dissemination metrics, such as Altmetric scores, which are key indicators of article visibility[10]. Moreover, studies in *Translational Behavioral Medicine* confirm that articles with GAs receive higher interaction rates compared to traditional text or figure-based formats, widening their reach and appeal[10]. These abstracts allow researchers to convey detailed scientific information in simplified, accessible ways, making them valuable for both specialists and broader audiences. GAs can help bridge language barriers, particularly in global healthcare settings. Visual representations condense complex research into universally understandable formats, enabling non-native English speakers to engage more effectively with scientific content[10,14].

This editorial strongly advocates for the widespread adoption of GAs in clinical reporting across disciplines. The objective is to enhance the speed and effectiveness of knowledge dissemination in medicine, ensuring that research findings become more accessible and have a greater impact on clinical practice. Encouraging the use of GAs will cultivate a more informed and engaged medical community, thereby improving patient outcomes and driving healthcare innovation.

ADVANTAGES OF GAs

GAs are valuable tools for enhancing the comprehension of complex clinical data, offering a visual means to distill intricate research findings. For instance, in a study focused on randomized controlled trial outcomes in medical research, GAs improved reader comprehension by 35% compared to traditional text abstracts[15]. This clarity is crucial in clinical environments where the rapid understanding of data directly impacts patient care. In addition, the format allows readers

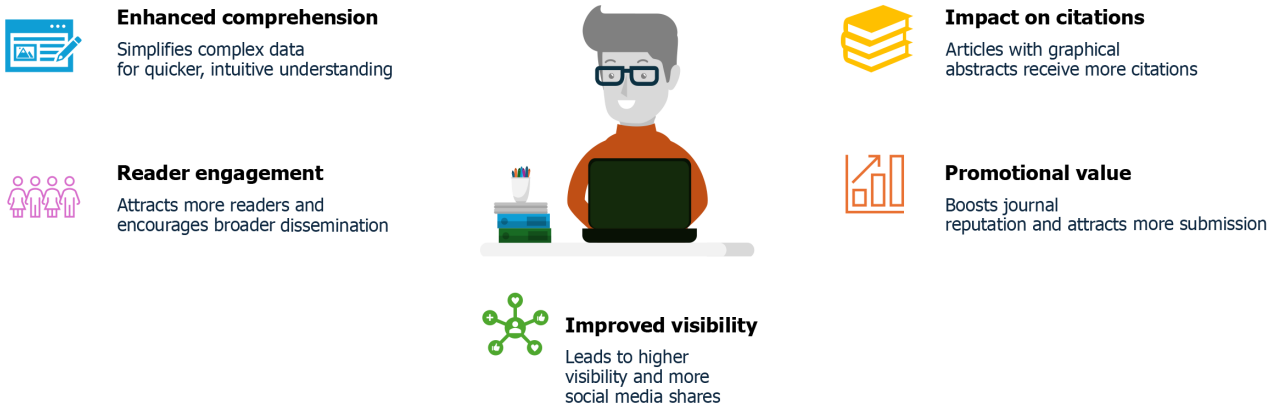

Figure 1 Benefits of graphical abstracts.

to extract key findings more quickly and effectively than from text alone, as demonstrated in several studies[8]. GAs also increase article visibility and engagement. Research in journals such as *Gastroenterology* has shown that articles featuring GAs not only attract more social media attention but also significantly increase citations. A study found that articles with GAs received 40% more citations and higher social media dissemination than those without[16]. While citations are an important measure of research impact, GAs also encourage interdisciplinary collaboration by making research accessible to a broader audience[15], which is particularly relevant in fields like clinical research where collaboration is essential [17–21]. Figure 1 illustrates the benefits of GAs, including improved citation rates, engagement, and broader interdisciplinary reach.

However, while GAs offer numerous advantages, they also present challenges. Creating a high-quality GA requires time, specialized skills, and resources[22–24]. Many researchers, particularly those working in more qualitative fields, may struggle with visually representing their data. Poorly designed Gas cluttered with excessive information or poorly labeled elements can mislead readers, reducing rather than enhancing clarity[17]. Moreover, there is limited standardization in GA design, meaning some journals may present overly simplistic or inconsistent visuals[16]. Figure 2 outlines best practices in GA design, emphasizing simplicity, relevance, and clarity to ensure effective communication of complex data.

DESIGN PRINCIPLES

The success of a GA depends largely on its clarity and simplicity. For example, in a study of oncology outcomes, a GA using a basic bar chart helped readers quickly understand the efficacy of various therapies[15]. A well-designed GA uses clean lines, minimal text, and a limited color palette to focus attention on the most critical data points[16]. Logical flow through the use of arrows or image sequences ensures that the audience can easily navigate the information[24,25]. Simplicity is vital to ensure that the visual enhances comprehension without overwhelming the reader.

Relevance is another key consideration. Each element of the GA must directly correspond to the research's main conclusions. Selecting appropriate visual representations, such as charts for quantitative data or flow diagrams for clinical processes, ensures that the GA reflects the study's key findings without omitting critical details[26,27]. Studies have shown that visually organized information is more likely to be retained and accurately interpreted by readers[15,17].

In the process of creating effective GAs, it is crucial to prioritize fundamental design principles that enhance clarity, readability, and visual appeal[8]. Rather than focusing predominantly on specific software tools, researchers should consider key elements such as data visualization best practices, color theory, and typography guidelines to create scientifically accurate and aesthetically engaging visuals. Data visualization best practices involve selecting the most appropriate type of graphic to effectively represent the data[28]. For example, bar charts may be suited for categorical comparisons, while scatter plots are more effective for illustrating correlations between variables. Clear labeling, appropriate scaling, and the elimination of unnecessary visual clutter are essential to ensure that the data are accurately conveyed without overwhelming the audience. Color theory plays a significant role in ensuring that visuals are accessible and comprehensible. Researchers should consider using color schemes that accommodate individuals with color vision deficiencies, such as colorblind-safe palettes, while maintaining sufficient contrast to highlight key findings. Furthermore, colors should be used intentionally to direct attention and differentiate between different elements in the design. Typography is another critical aspect, as the readability of the text significantly impacts how well the information is communicated. Researchers should prioritize legible fonts, maintain consistent font sizes, and use typographic hierarchy to emphasize key points without overcrowding the design with excessive text.

In terms of tools, while specific software packages like Adobe Illustrator, Canva, and BioRender are widely used and offer advanced features, the choice of software should align with the needs and expertise of the researcher. Instead of prescribing particular platforms, researchers should look for software that offers essential features, such as vector graphic capabilities for scalability, pre-designed templates for ease of use, and an intuitive interface that does not require advanced graphic design skills. Features such as drag-and-drop functionality, customizable icons, and export options for

Figure 2 Best practices for graphical abstracts design, emphasizing simplicity and logical flow.

high-resolution images are also beneficial for creating polished and professional visuals. For researchers who may not have advanced graphic design skills, there are more accessible solutions beyond individual tools. Detailed comparison of commonly available software is provided in Table 1. Collaboration with professional graphic designers can ensure that visuals meet high standards of design while allowing researchers to focus on content. Moreover, many academic institutions and journals now offer in-house design support or provide access to ready-made templates tailored for scientific content. These resources can be especially useful for researchers who want to ensure consistency with the journal's guidelines for GAs. Additionally, automatic design tools that leverage artificial intelligence and machine learning are emerging, allowing users to quickly generate visuals without in-depth design knowledge. These tools can suggest layouts, color schemes, and design elements based on the content input, making them valuable for researchers looking for efficient, high-quality solutions. Ultimately, by focusing on design principles and leveraging the right tools and resources, researchers can create GAs that are not only visually compelling but also scientifically accurate and accessible to a broad audience. This approach ensures that the visual elements support the communication of complex ideas in a clear, engaging, and effective manner[29].

CHALLENGES AND CONSIDERATIONS

GAs, while effective in simplifying and visually conveying complex medical information, face several significant challenges that must be addressed to ensure accuracy and reliability. One key concern is the risk of oversimplification, where essential elements like statistical variability or methodological intricacies are lost when transforming detailed findings into a visual form. For example, focusing solely on average outcomes without showing variability can give readers a false impression of the data's robustness. Similarly, omitting methodological nuances, such as sample size calculations or control variables, can lead to misinterpretations, distorting the study's validity and implications. It is essential to find the right balance between clarity and depth to avoid misleading conclusions while maintaining the integrity of the research[2]. Another challenge is the skill gap in graphic design. Many researchers lack the necessary skills to create effective and aesthetically coherent GAs, which require knowledge of visual hierarchy, color theory, and data visualization principles. Poorly designed abstracts, including inconsistent use of fonts, improper color schemes, or unclear visual cues, can fail to convey the intended message, reducing the impact of the research. Providing researchers

Table 1 Comparison of graphical abstract creation tools

Software	Free version	Paid pricing	Ease of use	Scientific focus	Key strengths	Key limitations
Canva	Yes	$12.99/month (Pro)	Very easy	No	Large template library, beginner-friendly	Lacks scientific icons, watermark on free plan
BioRender	Yes	$9/month (Academic Basic), $35/month (premium)	Easy	Yes	Extensive scientific icon library, designed for life sciences	Watermark in free version, limited export
Inkscape	Yes	Free	Moderate	No	Powerful vector design tool, open-source	Steeper learning curve, no scientific templates
Adobe Illustrator	No	$20.99/month (Academic)	Difficult	No	Professional-quality designs, unmatched customization	Expensive, requires design experience
Microsoft PowerPoint	No	Part of Office 365 ($69.99/year)	Very easy	No	Widely used, familiar interface	Limited graphic design capabilities
Mind the Graph	Yes	Starts at $5/month	Easy	Yes	Affordable, designed for researchers	Limited icon library compared to BioRender
GIMP	Yes	Free	Difficult	No	Free, full-featured image editor	More suited for image editing than vector-based abstracts
Smart Servier Medical Art	Yes	Free	Very easy	Yes	Free, high-quality medical and biological illustrations	Limited customization options

with training in basic design principles, along with hands-on experience with tools like Adobe Illustrator, BioRender, or PowerPoint, can help bridge this gap. These training programs can take the form of short online tutorials, intensive workshops, or design modules integrated into research curricula.

The absence of standardized guidelines across journals is a critical issue. While traditional abstracts follow clear editorial standards, GAs remain inconsistent in both format and content, making peer review more difficult and can lead to discrepancies in interpretation. This inconsistency can also hinder the reproducibility of research, as key information may be underrepresented or omitted in a visual format. Standardized guidelines, developed with input from both researchers and graphic designers, could resolve this problem by ensuring clarity, uniformity, and consistency across journals. Such standards should cover essential elements like the balance between imagery and text, acceptable design formats for different types of research, and guidance on including crucial methodological details[5]. To address these challenges, both the scientific community and publishers must collaborate. Journals should take the lead by establishing clear, actionable guidelines for GAs that cover all aspects of design, content, and data representation. Additionally, researchers should be offered opportunities to build essential graphic design skills through accessible training programs. These combined efforts would improve the quality, effectiveness, and standardization of GAs across scientific publications[8,17].

By addressing the key challenges outlined in Table 2, such as oversimplification, the design skills gap, the absence of guidelines, and time constraints, through targeted solutions, the scientific community can enhance both the quality and impact of GAs.

CASE EXAMPLES

GAs have demonstrated significant effectiveness in enhancing reader engagement and comprehension in clinical and scientific literature. Two notable examples illustrate this impact.

Gastroenterology

A study on the use of visual abstracts in *Gastroenterology* reported that these graphical summaries helped in distilling complex data into more digestible, visual snippets that were easier for both clinicians and patients to understand. The before-and-after impact was notable in that articles with visual abstracts received more views and social media engagement compared to those without, suggesting that visual abstracts could significantly amplify the reach and accessibility of complex medical information[30].

Suicide prevention research

In another example, the use of visual abstracts was evaluated in the dissemination of research findings in suicide prevention. A study conducted by the Rocky Mountain MIRECC used visual abstracts to disseminate findings on veterans' mental health and suicide prevention. It was found that this strategy significantly improved the reach and engagement of their publications, reaching a broader audience that included medical professionals, the general public and stakeholders in public health. This approach demonstrated the potential of GAs to effectively convey urgent and complex information across diverse audiences[31].

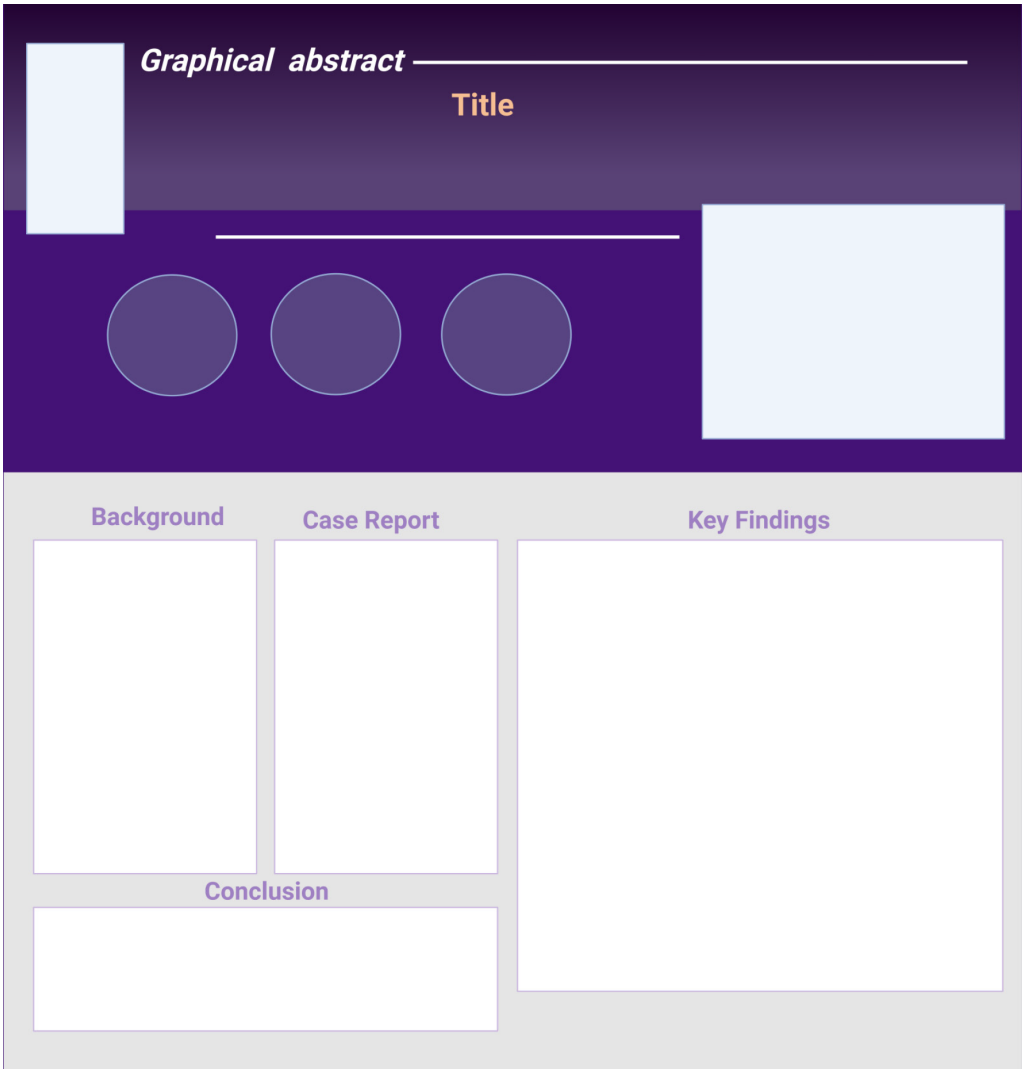

Figure 3 Template for creating graphical abstract for case reports.

These cases highlight the utility of GAs in both enhancing the accessibility of scientific findings and engaging a wider audience, thereby bridging the gap between complex research data and practical application. A template for creating GAs for a case report is given in Figure 3.

CONCLUSIONS

GAs have the potential to revolutionize medical literature by making complex clinical data more accessible and understandable. These visual summaries help both medical professionals and the public quickly grasp key information, leading to better decision-making and patient care. Studies show that GAs boost reader engagement, visibility, and citation rates, enhancing the impact of research publications. However, challenges such as the risk of oversimplification, researchers' lack of graphic design skills, and the absence of standardized guidelines must be addressed. To fully leverage GAs, journals should establish clear creation guidelines and offer training resources for researchers. This will ensure high-quality, standardized outputs, fostering a more informed medical community and improving healthcare outcomes through better communication and understanding of research findings.

Table 2 Challenges and recommendations for graphical abstracts

Challenge	Description	Consequences	Recommendation
Risk of oversimplification	Simplifying complex data may omit important details, such as variability and methodological context	Leads to misinterpretation or misconceptions about the research findings	Balance clarity and completeness; ensure crucial points like statistical variability are included
Skill gap in graphic design	Researchers often lack necessary skills in visual hierarchy, data representation, and design software	Poorly designed abstracts diminish the clarity and impact of the research	Provide targeted training in design software (*e.g.*, Adobe Illustrator, BioRender) and basic design principles through online courses or workshops
Lack of standardized guidelines	No universal standards for GAs exist, leading to inconsistencies in format and content across journals	Inconsistent formatting complicates peer review and interpretation, affecting reproducibility	Develop universal guidelines with input from researchers and designers, covering balance of text and imagery, and necessary methodological details
Complexity of visual data representation	Visualizing certain data types (*e.g.*, statistical results, methodological details) can be difficult without loss of context	Inappropriate visual choices may obscure key findings, confusing readers	Provide journals with examples of best practices for different types of data and create discipline-specific templates for GAs
Time and resource constraints	Creating high-quality GAs can be time-consuming and may require resources not available to all researchers	Researchers might rush through or avoid creating GAs, reducing their potential benefits	Journals could offer simplified design tools and templates, while institutions provide resources or personnel trained in graphic design to assist researchers
Subjectivity in visual design	Lack of clear guidelines can lead to subjective design choices that are inconsistent between researchers or disciplines	Reduces clarity and uniformity, complicating interpretation across publications	Journals should include specific visual design elements (font types, color palettes) in their guidelines to ensure uniformity

GA: Graphical abstract.

FOOTNOTES

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EDITORIAL

Musculoskeletal disorders in nursing staff

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Abstract

Nursing staff provides patient care in an occupational environment that often imposes challenges that affect significantly the musculoskeletal system. Work-related musculoskeletal disorders are common in nursing stuff and have a negative impact in their professional and daily activities. In the current editorial, the duties of nursing staff, the types of musculoskeletal disorders, the predisposing factors (including factors related to professional tasks/ergonomics and to working schedules, psychological, social and individual factors) and their impact on working ability and quality of life nursing staff are summarized and preventive measures are proposed.

Key Words: Musculoskeletal disorders; Nursing staff; Predisposing factors; Ergonomics; Prevention

Core Tip: Work-related musculoskeletal disorders (MSDs) are common in nursing staff and affect their working ability and quality of life. The specific requirements of nursing duties and ergonomics are analyzed in relation to the different types of MSDs. The role of the different factors related to the prevalence of MSDs is emphasized and preventive measures are discussed.

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INTRODUCTION

Nursing staff provides patient care in an occupational environment that often imposes challenges that affect significantly the musculoskeletal system. The specific requirements of nursing duties will be analyzed in relation to the different types of musculoskeletal disorders (MSDs). The role of the different factors that are related to the prevalence of these disorders will be emphasized to elucidate the impact on working ability and quality of life (QoL) of nursing staff, and to propose preventive measures.

NURSING STAFF: DUTIES AND SHIFTS

The main body of nursing staff types typically includes registered nurses (RNs), licensed practical nurses or licensed vocational nurses, and advanced practice RNs (APRNs). These categories represent different levels of education, training, and scope of practice within the nursing profession. RNs are licensed healthcare professionals who have completed a nursing program (typically an associate or bachelor's degree in nursing) and have passed the respective exam. They provide direct patient care, including assessing patients' health, developing care plans, administering medications, and educating patients and their families. Licensed practical nurses or licensed vocational nurses are licensed nurses who have completed a practical nursing program (usually a diploma or certificate program) and have passed the respective exam. They work under the supervision of RNs or physicians and provide basic nursing care, such as taking vital signs, dressing wounds, and administering medication. APRNs are RNs who have obtained additional education and training at the graduate level. APRNs have advanced clinical skills and are authorized to diagnose and treat patients, prescribe medications, and provide primary or specialty care in various healthcare settings. While these three categories encompass the majority of nursing roles, there are also other specialized nursing roles and certifications within each category, as well as variations in nursing practice based on factors such as geographic location, healthcare setting, and specific patient populations served.

Concerning the nursing shifts these include day shifts typically occurring during daytime hours (7:00 AM to 7:00 PM or 7:00 AM to 3:00 PM), evening shifts (3:00 PM to 11:00 PM) and night shifts, typically occur during nighttime hours (7:00 PM to 7:00 AM or 11:00 PM to 7:00 AM). Each type of shift has its own unique characteristics, and nurses may have preferences based on their personal and professional needs. Moreover, factors such as staffing levels, patient acuity, and organizational policies may influence the availability and scheduling of nursing shifts within specific healthcare facilities. Nurses working day shifts have more predictable schedules and may have more opportunities for interaction with patients, families, and other healthcare team members, while those working night shifts may experience disruptions to their sleep patterns and may face challenges with fatigue and maintaining alertness. Finally, nurses working evening shifts may have more flexibility with their schedules compared to day or night shifts. Rotating shifts involve working a combination of day, evening, and night shifts on a rotating basis, often predetermined. Nurses working rotating shifts may experience challenges with adjusting to different sleep schedules and maintaining work-life balance. Weekend shifts typically occur on Saturdays and Sundays, and may involve working either 8-hour or 12-hour shifts. Nurses working weekend shifts may have fewer staff members and resources available compared to weekdays. However, weekend shifts may offer additional compensation or scheduling flexibility for nurses who prefer to have weekdays off. *Pro re nata* shifts are as-needed shifts, where nurses may work on a temporary or occasional basis to fill staffing gaps.

TYPES OF MSDs

MSDs include injuries and pathological conditions of muscles, tendons, bones and joints, nerves and vessels that result in problems concerning the shape, support, stability and movement of the body. Many studies underlined the prevalence of lower back, shoulder, and ankle-feet symptoms in nursing staff. Sun *et al*[1] conducted a meta-analysis that consolidated the prevalence rates of work-related MSDs at various anatomical sites among nurses, across different countries. According to this meta-analysis the annual prevalence of work-related MSDs was 77.2%, and the anatomical sites with the highest prevalence of these disorders were the lower back, the neck and the shoulder.

FACTORS PREDISPOSING TO MSDs

Factors related to professional tasks and ergonomics

The occupational environment for nurses presents a variety of physical challenges that significantly impact their health and well-being. These challenges arise from a range of demanding tasks inherent to nursing duties, including lifting patients, moving heavy objects, maneuvering machinery, and executing motions that involve extreme postures. Heavy lifting and manual handling can increase the risk of back problems and other MSDs if proper lifting techniques and equipment are not used[2-4]. Furthermore, studies show that engaging in repetitive tasks, such as handling surgical sets and dealing with patients by moving, lifting, or lowering them, as well as pushing or pulling heavy loads, contributes to the escalation of musculoskeletal symptoms[5]. Prolonged standing or sitting, and assuming awkward or sustained postures during patient care activities, such as bending, twisting, or reaching, can place excessive strain on the musculoskeletal system and contribute to respective disorders[4]. The predominant activities observed include repetitive elbow flexion/extension, followed by repetitive movements of the wrist and fingers, and heavy lifting[6], while increased physical demands and workload due to understaffing lead to fatigue and increased risk of MSDs[7].

Another crucial factor is the type of department the nursing staff serves as well as the ergonomic factors. Concerning the department, surgical department and operating room nurses are the most vulnerable[3-5,8]. Positioning patients on the operating table, lifting and carrying instrument trays, organizing instrumentation, maintaining prolonged static postures while assisting surgeons in combination to the "sitting/standing policy" seriously burden the operating room nurses. Additionally, imperfect workspace design and poor maintenance of surgical carts and trays increases the likelihood of musculoskeletal symptoms, while the effect of time pressure on the musculoskeletal system is also underlined is different studies[3,4]. Finally, lack of training and education of nursing staff on prevention of MSDs can result in use of improper techniques that are opposed to ergonomic principles, ineffective use of equipment, and avoidance of self-care practices[9].

Factors related to working schedules

Irregular work schedules, extended shift schedules, night shifts, and rotating shifts can disrupt circadian rhythms, increase fatigue, and impair recovery, potentially contributing to MSDs among nursing staff[5,9]. Several studies showed that the prevalence of low back symptoms was significantly higher among shift or night workers compared to day workers[10,11].

Psychological and social factors

The correlation between psychological/social factors and MSDs is significant. Stress related to the specific professional environment including high patient volumes, time pressure and feeling of lack of control in combination to fatigue from specific manual tasks gradually burden the health of nursing staff. In addition, the effort-reward imbalance and the low respect are key factors leading to disorders of the musculoskeletal system[7,12,13]. There is also an important link between MSDs and somatic stress symptoms, including headache, muscle tension, and palpitations, while burnout is associated with increased risk of MSDs among nursing staff[14].

A frequently underestimated psychological factor related to MSDs and low back pain in nursing staff is kinesiophobia, which is a pain-related fear of movement/reinjury. This can cause a vicious cycle leading to physical inactivity which negatively affects recovery and relief from musculoskeletal pain and subsequently of QoL[15]. A critical factor affecting the wellbeing of nurses is the presence of depression. Studies show that comorbidity of MSDs and depression is prevalent among hospital nurses, which is worrying for both nurses' health and patient care[16,17]. Furthermore, sleeping disorders, especially insomnia, are associated with a higher risk of chronic musculoskeletal pain including low back pain [18]. Finally, the role of conflicts must be emphasized. Work-family conflict is a common type of role conflict between occupational and family demands. The association between work-family conflicts and MSDs has been underlined in several studies[14,16].

Individual factors

Age, gender, and body mass index are important factors affecting the likelihood of developing musculoskeletal symptoms in nursing staff, while daily exercise also has a distinct effect. Increasing age is associated with decreased muscle strength and flexibility, with decreased bone density and with increased rates of MSDs[19,20]. Abdollahzade *et al* [21] demonstrated an important relationship between working postures and age. Female gender is also correlated to working postures, as women are predisposed to uncomfortable postures, which leads to musculoskeletal symptoms[21]. Another notable individual factor for the development of musculoskeletal symptoms is body mass index: Being underweight is a recognized risk factor[5]. Finally, the effect of daily exercise on ergonomic postures is underlined in a recent study[21].

IMPACT ON WORKING ABILITY AND QoL

MSDs pose significant challenges to the working ability and QoL of nursing staff. Limitation in working ability due to MSDs include reduced mobility, limitations in lifting and transferring patients, limitations in equipment handling, avoidance of repetitive tasks, and restricted working hours. Thus, MSDs may lead to decreased productivity at work due to health issues (presenteeism) or to absence from work (absenteeism)[22-24]. Both presenteeism and absenteeism have an

impact on the workflow and on the quality of patient care, while the presence at work despite the MSDs amplifies vulnerability of the nursing staff and may limit career advancement opportunities and professional development, causing career dissatisfaction or even to the desire to leave the profession[24-27].

Concerning the QoL, MSDs affect negatively almost every aspect of nurses' QoL. According to a recent study, the more the musculoskeletal symptoms and the sites affected, the greater the deterioration in QoL[28]. MSDs affect physical and mental health and influence the work-life balance. Physical discomfort and pain reduce the ability and functionality with a direct effect on daily activities and hobbies apart of the effect on professional performance. Dealing with chronic pain and physical limitations can have an adverse effect on nurses' emotional well-being, that can lead to increased stress, anxiety, or depression. In addition, musculoskeletal pain is a significant risk factor for insomnia[29]. Inadequate sleep leads to a vicious cycle where fatigue and exhaustion can exacerbate physical symptoms and emotional distress, further impacting the overall QoL.

Finally, the financial impact of ongoing musculoskeletal pain can be substantial for individuals and their families, affecting their personal and social welfare. Difficulty in sustaining regular employment, increased absenteeism due to illness, and reduced activity levels contribute to financial strain related to musculoskeletal pain and disorders[30].

PREVENTION

Preventing MSDs in nurses requires a multifaceted approach that addresses individual, ergonomic and organizational factors. The risk of developing MSDs can be reduced through knowledge and application of ergonomic principles by nursing staff. Working under appropriate ergonomic conditions can increase nurses' motivation and job satisfaction while diminishing job stress, absenteeism, occupational diseases, and work-related accident[9,31].

Another beneficial prevention measure is use of assistive devices and lift teams that familiar with lifting techniques. It is well documented that patient handling can be conducted safely through usage of assistive equipment and devices, effectively eliminating hazards that can lead to MSDs. The implementation of assistive patient handling equipment not only reduces the risk of musculoskeletal injuries for nursing staff but also enhances the quality of care provided to patients[32]. Nurses' education and awareness play a crucial role in restricting MSDs by promoting proper techniques, identifying risk factors, encouraging self-care practices and facilitating early intervention. Prevention and prompt detection of MSDs averts progression to chronic and more serious diseases[31,33,34].

Finally, corrective exercise training involves the implementation of specific exercises and movements designed to address muscular imbalances, postural issues, and other biomechanical problems within the body. Exercise intervention is considered effective on controlling musculoskeletal symptoms in nursing staff. Safaeian *et al*[35] compared corrective exercise and ergonomic training, concluding that both are important, but corrective exercise training is more effective in reducing low back pain. Therefore, managers could devise exercise strategies tailored to address various musculoskeletal symptoms[36].

CONCLUSION

MSDs pose a significant challenge to the nursing profession, affecting both the physical well-being and professional performance of nursing staff. The combination of physically demanding tasks, irregular work schedules, and psychological stress creates a high-risk environment for the development of these disorders. As the prevalence of MSDs in nursing staff is alarmingly high, especially affecting the lower back, neck, and shoulder, it becomes clear that proactive measures must be taken to mitigate these risks. Ensuring proper ergonomic practices, providing education on safe patient handling techniques, and offering access to assistive devices can reduce the strain on nurses' musculoskeletal system. Additionally, fostering a supportive work environment that promotes regular exercise, healthy work-life balance, and addresses psychological stressors is crucial for improving nurses' overall QoL and work ability. By prioritizing the prevention and management of MSDs, healthcare organizations can enhance not only the health and well-being of their nursing staff but also the quality of patient care provided.

FOOTNOTES

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EDITORIAL

Enhancing the outcomes of diabetic vitrectomy with pharmacological adjuvants

Chun-Yao Cheng, Wen-Rui Hao, Tzu-Hurng Cheng

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Abstract

This editorial offers insights from a minireview by Venkatesh *et al*, who explored pharmacological adjuvants for diabetic vitrectomy. Specifically, they synthesized current knowledge and evaluated the efficacy of various adjunctive therapies in improving the outcomes of diabetic retinopathy and managing associated complications. Herein, we highlight the key roles of pharmacological adjuvants in optimizing surgical techniques, minimizing intraoperative challenges, and enhancing postoperative recovery. We further discuss the potential implications of this approach for clinical practice and future research directions in this evolving field. Overall, this editorial underscores the importance of incorporating pharmacological adjuvants into standard diabetic vitrectomy care to improve surgical outcomes and thus patients' quality of life.

Key Words: Diabetic vitrectomy; Pharmacological adjuvants; Surgical outcomes; Diabetic retinopathy; Clinical implications

Core Tip: Incorporating pharmacological adjuvants into diabetic vitrectomy can significantly enhance surgical outcomes and postoperative recovery. These therapies reduce intraoperative complications like bleeding and improve surgical precision while minimizing postoperative issues, including inflammation and fibrosis. Therefore, the incorporation of these adjunctive treatments into routine clinical practice is crucial for improving patient care, lowering complication rates, and enhancing long-term visual outcomes for those undergoing diabetic vitrectomy.

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INTRODUCTION

The field of diabetic vitrectomy surgery is evolving with the introduction of pharmacological adjuvants, as highlighted by Venkatesh *et al*[1]. Diabetic retinopathy, a leading cause of global blindness, often requires vitrectomy to address complications such as vitreous hemorrhage and tractional retinal detachment. Traditional surgical techniques face challenges like intraoperative bleeding and postoperative complications[1-3]. Pharmacological adjuvants offer promising solutions by reducing bleeding, enhancing visualization, and promoting retinal healing[4,5]. Venkatesh *et al*[1] provided a comprehensive review of these therapies, evaluating their efficacy and safety, underscoring their potential to transform diabetic vitrectomy practices[6]. Integrating these advancements into clinical protocols could simplify surgery and improve patient outcomes globally[7,8]. This editorial synthesizes key insights from recent research, highlighting the transformative role of pharmacological adjuvants in diabetic vitrectomy and advocating for their integration into standard surgical practice[9,10].

CURRENT CHALLENGES IN DIABETIC VITRECTOMY

Diabetic vitrectomy presents numerous challenges due to the complex pathology of diabetic retinopathy. A major issue is intraoperative bleeding, which obscures the surgical field and increases the risk of complications[2]. The presence of fibrovascular membranes adds further complexity, requiring delicate dissection to minimize retinal damage[4]. Incomplete vitreous clearance also remains a significant concern, contributing to postoperative complications like proliferative vitreoretinopathy (PVR) and macular edema[3]. Traditional surgical techniques, while effective, are limited in addressing these issues. Studies have demonstrated that preoperative anti-vascular endothelial growth factor (anti-VEGF) agents, such as ranibizumab, reduce intraoperative bleeding by decreasing neovascularization in fibrovascular membranes[6]. Enzymatic vitreolysis using reengineered collagenases offers an innovative method for improving vitreous clearance, reducing the need for mechanical manipulation[4]. Also, *in situ* cross-linked hyaluronan hydrogel shows promise in facilitating posterior vitreous detachment, aiding in vitreous removal[5]. Pharmacological adjuvants like mitomycin C have also been explored for their potential to prevent postoperative fibrosis and PVR, improving both functional and anatomical outcomes[3]. High-density silicone oil is another approach used to manage severe proliferative diabetic retinopathy (PDR), though it carries risks such as increased intraocular pressure[11]. Despite these advances, significant challenges remain in diabetic vitrectomy. The integration of pharmacological adjuvants and innovative surgical techniques is crucial for improving outcomes and reducing postoperative complications. As research progresses, combining traditional methods with emerging therapies will likely enhance the safety and efficacy of diabetic vitrectomy [1].

ROLE OF PHARMACOLOGICAL ADJUVANTS

Pharmacological adjuvants play a crucial role in enhancing the efficacy of diabetic vitrectomy by addressing both intraoperative and postoperative challenges. Anti-VEGF agents, such as ranibizumab and bevacizumab, have proven effective in reducing intraoperative bleeding and facilitating the removal of fibrovascular membranes, both essential for successful outcomes in patients with PDR. These agents inhibit neovascularization, improving intraoperative visualization and reducing the risk of postoperative vitreous hemorrhage[2,6]. Preoperative anti-VEGF administration also appears to mitigate the angiogenic and fibrotic responses associated with diabetic retinopathy, enabling more precise and safer surgeries[2]. Corticosteroids, particularly dexamethasone implants, play a pivotal role in controlling postoperative inflammation, which accelerates patient recovery. Their anti-inflammatory effects help minimize the risk of macular edema and fibrosis, thus improving both functional and anatomical outcomes[12]. Mitomycin C, an antifibrotic agent, has also been shown to reduce the risk of PVR, improving surgical outcomes in cases of severe tractional retinal detachment [3]. Enzymatic vitreolysis is another innovative approach in diabetic vitrectomy. Reengineered collagenases, such as those derived from *Vibrio mimicus*, facilitate vitreous liquefaction, simplifying its removal and reducing the need for mechanical

manipulation. This approach lowers the risk of retinal tears and postoperative complications[4]. Alike, cross-linked hyaluronan hydrogels have been explored to ease posterior vitreous detachment, further improving surgical efficiency [5]. As well, novel therapies like fibrin glue show promise in reducing the risk of postoperative vitreous hemorrhage, a common complication after diabetic vitrectomy. By promoting clot stabilization and reducing intraocular bleeding, fibrin glue contributes to better surgical outcomes[13]. Overall, the integration of pharmacological adjuvants in diabetic vitrectomy not only enhances surgical precision but also improves patient outcomes by addressing the complexities of diabetic retinopathy. As research continues to advance, the role of these adjuvants in clinical practice will likely expand, offering new avenues for improving the management of diabetic eye disease[1].

EVIDENCE FROM RECENT STUDIES

Recent studies have deepened our understanding of the role pharmacological adjuvants play in improving outcomes in diabetic vitrectomy. Venkatesh *et al*[1] provided comprehensive evidence on the efficacy and safety of these adjuncts in vitrectomy for diabetic retinopathy. Their research highlighted significant improvements in surgical success rates, visual acuity, and reductions in complications compared to traditional methods without adjuvants, underscoring the potential of these agents to mitigate the complexities of diabetic retinopathy surgery and enhance patient care. Similarly, Fadakar *et al*[2] investigated the effects of preoperative anti-VEGF treatment on fibrovascular membranes in patients with PDR. Their study found that anti-VEGF therapy not only reduces intraoperative bleeding but also modulates the angiogenic and fibrotic environment, contributing to more successful surgical outcomes. This aligns with the findings of Gao *et al*[6], who demonstrated the benefits of combining intravitreal ranibizumab with vitrectomy, particularly in cases involving neovascular glaucoma and diabetic vitreous hemorrhage. These therapies have been linked to improved anatomical and functional outcomes, further validating their role in enhancing surgical precision and reducing postoperative complications. Santra *et al*[4] explored enzymatic vitreolysis with collagenase to facilitate vitreous detachment in diabetic patients, showing promise in simplifying the surgical process. Building on this, Hisatomi *et al*[5] developed *in situ* cross-linked hyaluronan hydrogels, which aid in removing the posterior vitreous cortex, reducing the complexity of diabetic vitrectomy. Further supporting the use of pharmacological adjuvants, Gurelik *et al*[3] demonstrated that mitomycin C improves both functional and anatomical outcomes in patients with severe diabetic tractional retinal detachment, a challenging complication of PDR. Collectively, these studies underscore the importance of integrating pharmacological adjuvants into diabetic vitrectomy practice. These agents not only enhance surgical success rates and improve patient outcomes but also reduce the risk of complications such as recurrent hemorrhage and fibrosis. However, continued research is needed to fully elucidate their long-term benefits and refine optimal protocols for their use in clinical settings.

CLINICAL IMPLICATIONS AND ADOPTION CHALLENGES

Pharmacological adjuvants in diabetic vitrectomy have shown significant potential in improving surgical outcomes. Agents like anti-VEGF therapies (*e.g.*, ranibizumab and conbercept) and enzymatic vitreolysis agents help reduce intraoperative complications by facilitating the removal of fibrovascular membranes and controlling bleeding[1,2]. However, several challenges hinder their widespread adoption in clinical practice. One of the main barriers is the high cost associated with these treatments. Anti-VEGF medications are expensive, raising concerns about cost-effectiveness, particularly in regions with limited healthcare resources[1,6]. This financial burden restricts access for many patients, making it crucial for healthcare providers to balance the benefits of these therapies against their costs. As well, variability in efficacy across patient populations presents another challenge. While anti-VEGF agents improve outcomes for many, their effectiveness can depend on factors such as the timing of administration and disease severity[2,8]. For instance, preoperative anti-VEGF injections significantly reduce intraoperative bleeding in patients with PDR[2], but outcomes may vary based on individual patient characteristics. This variability necessitates a personalized approach, complicating efforts to standardize these treatments in clinical practice. A further concern is the lack of comprehensive long-term safety data. While short-term studies show promising results, particularly in reducing postoperative complications like macular edema, the long-term effects of repeated anti-VEGF injections or enzymatic vitreolysis remain under investigation[4,14]. There are concerns about potential adverse outcomes, including an increased risk of fibrosis or retinal detachment, which complicates the adoption of these therapies without more extensive evidence. Regulatory challenges also contribute to the slow adoption of newer pharmacological adjuvants, such as hyaluronan-based hydrogels. Issues with approval and regional availability make it difficult to integrate these therapies into routine care[5,7]. Healthcare providers must navigate these regulatory landscapes while staying updated on emerging pharmacological options to ensure the best care for their patients. To address these challenges, further research is essential. Ongoing clinical trials and studies are critical for refining treatment protocols, optimizing dosing strategies, and clarifying the long-term safety profiles of adjuvant therapies[1]. Large-scale, multicenter studies could help mitigate the variability in treatment outcomes and provide more definitive evidence to support broader adoption[3]. Additionally, developing cost-effective models and securing wider regulatory approval for innovative agents could enhance their clinical utility. Overall, while pharmacological adjuvants hold great promise in diabetic vitrectomy, their integration into routine practice faces barriers related to cost, variable efficacy and safety concerns. Ongoing research, along with collaborative efforts between clinicians, researchers and policymakers, is crucial to overcoming these challenges and ensuring that patients benefit from these advancements in diabetic retinopathy management.

FUTURE DIRECTIONS AND RESEARCH OPPORTUNITIES

The future of pharmacological adjuvants in diabetic vitrectomy is set to advance significantly through a comprehensive research strategy. A key focus will be refining existing therapies while exploring new agents and combination treatments to address the complexities of diabetic retinopathy. For example, ongoing work with hyaluronan-based hydrogels aims to simplify posterior vitreous cortex removal, potentially improving surgical outcomes[5]. Equally, research into reengineered collagenase demonstrates the promise of enzymatic vitreolysis for safer, more effective procedures[4]. Future studies should emphasize long-term efficacy and safety, particularly concerning outcomes like recurrence rates and visual stability. Randomized clinical trials will be critical in assessing the sustained benefits of preoperative anti-VEGF injections and other adjuvants, with early data suggesting reductions in intraoperative complications and postoperative inflammation[2]. Large-scale comparisons of agents like conbercept and ranibizumab are also needed to establish standardized protocols for different stages of diabetic retinopathy[6,8]. Moreover, research should explore the integration of pharmacological adjuvants with emerging surgical techniques. Combination therapies, such as intravitreal steroids with vitrectomy, could enhance both anatomical and functional outcomes by mitigating postoperative complications like macular edema[15]. Furthermore, the use of mitomycin C in conjunction with vitrectomy for severe tractional retinal detachment shows potential for improving functional results[3]. Another important area for research is the assessment of quality-of-life measures and patient-reported outcomes. Since diabetic retinopathy often requires long-term management and multiple interventions, understanding how pharmacological adjuvants affect patients' daily lives and overall satisfaction is essential. Incorporating these patient-centered outcomes into clinical trials will guide treatment decisions and ensure that new therapies align with patient needs and expectations[1]. To drive these innovations, interdisciplinary collaboration is crucial. Partnerships between ophthalmologists, pharmacologists and bioengineers will accelerate the development of advanced drug delivery systems and more effective adjuvants. Such collaboration will ensure a holistic approach to diabetic vitrectomy, moving the field toward more personalized and patient-centered care[7]. In brief, advancing the role of pharmacological adjuvants in diabetic vitrectomy requires robust clinical research and cross-disciplinary innovation. By focusing on long-term efficacy, personalized treatment approaches, and enhancing patient-reported outcomes, the field can improve the surgical management of diabetic retinopathy, ultimately delivering better visual outcomes and quality of life for patients.

CONCLUSION

The integration of pharmacological adjuvants into diabetic vitrectomy surgery marks a significant advancement in enhancing surgical outcomes and elevating patient care standards. As detailed, these adjunctive therapies effectively address critical challenges such as intraoperative bleeding, postoperative inflammation and complications associated with diabetic retinopathy (Table 1). The comprehensive review by Venkatesh *et al*[1] substantiates their efficacy and safety, providing a strong foundation for their strategic implementation in clinical practice[6]. Looking ahead, healthcare providers must navigate the challenges of adopting these therapies while leveraging evolving evidence to tailor treatment strategies that effectively meet individual patient needs. Continued research efforts are crucial for refining existing adjuvants, exploring novel therapeutic avenues, and establishing comprehensive guidelines for their optimal use[5,16]. Longitudinal studies focusing on long-term outcomes and patient-reported quality of life will further enhance clinical decision-making in this evolving field. In conclusion, incorporating pharmacological adjuvants into diabetic vitrectomy protocols holds great promise for significantly improving surgical outcomes and ultimately enhancing the quality of life for patients with diabetic retinopathy. By embracing these advancements, healthcare providers can achieve superior visual outcomes and effectively alleviate the global burden of diabetic eye disease[4,8].

Table 1 Comparison of novel and traditional treatment modalities for diabetic retinopathy: Advantages and disadvantages

Treatment modality	Advantages	Disadvantages	Ref.
Novel: Pharmacological adjuvants in vitrectomy	Enhances vitreous clarity, improving surgical visibility; mitomycin C and other agents can improve functional outcomes	Adverse effects such as retinal toxicity in some cases; not universally adopted	Venkatesh *et al*[1], 2024; Gurelik *et al*[3], 2024
Novel: Anti-VEGF therapy	Reduces neovascularization and macular edema; short-term reduction in angiogenic and fibrotic factors in fibrovascular membranes	Requires repeated injections; potential ocular pain with multiple intravitreal injections	Fadakar *et al*[2], 2024; Zhou *et al*[14], 2024; Damasceno *et al*[17], 2024
Novel: Hyaluronan hydrogel adjuvant in vitrectomy	Facilitates easier removal of posterior vitreous cortex; biocompatible and injectable, improving surgical outcomes	Still under clinical evaluation; potential complications in certain patients	Hisatomi *et al*[5], 2024; Suzuki *et al*[7], 2023
Novel: Conbercept and ranibizumab pre-vitrectomy	Enhances anatomical outcomes by reducing vitreous hemorrhage; improves outcomes in complex cases such as neovascular glaucoma	Costly and not universally accessible; timing of administration critical for efficacy	Gao *et al*[6], 2023; Yang *et al*[8], 2023; Wang *et al*[16], 2023
Traditional: Laser photocoagu-	Well-established, reduces risk of vision loss	Can cause permanent retinal scarring;	Venkatesh *et al*[1], 2024;

lation	from proliferative diabetic retinopathy	limited effect on macular edema	Chauhan *et al*[18], 2024
Traditional: Pars plana vitrectomy	Effective in treating advanced proliferative diabetic retinopathy; can remove vitreous hemorrhage and fibrovascular tissue	High risk of complications, including postoperative vitreous hemorrhage; prolonged recovery period	Mansour *et al*[13], 2023; Rohowetz *et al*[19], 2024; Thapa *et al*[20], 2024
Traditional: Intravitreal steroids	Reduces inflammation and macular edema; long-lasting effect compared to anti-VEGF	Increases risk of intraocular pressure elevation; risk of cataract formation	Salvetat *et al*[12], 2024; Wang *et al*[15], 2024

This table compares the advantages and disadvantages of novel and traditional treatments for diabetic retinopathy. Novel therapies, including pharmacological adjuvants and anti-vascular endothelial growth factor agents, offer advancements in managing complications but may involve higher costs and specific risks. Traditional approaches, such as laser photocoagulation and pars plana vitrectomy, remain effective but have limitations, including retinal scarring and extended recovery times. References are provided for further review of the supporting evidence. VEGF: Vascular endothelial growth factor.

FOOTNOTES

Author contributions: Cheng CY and Hao WR contributed equally to this editorial, with both authors collaboratively drafting the initial content and structuring the editorial's key messages. Hao WR and Cheng TH provided critical oversight during the revision process, ensuring the editorial accurately reflected recent advances in the field and maintained high scientific integrity. Cheng CY, Hao WR, and Cheng TH were actively involved in refining the content and enhancing the clarity of the argument. All authors read and approved the final manuscript. As co-corresponding authors, Hao WR and Cheng TH equally contributed to the editorial's conceptual direction, revision process, and approval, ensuring the editorial's alignment with the latest research and clinical practices.

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EDITORIAL

Advancements in diabetic retinopathy: Insights and future directions

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Abstract

This editorial discusses recent advancements and ongoing challenges in diabetic retinopathy, as reviewed by Morya *et al* in their comprehensive analysis. In their review, Morya *et al* discussed the pathophysiology of diabetic retinopathy and explored novel treatment modalities. This editorial highlights the importance of these advancements and emphasizes the need for continued research and innovation for the enhanced management of diabetic retinopathy. It also reflects upon the implications of the authors' review findings for clinical practice and future research directions, underscoring the potential of emerging therapies for improving patient outcomes and providing a deeper understanding of disease mechanisms.

Key Words: Diabetic retinopathy; Pathophysiology; Novel treatments; Review analysis; Clinical implications

Core Tip: This editorial provides key insights into the review of diabetic retinopathy by Morya *et al*, emphasizing advancements in pathophysiology and emerging treatment strategies, and discusses their clinical implications of emerging therapies for improving patient outcomes.

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INTRODUCTION

Diabetic retinopathy remains a leading cause of vision impairment and blindness worldwide, primarily due to diabetes mellitus. This chronic, progressive condition results from prolonged hyperglycemia, which causes retinal vascular damage. Understanding the complex pathophysiological mechanisms underlying diabetic retinopathy is essential for developing effective treatment strategies. Morya *et al*[1] provide a comprehensive review of these mechanisms, along with the latest therapeutic advancements, offering a critical overview of emerging treatments aimed at more effectively combating diabetic retinopathy. This editorial situates the findings of Morya *et al*[1] within the broader context of diabetic retinopathy research. By examining their review, we gain a clearer understanding of the evolving strategies for managing diabetic retinopathy and identifying gaps in current treatment protocols. Recent studies have introduced innovative approaches, such as nanotechnology-based drug delivery systems for treating posterior segment ocular diseases[2] and glucose-responsive hydrogels that inhibit retinal blood-retinal barrier injury[3]. Additionally, predictive models for type 2 diabetic retinopathy have been externally validated, providing new tools for early diagnosis and intervention[4]. The integration of deep learning and language models into primary diabetes care has also shown promise in improving diagnostic accuracy and patient outcomes[5]. Advances in imaging techniques, such as widefield optical coherence tomography angiography, have further enhanced our ability to assess the severity of diabetic retinopathy[6]. These technological advancements underscore the ongoing need for innovation and research in this critical area of ophthalmology. By analyzing the contributions of Morya *et al*[1] and other recent studies, we can better appreciate the progress in the field and recognize the importance of continued research to address the challenges of diabetic retinopathy. This editorial will explore the implications of these advancements for clinical practice, emphasizing the need for sustained efforts to refine treatment strategies for diabetic retinopathy.

ADVANCES IN PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY

Morya *et al*[1]'s review provides a comprehensive analysis of the complex mechanisms driving diabetic retinopathy. It emphasizes the interplay of chronic hyperglycemia, oxidative stress, and inflammation in retinal damage. A key aspect of this process is the accumulation of advanced glycation end-products (AGEs), which activate inflammatory pathways and contribute to diabetic retinopathy progression. Understanding these mechanisms is crucial for identifying effective therapeutic targets[1]. Hyperglycemia plays a central role in diabetic retinopathy pathogenesis by increasing oxidative stress and generating reactive oxygen species (ROS). These ROS exacerbate cellular damage and inflammation, creating a vicious cycle that accelerates retinal degeneration. Additionally, hyperglycemia-induced oxidative stress promotes AGE formation, which binds to receptors (RAGEs) on retinal cells, triggering inflammatory responses that lead to increased vascular permeability and neovascularization[2,3]. Inflammation is a significant driver of diabetic retinopathy progression. The activation of transcription factors like nuclear factor kappa B (NF-κB) upregulates pro-inflammatory cytokines and adhesion molecules, promoting leukostasis, endothelial dysfunction, and vascular permeability — hallmarks of diabetic retinopathy. Recent studies have identified various inflammatory mediators, such as interleukins, tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF), as potential therapeutic targets[7,8]. Innovative research has also highlighted the role of epigenetic modifications and microRNAs in diabetic retinopathy. These molecular changes alter gene expression, contributing to the chronic inflammatory state seen in the disease. Targeting specific microRNAs and epigenetic regulators holds promise for developing new therapies that could halt or even reverse diabetic retinopathy progression[9]. Morya *et al*[1]'s review underscores the importance of understanding the multifaceted pathophysiology of diabetic retinopathy. By dissecting the roles of hyperglycemia, oxidative stress, and inflammation, this research lays the foundation for developing targeted therapies. Future treatments are likely to focus on disrupting these pathogenic pathways, offering more precise and effective interventions for diabetic retinopathy[1].

NOVEL TREATMENT MODALITIES FOR DIABETIC RETINOPATHY

Morya *et al*[1]'s review provides a significant contribution by detailing the latest advancements in treatment options for diabetic retinopathy, highlighting a shift towards more targeted interventions aimed at improving patient outcomes. Key

among these advancements are anti-VEGF agents, corticosteroids, and emerging gene therapies, which mark a departure from traditional treatment methods (Table 1). Anti-VEGF therapies, such as ranibizumab and aflibercept, have become foundational in diabetic retinopathy management. These agents inhibit VEGF, a key driver of pathological neovascularization and increased vascular permeability. Clinical studies have demonstrated their effectiveness in reducing retinal edema and preventing vision loss, making them a cornerstone of diabetic retinopathy treatment[2,10]. Corticosteroids, including dexamethasone implants and intravitreal triamcinolone, provide another potent treatment option by modulating the inflammatory response and reducing vascular leakage. However, their use is often limited by side effects, such as cataract formation and increased intraocular pressure, necessitating careful patient selection and monitoring[5, 11]. Emerging gene therapies represent a promising frontier in diabetic retinopathy treatment. These approaches aim to correct underlying genetic defects or modulate gene expression to prevent or reverse retinal damage. Techniques such as CRISPR/Cas9-mediated gene editing and adeno-associated virus vector-based gene delivery are being explored for their potential to offer long-lasting solutions with fewer side effects than traditional therapies. Although still in experimental stages, early results suggest these therapies could have a transformative impact on diabetic retinopathy management[2, 3]. Innovative drug delivery systems, including nanoparticles and sustained-release formulations, are enhancing the effectiveness of existing treatments. These technologies improve the bioavailability and duration of therapeutic agents, reducing the frequency of intravitreal injections and associated complications. For example, nanotechnology has been used to develop biodegradable nanoparticles that deliver anti-VEGF drugs more efficiently, potentially lowering the treatment burden for patients[2]. While these novel treatments offer substantial benefits, they also present challenges. The high cost of anti-VEGF agents and gene therapies can limit accessibility, particularly in low-resource settings. Additionally, the long-term safety profiles of these new interventions remain to be fully established, requiring ongoing research and post-market surveillance. Individualized treatment plans that consider patient-specific factors such as disease stage, genetic predisposition, and comorbidities are essential for optimizing outcomes[1,5]. Overall, Morya *et al*[1] 's review underscores the potential of novel therapies to revolutionize diabetic retinopathy treatment. By critically analyzing these advancements and comparing them to traditional approaches, the review provides valuable insights into the efficacy, safety, and accessibility of these interventions. The continued evolution of these treatment modalities holds great promise for significantly improving the quality of life for patients with diabetic retinopathy[1].

DOSAGE AND TIMING OF PHARMACOLOGICAL ADJUVANTS

Recent advances in diabetic retinopathy therapies have underscored the importance of pharmacological adjuvants, particularly anti-VEGF agents and corticosteroids, in managing diabetic retinopathy-associated edema and neovascularization. While these therapies have proven effective, optimizing their dosage and timing remains a key challenge in maximizing therapeutic outcomes while minimizing adverse effects. Morya *et al*[1] reviewed the current landscape of pharmacological interventions, emphasizing the need for more refined strategies, especially regarding adjuvant therapies. Studies exploring anti-VEGF treatments, such as those by Shiraki *et al*[11] and Wu *et al*[2], reveal variability in both dosage frequency and quantity, with protocols ranging from monthly injections to extended-interval dosing based on individual patient response. For example, Li *et al*[5] found that while higher doses of anti-VEGF agents can produce more immediate therapeutic effects, they also increase the risk of complications like retinal atrophy. Similarly, corticosteroid therapies, often employed to reduce inflammation, present challenges in achieving standardized dosing. Shiraki *et al*[11] reported that the timing of corticosteroid administration can significantly influence outcomes. Some studies suggest early intervention may lead to better edema resolution, while others point to potential risks of ocular hypertension and cataract formation with prolonged use. Innovative drug delivery systems, such as nanotechnology-based methods highlighted by Wu *et al*[2], offer promising solutions for improving the efficacy and safety of adjuvant therapies. These systems allow for controlled, sustained release of therapeutic agents, reducing the frequency of injections and potentially improving patient compliance. Glucose-responsive hydrogels, discussed by Zhou *et al*[3], also provide a novel, physiologically responsive method for drug delivery, further reducing variability in treatment outcomes. Given the wide variability in dosages and outcomes across these studies, further research is needed to develop more consistent treatment protocols. Future trials should focus on identifying optimal dosing regimens tailored to individual patient needs, taking into account factors such as disease severity, comorbidities, and response to initial treatments. Standardizing these protocols will be essential to ensuring both the safety and efficacy of pharmacological adjuvants in diabetic retinopathy management.

LIMITATIONS OF PHARMACOLOGICAL ADJUVANTS IN DIABETIC RETINOPATHY TREATMENT

Pharmacological adjuvants, such as anti-VEGF agents and corticosteroids, have significantly advanced the treatment of diabetic retinopathy. However, their widespread use faces critical challenges, including high costs, limited accessibility, variable patient response, and potential side effects. These factors limit their overall efficacy across diverse populations. One of the major barriers to the accessibility of anti-VEGF treatments is their financial burden, particularly in resource-limited settings. Morya *et al*[1] emphasize that the high cost of these therapies prevents patients in lower-income regions from accessing essential treatments, exacerbating global health inequities in diabetic retinopathy care. The need for recurrent monthly or bi-monthly injections adds to this financial strain on both healthcare systems and patients. As Shiraki *et al*[11] note, despite their proven efficacy, the affordability and availability of anti-VEGF therapies remain inconsistent, particularly in regions with less-developed healthcare infrastructures. In these areas, the prohibitive costs may cause patients to delay or forgo treatment, increasing the risk of vision loss. This gap underscores the urgent need for

Table 1 Comparative analysis of novel and traditional treatment modalities for diabetic retinopathy

Treatment modality	Description	Advantages	Limitations	Ref.
Anti-vascular endothelial growth factor (VEGF) agents	Inhibits VEGF to reduce neovascularization and vascular permeability	Effective in reducing retinal edema and preventing vision loss	High cost; requires frequent intravitreal injections; long-term safety not fully established	Morya *et al*[1], 2024; Wu *et al*[2], 2024; and Hartnett *et al*[10], 2024
Corticosteroids	Reduces inflammation and vascular leakage. Includes dexamethasone implants and intravitreal triamcinolone	Potent anti-inflammatory effects; effective in reducing retinal edema	Risk of cataract formation and increased intraocular pressure; requires careful patient selection and monitoring	Shiraki *et al*[11], 2024; and Li *et al*[5], 2024
Gene therapies	Corrects genetic defects or modulates gene expression to prevent/reverse retinal damage	Potential for long-lasting solutions; fewer side effects compared to traditional therapies	Experimental stages; high cost; accessibility issues; long-term effects unknown	Wu *et al*[2]; and Zhou *et al*[3], 2024
Nanotechnology-based drug delivery	Utilizes nanoparticles for efficient drug delivery and sustained-release formulations	Improved bioavailability and duration of therapeutic agents; reduces frequency of injections	Still under research; long-term safety and efficacy data needed	Wu *et al*[2], 2024
Traditional laser therapy	Uses laser photocoagulation to prevent neovascularization	Long-standing treatment; can prevent severe vision loss	Can cause peripheral vision loss and other complications; less effective in advanced stages	Morya *et al*[1], 2024
Vitrectomy	Surgical removal of vitreous gel to manage severe cases	Effective in clearing vitreous hemorrhage and relieving traction on the retina	Invasive procedure; risks include retinal detachment and infection	Morya *et al*[1], 2024; and Shiraki *et al*[11], 2024
Oral medications (*e.g.*, Fenofibrate)	Used to manage dyslipidemia and inflammation associated with diabetic retinopathy	Convenient; can reduce the progression of diabetic retinopathy in some patients.	Variable effectiveness; side effects may include liver dysfunction and muscle pain	Morya *et al*[1], 2024

This table offers a comprehensive comparison of treatment options for diabetic retinopathy, contrasting novel therapies with traditional methods. Anti-vascular endothelial growth factor agents, such as ranibizumab and aflibercept, work by inhibiting vascular endothelial growth factor, which reduces neovascularization and vascular permeability. While these agents are highly effective at reducing retinal edema and preventing vision loss, they are costly and require frequent injections[1,2,10]. Corticosteroids, including dexamethasone implants and intravitreal triamcinolone, help reduce inflammation and vascular leakage. However, they carry risks such as cataract formation and increased intraocular pressure, necessitating careful patient selection and monitoring[5,11]. Emerging gene therapies offer a cutting-edge approach by targeting genetic defects or modulating gene expression, potentially providing long-lasting solutions with fewer side effects. Despite their promise, these therapies are still in experimental stages, are expensive, and have unknown long-term safety profiles[2,3]. Nanotechnology-based drug delivery systems utilize nanoparticles and sustained-release formulations to enhance drug bioavailability and extend therapeutic duration. Although these innovations improve the efficiency of drug delivery, further research is required to validate their long-term efficacy and safety[2]. Traditional laser therapy, through laser photocoagulation, remains a common method to prevent neovascularization. While effective at preventing severe vision loss, it may lead to complications like peripheral vision loss, especially in advanced stages of diabetic retinopathy[1]. Vitrectomy, a surgical intervention to remove the vitreous gel, is beneficial in managing severe cases by addressing vitreous hemorrhage and relieving retinal traction. However, this invasive procedure carries risks such as retinal detachment and infection[1,11]. Oral medications, like fenofibrate, are used to address dyslipidemia and inflammation linked to diabetic retinopathy. These medications are convenient and can slow disease progression in some patients, though their effectiveness varies, and they may come with side effects[1].

cost-effective alternatives, such as biosimilars or locally produced drugs, to improve equitable access to care. Another complication in the use of pharmacological adjuvants is the variability in patient response. Li *et al*[5] report that while anti-VEGF therapies are effective for many, a subset of patients fails to respond adequately, necessitating alternative treatments. This variability is likely influenced by factors such as disease progression, genetic differences, and comorbidities. Research into predictive biomarkers, such as the study by Zhang *et al*[12], could help identify patients more likely to benefit from specific treatments. However, until precision medicine approaches are more widely available, physicians must rely on trial-and-error methods, which may delay optimal treatment. The potential for adverse effects further complicates the use of pharmacological adjuvants. Corticosteroids, although effective in reducing inflammation, carry risks of ocular hypertension, cataract formation, and glaucoma, especially with long-term use. While anti-VEGF agents are generally safer, they are not without risks. Complications such as endophthalmitis, retinal detachment, and increased intraocular pressure, although rare, have been reported. Furthermore, contraindications, particularly in patients with a history of stroke, myocardial infarction, or other vascular events, limit the application of these therapies in high-risk populations. Wu *et al*[2] suggest that advanced drug delivery systems, such as nanotechnology-based formulations, may help mitigate some of these side effects by allowing more targeted, controlled release of the drugs. However, these innovations remain in early stages and are not yet widely available. Given these challenges, the development of more affordable, accessible, and safer alternatives to current pharmacological adjuvants is imperative. Zhou *et al*[3] propose innovations like glucose-responsive hydrogels, which offer promising solutions by enabling sustained, physiologically responsive drug delivery, thereby reducing both the frequency of administration and associated risks. Additionally, biosimilar drugs present a cost-effective alternative to brand-name anti-VEGF agents, though more research is required to

confirm their long-term efficacy and safety. While pharmacological adjuvants have revolutionized diabetic retinopathy treatment, their high costs, unequal accessibility, variability in patient response, and potential side effects highlight the need for continued innovation and standardization. Future research should focus on developing cost-effective therapies and refining treatment protocols to ensure that patients from all socioeconomic backgrounds can benefit from these advancements.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

The editorial offers a comprehensive analysis of diabetic retinopathy management, presenting critical insights for clinical practice. A key takeaway is the growing importance of incorporating advanced therapies — such as anti-VEGF agents, corticosteroids, and gene therapies — into routine care. These novel treatments hold promise for improving outcomes by providing more targeted care, which is essential for managing diabetic retinopathy progression. Additionally, the editorial emphasizes the value of personalized treatment approaches. Tailoring care to a patient's genetic and metabolic profile not only enhances therapeutic efficacy but also reduces the risk of adverse effects. This personalized strategy underscores the need for further research into biomarkers and genetic predictors of treatment response, a field with great potential to refine diabetic retinopathy management[1]. The editorial also highlights advancements in diagnostic tools, particularly the use of optical coherence tomography angiography, which enables earlier detection and continuous monitoring of diabetic retinopathy progression. Integrating such technologies into routine clinical workflows could help identify patients at risk for severe complications and ensure timely interventions, thereby improving long-term outcomes [5]. However, the editorial notes that diabetic retinopathy management is still evolving, particularly in terms of optimizing combination therapies and treatment regimens. Current treatments, while promising, require further evaluation to determine the most effective dosages and combinations, especially when anti-VEGF agents are used alongside corticosteroids or gene therapies[2,11]. Future clinical trials should focus on these areas to clarify the most effective therapeutic strategies. A significant challenge in diabetic retinopathy treatment is ensuring patient adherence to prescribed regimens. Improving patient education and developing more accessible treatment options — such as sustained-release drug delivery systems — could enhance outcomes. Research into the psychosocial factors influencing adherence and interventions designed to improve it will be crucial for ensuring treatment success[3]. While the editorial draws on secondary sources, it underscores the need for empirical validation through clinical trials and long-term studies. Future research should investigate the integration of pharmacological adjuvants into surgical protocols, exploring how newer agents might offer additional therapeutic benefits. Researchers are encouraged to explore these areas to advance diabetic retinopathy treatment further[13,14]. By advocating for continued innovation, personalized care, and patient-centered approaches, the editorial provides a roadmap for future research that could bridge current gaps in knowledge and lead to improved patient outcomes.

CONCLUSION

The review by Morya *et al*[1] offers significant advancements in our understanding of diabetic retinopathy, particularly in elucidating its pathophysiological mechanisms and exploring novel treatment modalities. Their analysis highlights the complex relationships between hyperglycemia, oxidative stress, and inflammatory processes, providing critical insights into the progression of the disease[1]. By detailing the roles of AGEs and inflammatory pathways, the review delivers a comprehensive view of the cellular and molecular mechanisms driving diabetic retinopathy[5,11]. Furthermore, the review underscores the transformative potential of emerging therapies, including targeted treatments like anti-VEGF agents, corticosteroids, and gene-based therapies, in improving patient outcomes[2,3]. These approaches represent a departure from traditional methods, offering more precise and effective strategies to manage diabetic retinopathy and reduce the risk of vision impairment and blindness associated with the disease[10]. Looking ahead, it is essential to integrate these findings into clinical practice to enhance diabetic retinopathy management. The adoption of personalized medicine, which leverages genetic and biomarker data, can optimize treatment regimens and improve therapeutic outcomes[3]. Continued research is necessary to address remaining challenges, such as refining combination therapies and improving patient adherence to treatment protocols[11]. A multidisciplinary approach, combining scientific innovation with clinical application, will be key to furthering progress in this field. Collaboration among researchers, clinicians, and healthcare providers is critical to translating these advancements into meaningful improvements in patient care[1,2]. By fostering innovation and integrating cutting-edge research into practice, we can significantly enhance outcomes for individuals affected by diabetic retinopathy and help reduce the global burden of this debilitating condition.

FOOTNOTES

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REVIEW

Gut virome: New key players in the pathogenesis of inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory illness of the intestine. While the mechanism underlying the pathogenesis of IBD is not fully understood, it is believed that a complex combination of host immunological response, environmental exposure, particularly the gut microbiota, and genetic susceptibility represents the major determinants. The gut virome is a group of viruses found in great frequency in the gastrointestinal tract of humans. The gut virome varies greatly among individuals and is influenced by factors including lifestyle, diet, health and disease conditions, geography, and urbanization. The majority of research has focused on the significance of gut bacteria in the progression of IBD, although viral populations represent an important component of the microbiome. We conducted this review to highlight the viral communities in the gut and their

expected roles in the etiopathogenesis of IBD regarding published research to date.

Key Words: Inflammatory bowel disease; Pathogenesis; Gut virome; Bacteriophage; Eukaryotic viruses

Core Tip: Inflammatory bowel disease (IBD) is a chronic multifactorial inflammatory disease involving the gastrointestinal tract. The exact etiopathogenesis is unknown, but it's believed that gut microbiome dysbiosis is a cornerstone in triggering disease progression. The gut virome forms a significant part of the gut microbiome and participate in health and disease conditions. Until 2015, researchers paid little attention to their role in IBD. Subsequently, numerous studies have followed this line of inquiry, using advanced techniques to clarify this role. Herein, we emphasize the viral populations in the gut and their predicted roles in the etiopathogenesis of IBD based on current studies.

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic condition characterized by chronic inflammation of the gastrointestinal tract (GIT)[1]. The precise etiology of IBD is complex and still not fully understood. However, studies have revealed that the onset and course of IBD are controlled by a variety of factors, including the interaction between environmental factors (*e.g.*, intestinal microbiota) and the host immune response in genetically susceptible people[2-6]. After birth and in the early days of life, the gut microbiota begins to colonize the GIT, where they coexist in an equilibrium process and actively interact with the host[7]. In healthy settings, the composition of microbiota changes until adulthood, when it becomes more stable[8]. In particular, the gut microbiota maintains the integrity of the gut barrier, promotes the generation of nutrients (*e.g.*, short-chain fatty acids [SCFAs] and vitamins), regulates the immunological response, and participates in the metabolism of drugs and nondigestible food, and defense against pathogenic organisms[9,10]. Typically, gut microbiota consists of bacteria, viruses, fungi, and archaea. Bacteria have received the most attention from these microbes and have been associated with developing mucosal immunity and reducing mucosal inflammation[11-14]. An abnormality in one of these immunological pathways can have a negative impact on IBD development. For instance, alterations in the function of the bacterial microbiome or a decrease in *Bacteroidetes* and *Firmicutes* levels and an increase in less prevalent bacterial species (spp.) have all been linked to IBD[15]. Nonbacterial elements of the gut microbiota have been neglected in previous studies for a variety of reasons, including their low absolute prevalence in the intestinal microbiota of humans and a scarcity of competent and specific diagnostic methods for nonbacterial genome analysis[16].

Early studies defining the gut microbiota focused on culturing bacteria, which had little success since only a tiny fraction of gut microbes can be cultivated[17]. Following that, in the early 2000s, next-generation sequencing technology emerged and allowed scientists to investigate the diversity of gut microbiota. This scientific advancement led to the emergence of the "microbiome" era, which aims to study the whole microbial genomes, paving the way for the development of the subfield of "virome research"[18]. The gut virome is still a little-studied subsection of the whole microbiome despite this significant development[19]. Regardless of the lack of representation, several publications have demonstrated that a disturbed gut virome is linked to several illnesses including type 1 and type 2 diabetes[20,21], cystic fibrosis[22], obesity[23,24], graft *vs* host disease[25], acquired immunodeficiency syndrome[26], colorectal cancer[27], malnutrition[28], liver diseases[29], severe acute respiratory syndrome coronavirus 2[30], as well as IBD[31].

This review provides deep insights into gut virome dysbiosis and its role in the etiopathogenesis of IBD.

AN OVERVIEW OF THE GUT VIROME

The GI system has a complex ecosystem, including bacteria, viruses, fungi, and protozoans. The overall GI microorganism communities and their constituent genes are known as the gut microbiome[32]. The gut microbiome plays a key role in developing and maintaining homeostasis and a balanced immune system through interactions with epithelial and immune cells and regulating metabolic processes (such as SCFAs and bile acids)[33-35]. Viruses form a significant part of the gut microbiome and participate in maintaining homeostasis[36].

The two main forms of viruses in the gut microbiome are phages, which infect bacteria, and viruses, which infect eukaryotic cells (such as human cells). Although both kinds have been observed in the human GIT, phages account for the vast majority of viral spp.[37] Both forms either contain DNA or RNA (single or double strand) as genetic material

[38]. A phage enters its cellular host and uses its machinery to start its own reproduction process. There are two major lifecycles that characterize this process: lytic or lysogenic cycle[39]. The lytic cycle comprises attachment, entry, replication, and creation of virions, which are mainly completed through lysis of the host cell (Figure 1)[40]. The lysogenic cycle involves the formation of extrachromosomal plasmids in the cytoplasm or the integration of phage genetic material into the host genome[40]. The lysogenic cycle allows viruses to remain latent (as prophages), which ensures that the genetic material will be passed on to cellular progeny during cell division[37,41]. Induction of prophage happens either naturally at a low rate or is activated by outside stresses, initiating the DNA damage response or SOS response (Figure 1) [41,42]. Moreover, Erez *et al*[40] discovered the "arbitrium system," a phage-specific communication mechanism that enables the phages to detect their levels in the surroundings and choose whether to start the lytic or lysogenic cycle. Using this approach, phages lysogenize the host at high arbitrium concentrations and lyse the host at low arbitrium concentrations[40]. Prophage serves as a reservoir for phage-encoded genes that the bacterial host may acquire[43]. This genetic reservoir may have genes that increase stress tolerance and immunity, promote virulence and biofilm production, and provide metabolic and antibiotic resistance[44-48]. As a result, these acquired bacterial activities might be advantageous (as boosting immunity) or damaging (as virulence factors) to the human host[49]. For instance, prophages can protect bacterial host cells from subsequent infection from closely related phages[49]. Moreover, prophages have the ability to disseminate virulence components that turn some commensal gut microbiota into pathogenic ones[46,50]. For instance, phages from the *Inoviridae* family that encode cholera toxin can incorporate with the bacterial host, transport toxin genes, and produce dangerous organisms[50,51].

GUT VIROME IN NORMAL HEALTHY CONDITIONS

Each human has a large number of viruses, approximately 10^{13} particles per person, the majority of which are located in the gut[52-54]. According to growing data, the gut microbiome is initially quite basic, changes quickly during the first days after childbirth, and eventually becomes more diversified and stable over time[55-58]. Breitbart *et al*[59] conducted the first investigation documenting the gut phage population in fresh fecal samples in newborns. According to their investigation, the meconium, a newborn's initial fecal excretion, failed to include any virus-like particles (VLPs) when examined by a direct epifluorescence microscope. On the other hand, towards the end of the first week, 10^{8} VLPs per gram of moist feces were found[59].

Furthermore, in 2015, two additional studies revealed that the gut phage population exhibited considerable changes throughout the first 2 and 2.5 years of life, respectively[60,61]. Lim *et al*[60] documented the existence of the *Microviridae* family in the dominant phages in addition to the *Caudovirales* class, as well as a shift from *Caudovirales* to *Microviridae* at the first 24 mo of age. Additionally, they discovered that the abundance as well as diversity of intestinal phages were maximized in the first 4 d of life and subsequently declined as individuals aged[60].

Members of the phage classes *Malgrandaviricetes* (spherical single-strand DNA [ssDNA]) and *Caudovirales* (tailed double-strand DNA) make up the biggest known populations of viruses living in a healthy human GIT[57,62]. *Caudovirales* are believed to infect *Bacteroidetes, Firmicutes*, *Verrucomicrobia*, *Actinobacteria*, and *Proteobacteria*, while *Malgrandaviricetes* are believed to infect *Enterobacteria* or intracellular microorganisms (such as *Spiroplasma, Chlamydia,* and *bdellovibrio*)[63,64]. The crAss-like phage, a newly identified monophyletic clade within the *Caudovirale*s class, is thought to be the most abundant phage in the healthy human gut[62,65,66]. After the identification of crAss-like phages, several other prevalent and common viral clades, including *Flandersviridae*, *Gubaphag*e, *giant Lak phages*, and *LoVEphage*, were discovered[67-69]. Small circular ssDNA viruses, such as *Anelloviridae* and *Caudovirales*, are among the most common eukaryotic viruses[62,70]. It was reported that *Anelloviruses* are not particularly common, but they form a very diverse and common eukaryotic viral class at the beginning of life and are reduced gradually as the microbiome matures[63]. Plant viruses are another type of eukaryotic virus that is typically observed in elevated concentrations in the healthy human GIT[71]. They are often gained by food and passed to the GIT[62,72].

Viral complexity is defined by substantial interindividual variations or notable uniqueness of viral contigs[62,73]. While people significantly differ from one another, a person's virome can remain quite constant over time, as demonstrated by low intraindividual variance[74,75]. Generally, it is believed that the healthy gut microbiota is a diverse ecosystem, and any dysbiosis or imbalance in this ecosystem is frequently linked to the progression of diseases[76] such as IBD[6,77,78], irritable bowel syndrome[79-81], and colorectal cancer[82-84]. Although the patterns of diversity in the healthy gut virome are still out of reach, it is believed that they have a positive impact on the diversity of the microbiome [85].

ENVIRONMENTAL AND HOST FACTORS THAT AFFECT THE GUT VIROME

Many factors can affect and shape the gut virome. One of these is anthropometric factors that measure the physical properties of the host such as height, weight, age, and body mass index, among others[62,86,87]. Other factors can be divided into a number of main groups, including nutrition and its relationship to stool uniformity, lifestyle, and physical activity, diseases and medications, as well as geographical location[24,74,86,88-90]. As mentioned above, the diversity of the gut virome reaches its maximum level in the first days after birth and decreases with age[60]. Also, it is thought that people's dietary habits impact the type of viruses in their GIT[74,91,92]. For example, consuming coffee and dairy products and consuming fruit have a positive association with the diversity of the gut virome and affect the Shannon diversity index and Bristol Stool Score[74,86,93,94]. In addition, consumption of high quantities of fats is linked to a low

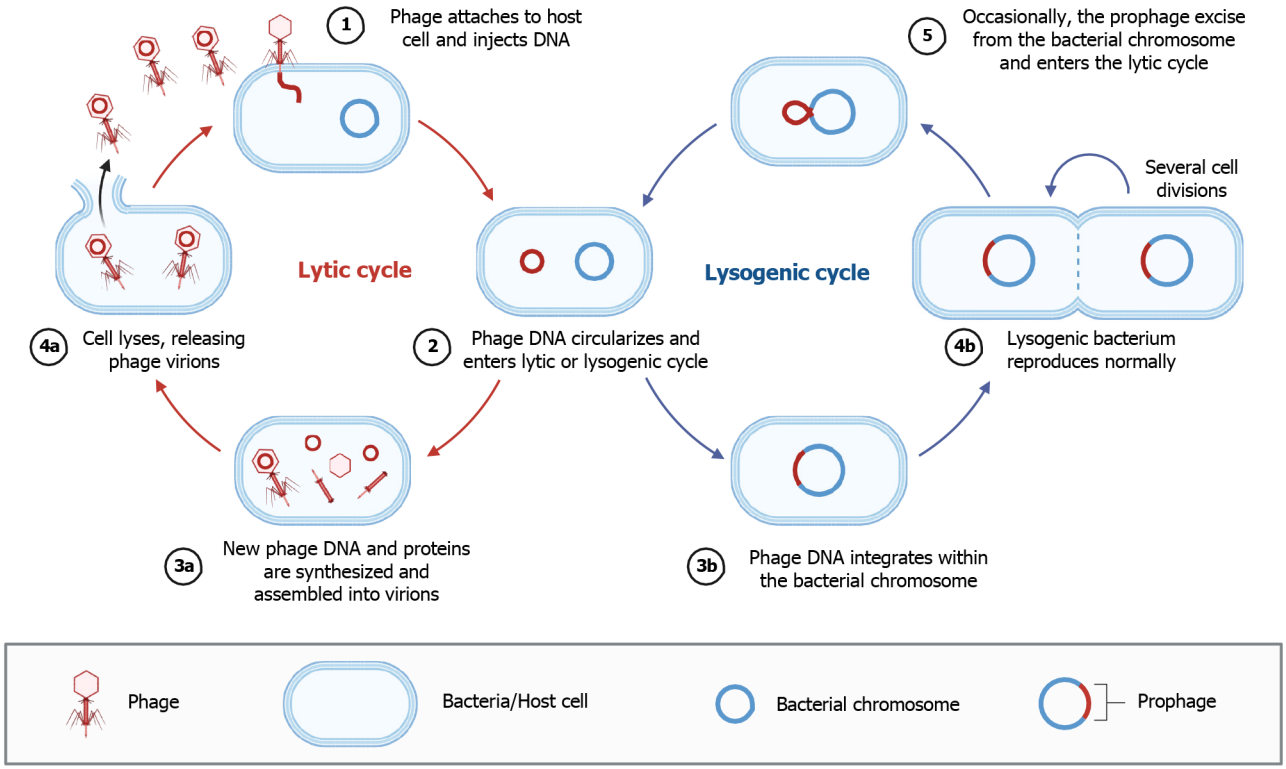

Figure 1 Two major lifecycles of bacteriophage (lytic and lysogenic).

proportion of *Caudovirales* phages and a large proportion of *Malgrandaviricetes* phages, as well as reduced lysogenic capacity[92]. Several investigations have shown that the medications might activate prophages inside their hosts, modifying the virome of the gut, and subsequently, the life cycle[95,96]. A complex equilibrium between lytic and lysogenic phages is therefore believed to exist in a healthy condition[57]. For instance, a lysogenic lifestyle results in a higher bacterial cell number, but activation of lytic activity results in a lower bacterial cell number[57,97]. Higher microbial cell numbers probably give phages an easier means to replicate their incorporated genomes *via* bacterial replication instead of lysing the bacterial host[97]. *Caudovirales* phages, which are mainly lysogenic, are abundant in the early stages of the development of the neonatal gut virome, but as time goes on, *Malgrandaviricetes* phages, which are obligatorily lytic, become more prevalent[60,62,98]. This means that a reduced lysogenic and greater lytic capacity of the intestinal virome occur toward adulthood[63].

In conclusion, lysogenic and lytic phages are in a dynamic equilibrium in a healthy adult gut, and some factors can disrupt this equilibrium and encourage the induction of prophages.

PATHOPHYSIOLOGY OF IBD WITH THE ROLE OF THE GUT VIROME IN IBD

Research conducted over the past 30 years on human intestinal tissue and *in vivo* mouse models has revealed that intestinal homeostasis, which governs the host-microbiome interaction, is largely dependent on the integrity of the epithelial barrier, host defense mechanisms, immunological modulation, and tissue repair. Any disruption of these pathways or the cytokine networks that regulate them can result in IBD[5,99,100]. IBD is a multifactorial disease. The pathophysiology may be initiated by dysbiosis in the gut ecosystem as a result of some environmental or genetic factors [101]. Subsequently, dysbiosis triggers several inflammatory pathways[33,102,103] (Figure 2)[104]. However, the exact association between dysbiosis and inflammation in IBD is yet to be understood. Whether dysbiosis is the cause of inflammation or the inflammation leads to dysbiosis, the final result is the coexistence of dysbiosis and inflammation and the progression of IBD[104].

The onset and progression of IBD are influenced by several critical risk factors including genetics[105,106], diet[107,108], smoking[109], medicines, stress, mental health, and others[110]. Up to 12% of cases indicate a family history of illness, making genetics the most significant known risk factor. Additionally, diet and dietary habits have significant effects on the initiation of IBD[107]. More precisely, a low-fiber diet is thought to switch the gut microbiome from digesting fiber-derived glycans to digesting mucus-derived glycans, destroying the mucous protective layer of the gut and enhancing pathogen penetration with subsequent activation of inflammatory cascades[111]. These inflammatory responses are characterized by gut microbiome dysbiosis, including virome dysbiosis. Gut virome dysbiosis includes the reduction of *Microviridae* and crAss-like phages as well as the propagation of *Caudovirales* and perhaps other phages with lysogenic potential[31,112,113]. Regarding eukaryotic viruses, it has been revealed that patients with IBD have higher prevalence rates of particular viral families (*e.g.*, *Herpesviridae* and *Anelloviridae*) than normal controls[31,112,114,115].

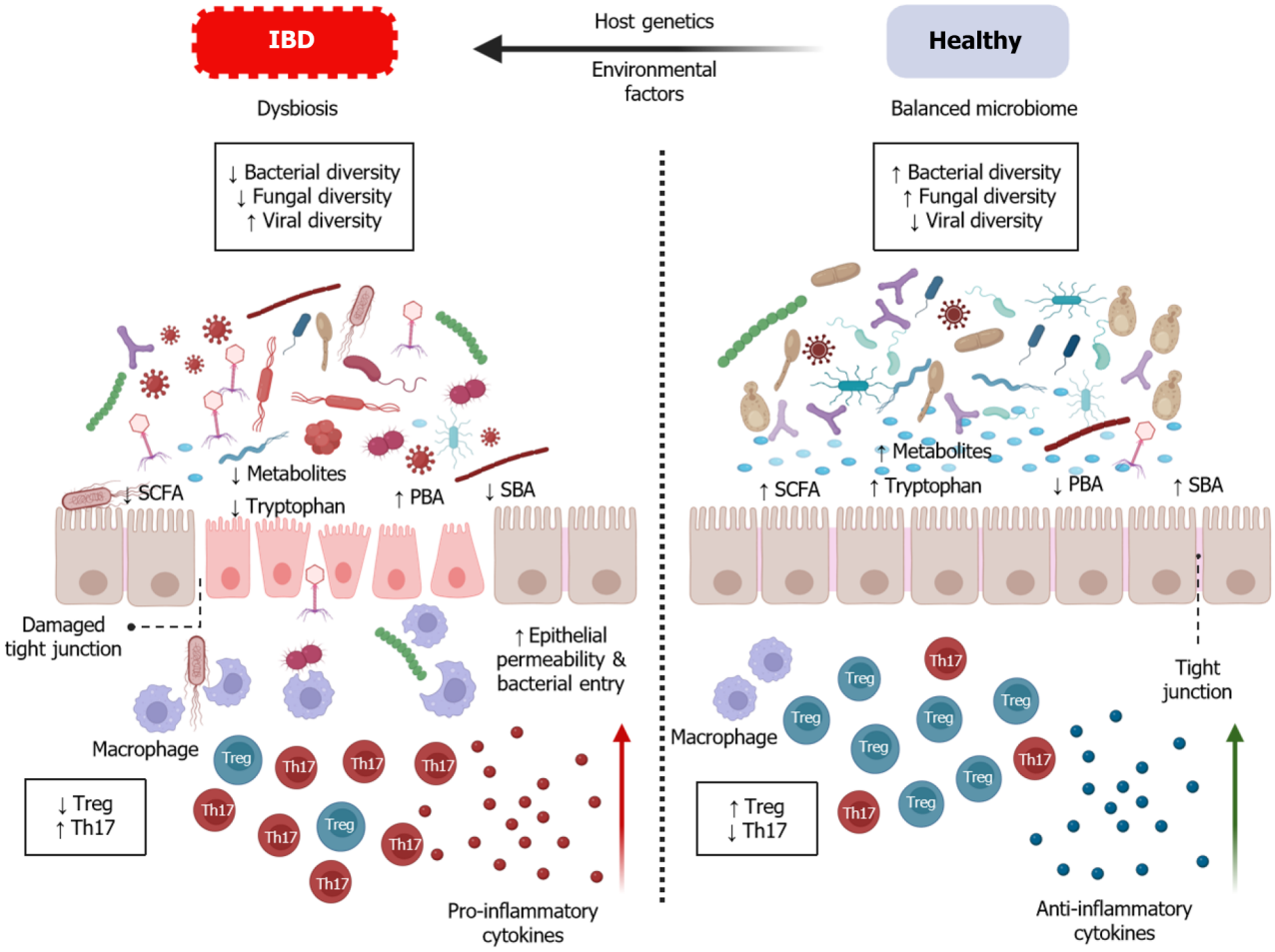

Figure 2 Role of gut microbiome in health condition and inflammatory bowel disease progression. In a healthy state, a balanced microbiome helps maintain homeostasis and the production of beneficial metabolites that build tight junctions and keep gut epithelium barrier integrity. On the other hand, gut microbiome dysbiosis participates in damaging tight junctions as well as dysregulating the gut barrier. This enhances the interaction of pathogens with gut epithelium and increases their penetration to the gut lumen with subsequent stimulation to immunological response and immune cells and overproduction of proinflammatory cytokines and progression of inflammatory bowel disease. PBAs: Primary bile acids; SBAs: Secondary bile acid; SCFAs: Short-chain fatty acids; IBD: Inflammatory bowel disease.

IMPLEMENTATION OF PHAGE IN IBD

After reviewing the literature, we found that gut phages may influence IBD pathogenesis by three mechanisms: (1) Change of gut phage community; (2) Modulation of gut microbial population; and (3) Modification of the local immune response.

Change of gut phage community

Regarding the alteration of the gut phage community, the majority of investigations depend on metagenomic sequencing of stool samples and intestinal biopsies. Variations among normal people and patients with IBD or experimental models have been discovered (Table 1).

In 2008, Lepage *et al*[116] published the first study connecting phages to IBD. They used epifluorescence and electron microscopy to compare populations of VLP in biopsies from patients with CD and healthy controls. They discovered that patients with CD had considerably more VLPs compared to healthy people[116]. This opened the door for further research to demonstrate the gut virome in different IBD subtypes and shed light on the role of the virome in the progression of IBD. Wagner *et al*[117] conducted a study on pediatric patients with CD to compare the alteration in phage population in GI biopsies from different sites and gut wash between patients and control individuals. They collected tissue biopsies from the ileum and colon as well as gut wash and analyzed them through metagenomic analysis. They found a significant excess of phages in biopsies and gut washes of pediatric CD patients compared to healthy controls. Furthermore, they discovered that the *Bacteroides* phages (B10-8 and B124-14) were the most predominant, and the composition of *Mycobacterium* phage differed between CD patients and controls in ileum tissue samples[117]. Further metagenomics examination of colonic specimens revealed that about 50% of phages were connected to the bacterial strains found in the colon specimens[118]. Subsequently in 2015, Pérez-Brocal *et al*[114] demonstrated variations in the gut bacteriome and virome communities in various types of specimens from adult patients with CD at various stages. They discovered that the phage counts in stools were three times greater than in biopsies and that the bacterial community

Table 1 Overview of the alteration in the gut phage ecosystem in patients with inflammatory bowel disease and animal models

Disease	No. of patients included in the study	Sample type	Interpretation of result	Ref.
CD	19	Biopsies	CD patients had considerably more VLPs than normal controls	[116]
CD	6	Ileal biopsies, colonic biopsies, gut wash samples	A significant excess of phages in biopsies and gut washes, *Bacteroides* phages (B10-8 and B124-14) were most predominant, and the composition of *Mycobacterium* phage differed between CD patients and controls in ileum tissue samples	[117]
CD	20	Stool samples, biopsies	Phage counts in stools were three times greater than in biopsies, CD patients had higher levels of *Alteromonadales* and *Clostridiales* phages	[114]
IBD	10	Colonic biopsies	Phages make up the bulk of the DNA viruses within the virome, about 50% of the phages were connected to the bacterial strains found in the colon specimens	[118]
UC and CD	(42 for UC) and (18 for CD)	Stool samples	Patients with IBD had a considerable increase in *Caudovirales* phages, and virome community in UC and CD patients were disease and cohort-specific	[31]
UC and CD	(5 pt. for UC) and (7 pt. for CD)	Stool samples	*Caudovirales* phage proportions in patients with IBD and normal controls were greater than *Microviridae* phage proportions. However, the *Caudovirales* phages were more prominent in CD than UC but not in controls. On the other hand, control persons had a larger diversity of *Microviridae* phages than CD patients, but not UC patients	[119]
UC	97	Rectal mucosa	*Caudovirales* phages were more abundant in UC cases compared to normal controls, but with lower richness, diversity, and balance, and UC patients' mucosa had much more *Enterobacteria* and *Escherichia* phages than healthy controls	[113]
UC and CD	(42 pt. for UC) and (27 pt. for CD)	Stool samples	A stable virulent core virome is associated with a healthy gut and switched from a lysogenic to lytic cycle in temperate phages may be related to CD	[112]
CD	5	proximal and distal colonic wash samples	Considerable interpatient diversity and little, but significant, intrapatient variations between various regions	[120]
(VEO) IB	45	Stool samples	No detectable difference in the overall number of VLPs among VEO-IBD patients and normal controls, but the *Caudovirales* vs *Microviridae* ratio is larger in the VEO-IBD patients than in the controls	[121]
UC and CD	(38 pt. for UC) and (65 pt. for CD)	Stool samples	The prevalence of phages varied among patients with IBD and normal controls as well as the components of the temperate phage population were extremely distinctive to each individual. Moreover, compared to normal controls, active UC patients had a higher prevalence of temperate phages infecting *Bacteroides thetaiotaomicron* and *Bacteroides uniformis*	[122]
IBD	455	Stool samples	crAss-like phageome of the human gut has remained largely stable for 4 yr and individuals with IBD had lower levels of gut crAss-like phages	[65]
CD	19	Stool samples	CD patients had a considerably higher prevalence of crAss-like phages as well as no difference in the richness and evenness of the gut virome among CD patients and controls, but there was a substantial difference in the virome's overall structure	[123]
Colitis	3 from C57BL/6 mice	Stool samples	The intestinal phage populations were altered and shifted to dysbiosis in the mice model, and a decrease in the variety of the phage community, such as *Clostridiales* phages during colitis	[124]

CD: Crohn's disease; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; VEO: Very early onset; VLPs: Virus-like particles.

rather than the viral populations are a better predictor of an individual's illness status. Also, they discovered that individuals with CD had higher levels of phages infecting the bacterial orders *Alteromonadales* and *Clostridiales*, including *Clostridium acetobutylicum* spp. as well as *Retroviridae* family[114]. In the same year, Norman *et al*[31] established a metagenomic analysis to demonstrate the differences in gut phage populations in stool samples among UC and CD patients *vs* healthy controls. They showed that, compared to healthy groups, patients with IBD had a considerable increase in *Caudovirales* phages. Additionally, the CD and UC patients' gut phage community was disease and cohort-specific[31]. Later, in 2019, Fernandes *et al*[119] examined the virome of fecal samples in children with CD, UC, and healthy controls of the same age. The result showed that *Caudovirales* phage proportions in both patients with IBD and normal controls were greater than *Microviridae* phage proportions. However, the *Caudovirales* phages were more prominent in CD than UC but not in controls. On the other hand, the control group showed a larger diversity of *Microviridae* phages than patients with CD, but not those with UC[119]. Moreover, another study by Zuo *et al*[113] identified the virome communities of the mucosa of patients with UC. According to their investigation, *Caudovirales* phages were more abundant in UC cases compared to normal controls but had lower richness, diversity, and balance. They also discovered that the mucosa of patients with UC had much more *Enterobacteria* and *Escherichia* phages than healthy controls[113]. Interestingly, Clooney *et al*[112] employed a whole-virome sequencing technique to re-analyze previously published data and provide extensive insights into the activity of the gut virome and its possible involvement in IBD[112]. They found that a stable virulent core virome is associated with a healthy gut, and switching from a

lysogenic to lytic cycle in temperate phages may be related to CD[112]. A new virome sequencing analysis using pediatric CD patients' proximal and distal colonic wash samples revealed considerable inter-patient diversity and little but significant intra-patient variations among different regions[120]. In another study, Liang *et al*[121] evaluated the dynamics of the virome in stool samples collected from children classified with very early onset (VEO) IBD, defined as IBD with onset prior to the child's sixth birthday. They found that there is no detectable difference in the overall number of VLPs among VEO-IBD patients and normal controls but that the *Caudovirales vs Microviridae* ratio is larger in VEO-IBD patients than in the controls[121]. By utilizing whole-metagenome shotgun sequencing data, Nishiyama *et al*[122] showed the ecological composition of the temperate phage population in the human gut. They discovered that the prevalence of phages varied among patients with IBD and normal controls, and the components of the temperate phage population were extremely distinctive to each individual. Moreover, compared to normal controls, patients with active UC had a higher prevalence of temperate phages infecting *B. thetaiotaomicron* and *B. uniformis*[122]. In the most recent study, Gulyaeva *et al*[65] performed metagenomic sequencing on feces specimens collected from 1950 individuals, to investigate the vital function and diversity of crAss-like phages in clinical cohorts and human populations. They found that the crAss-like phageome of the human gut remained stable for 4 years and that individuals with IBD had lower levels of gut crAss-like phages [65]. Furthermore, Imai *et al*[123] analyzed stool samples collected from Japanese patients with CD using shotgun metagenomic sequencing. In contrast, they found that patients with CD had a considerably higher prevalence of crAss-like phages as well as no difference in the richness and evenness of the gut virome among CD patients and controls, but there was a substantial difference in the overall structure of the virome[123].

Animal studies additionally represent an essential tool for investigating the functions of intestinal phages in the pathophysiology of IBD. Duerkop *et al*[124] reported that in an animal model of colitis, the intestinal phage populations were altered and shifted to dysbiosis[124]. Also, they noticed a decrease in the variety of the phage community, such as *Clostridiales* phages, during colitis.

In summary, recent studies employed metagenomic sequencing and bioinformatic analysis to describe fecal and mucosal phage ecosystems. Most studies found that *Caudovirales* phages were more frequent and less diverse in patients with CD and UC than normal controls. However, different results were found in a recent study that showed no substantial variation in the number of intestinal phages between patients with IBD and normal controls[121]. Additionally, the abundance of crAss-like phage and *Microviridae* was decreased. Some investigations also revealed changes in specific phages, such as elevated levels of *Alteromonadales* and *Clostridial* phages in CD patients, elevated levels of *Escherichia* and *Enterobacteria* phages in UC mucosa, and decreased levels of *Clostridial* phages during colitis.

Modulation of the gut microbial population through bacteriophages

Virulent phages, which have the ability to lyse the bacterial host cell, are frequently identified in the GIT of patients with IBD[112]. It has been demonstrated that the invasion of phage to its bacterial host leads to modification and alteration in bacterial community with subsequent change in the abundance of certain spp.[125]. Researchers have shown that individuals with CD and UC exhibit dysbiosis in their gut microbiome, which is characterized by reduced diversity, increased hazardous *proteobacteria* (*e.g.*, *E. coli* and *Fusobacteria*), and decreased beneficial *Firmicutes* (*e.g.*, *Clostridium clusters IV* and *XIVa, Faecalibacterium prausnitzii*, and *Ruminococci*)[126-128]. Additionally, Nishiyama *et al*[122] found a significant increase in the prevalence of phages infecting *B. thetaiotaomicron* and *B. uniformis*, as well as a reduction in the population of their bacterial host. Considering the aforementioned studies, we conclude that there is a link between the abundance of phage and its bacterial host population. Germ-free (GF) animals are the ideal model for investigations related to the gut microbiome since they don't have any microbial colonization in their guts[129,130]. In GF murine models, a recent investigation revealed that phage invasion directly affects vulnerable bacteria, with subsequent cascade affecting other bacterial spp. and gut metabolome[131,132].

Other than virulent phages, temperate phages can affect the viability and diversity of gut bacteriome[133]. For instance, temperate phages significantly increase the genetic variation of bacteria *via* horizontal gene transfer and increase the mutation rates[46,133-135]. Moreover, the induction of latent prophage through environmental stressors may activate its lytic cycle and decrease the number of bacterial hosts. In a metagenomic study conducted by Cornuault *et al*[136], they found a greater abundance or quantity of phages infecting *F. prausnitzii* in feces samples from patients with IBD in comparison to normal controls[136]. While less *F. prausnitzii* abundance has been demonstrated in patients with IBD, they concluded that phages might exacerbate this reduction of *F. prausnitzii*[136].

In summary, the relevant information is still inadequate, and theories about how phages directly or indirectly affect bacterial populations are still out of reach. So further investigations are required to fully understand the complex phage-bacteria interactions in IBD.

Modification of the local immune response through bacteriophages

After prophage induction, a process known as phage-mediated lysis describes the positive feedback inflammatory response between phage induction and gut inflammation-begins[133,137]. In this situation, intestinal inflammation induces the production of stressors by enterocytes, such as reactive oxygen species and reactive nitrogen species, which cause the host bacteria to respond to stress (SOS response)[138]. Increased bacterial host cell lysis is followed by a rise in pathogen-associated molecular patterns (PAMPs) (such as lipopolysaccharides and bacterial DNA) that activate more enterocyte receptors[133,137]. This leads to activation of a positive feedback inflammatory response and dysregulation of the immune system (Figure 3). Additionally, in the presence of a thin lining mucous layer and disrupted tight junction, large amounts of PAMPs can penetrate gut epithelium and activate Toll-like receptors (TLRs) and other immune cells located on gut epithelium[31,139-141]. As a result, inflammatory pathways are activated, resulting in increased generation of pro-inflammatory cytokines and decreased generation of anti-inflammatory cytokines[142-145] (Figure 4). A recent *in vivo* investigation conducted in GF mice showed upregulation in both innate and acquired immunity after

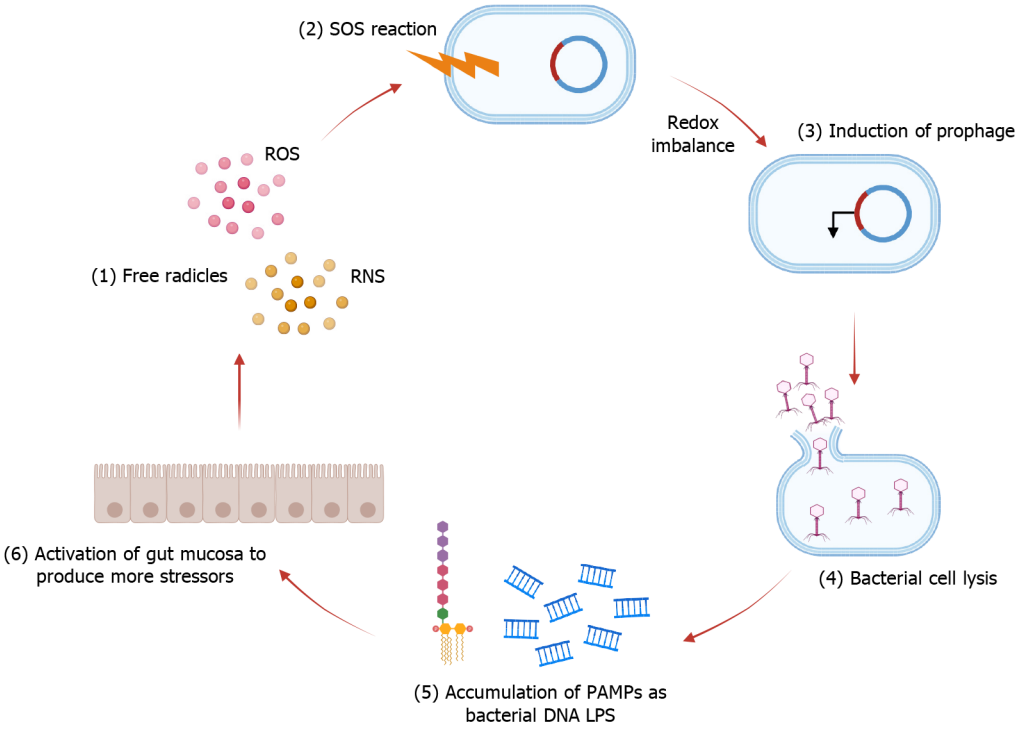

Figure 3 Activation of positive feedback inflammatory response through induction of latent prophage and lysis of bacterial host cell. (1) Intestinal inflammation induces gut mucosa to generate stressors (like reactive oxygen species [ROS] and reactive nitrogen species [RNS]); (2) Production of stressors aggregates the stressor response (SOS) in the bacterial host cell (SOS reaction) and redox imbalance; (3) This imbalance leads to damage of bacterial DNA and induction of latent phage; (4) Switch to lytic cycle with subsequent bacterial cell rupture; (5) Accumulation of pathogen-associated molecular patterns (PAMPs) as lipopolysaccharide (LPS) and DNA, that results from bacterial lysis; (6) PAMPs activate receptors in the gut mucosa and stimulate the production of more stressors.

administration of a phage cocktail. The results demonstrated a considerable increase in overall CD8+ and CD4+ T cells, in addition to interferon gamma (IFN-γ)-producing T helper 1 cells[146]. Furthermore, an *in vitro* study indicated that the detection of phage DNA by dendritic cells triggers the generation of IFN-γ through a TLR9-dependent mechanism[147].

On the other hand, phages may play a significant role in protecting the intestinal barrier against bacteria and provide non-host-derived immunity[148]. Phages can stick to the mucus layer of the gut and reduce the colonization of pathogens. This adhesion was controlled by interactions between immunoglobulin-like domains, which are present on phage capsid proteins, and glycan residues, which are found in mucin glycoprotein[148].

In summary, little information is currently known about gut phages' impact on IBD through immunological modulation. Therefore, there is an urgent need for more research on how gut phages and the immune system interact in IBD.

IMPLEMENTATION OF EUKARYOTIC VIRUSES

Early in life, eukaryotic viruses begin to colonize the gut mucosa. These viruses are members of the *Anelloviridae*, *Adenoviridae*, *Picornaviridae*, *Picobirnaviridae*, *Astroviridae,* and *Parvoviridae* families, and they become more diverse with age[60]. Such viruses may cause pathological changes or may remain dormant in healthy persons for many years, exerting significant benefits[141,149-151]. Eukaryotic virome dysbiosis, such as phage dysbiosis, has been linked to IBD pathophysiology[152-154] as eukaryotic-targeting viruses incorporate their genetic element into the human genome and can affect the physiological condition of enterocytes[141,151,154]. Patients with UC had greater levels of the eukaryotic *Pneumoviridae* family than controls, according to a metagenomic study involving a large cohort of UC patients. However, control individuals had higher levels of the eukaryotic *Anelloviridae* family[113]. On the other hand, another investigation demonstrated that patients with UC and CD had greater levels of the *Herpesviridae* family than normal controls[118].

Epstein-Barr virus and cytomegalovirus are the most studied eukaryotic viruses that may cause intestinal inflammation[150]. However, their role in the pathophysiology of IBD has yet to be fully understood, as their reactivation may be brought on by immunosuppressive or stressful situations that are prominent in patients with IBD, making them more likely to serve as bystanders than true disease-causing factors.

Norovirus infection was found to be a significant colitogenic factor, significantly dependent on the presence of gut microbiome, in the interleukin 10-deficient mouse model of spontaneous colitis[155]. Likewise, IBD-susceptibility gene *Atg16L1*^{HM} mouse models have shown that Norovirus infection leads to the progression of intestinal inflammation[156]. Hence, it appears that the development of colitis is accelerated by a synergistic interaction between genetic makeup and Norovirus infection as a trigger of intestinal inflammation.

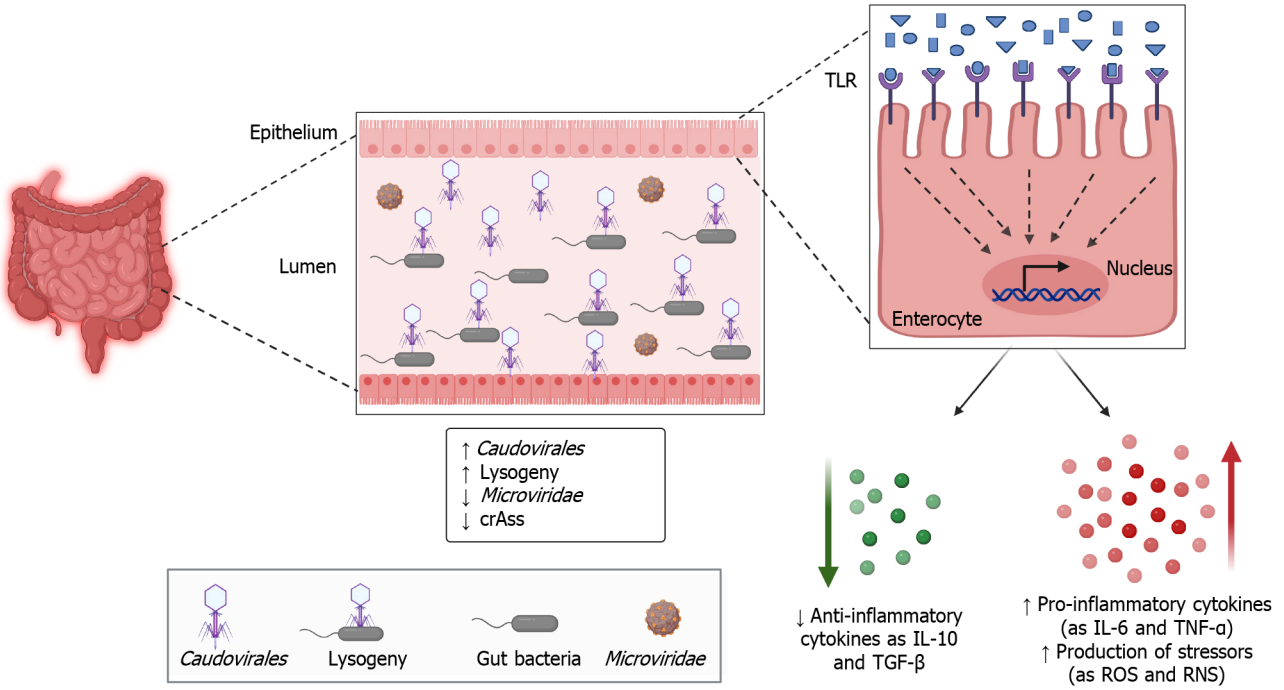

Figure 4 Modification of local immune response through bacteriophage. An inflamed gut is characterized by microbiome imbalance including virome. An imbalanced virome is distinguished by an expansion of *Caudovirales* phages and lysogenic lifecycle as well as a decline in the relative abundance of the *Microviridae* family and crAss-like phage. Additionally, in the presence of a thin mucus lining or broken tight junction, microbial antigens (like viral antigens) can penetrate the intestinal epithelium, activate Toll-like receptor (TLR), upregulate pro-inflammatory cytokines production, and dysregulate anti-inflammatory cytokines production. IL: Interleukin; RNS: Reactive nitrogen species; ROS: Reactive oxygen species; TGF-β: Transforming growth factor beta; TNF-α: Tumor necrosis factor alpha.

These aforementioned investigations specifically focused on enterotropic viruses, which are often restricted to the GI system. On the other hand, a recent investigation using metatranscriptomic processes revealed that some eukaryotic RNA viruses with a physiological hepatic tropism were found in the gut mucosa of patients with IBD[151]. In a recent study, Massimino *et al*[157] discovered how the hepatitis B virus X protein, a virome-associated protein encoded by the *Orthohepadnavirus* genus, contributes to the pathogenesis of UC.

In summary, previous findings have indicated a link between these eukaryotic virus families and IBD pathogenesis, and more research is urgently required to demonstrate their roles in producing chronic intestinal inflammation.

CHALLENGES AND LIMITATIONS AND FUTURE TRENDS IN VIROME DESCRIPTION

Analysis of the gut virome has been neglected due to the difficulty in producing an *in vitro* composite culture environment that would support the simultaneous development of different microorganisms[158]. It is still challenging to recognize and categorize viral DNA in microbiological samples. Viral spp. are difficult to classify into closely related spp. due to their extraordinarily high diversity, low gene content, and quick acquisition of mutations[159]. Moreover, it is impracticable to sequence viral DNA using a targeted amplicon-like strategy as there are non-common genes that might be utilized as markers for identification[160]. Unfortunately, it can be challenging to cultivate viruses as well. Because viruses are parasitic and depend on host cells for energy and multiplication, these hosts must also be discovered and cultivated. Additionally, many GIT microorganisms cannot be cultivated, making it problematic to culture their related viruses[115].

Metagenomic analysis of the virome may appear to be a difficult process, but various approaches might help with this issue. For instance, before sequencing, viral particles from a microbiome sample can be separated and purified using size selection by centrifugation, filtration (using 0.2-μm to 0.45-μm filters), and particle precipitation using polyethylene glycol [161]. Despite these helping approaches, the metagenomic technique possesses great limitations, such as dependence of the result on the degree of fragmentation of viral genome as well as analysis of DNA sequence only and ignoring RNA [162]. Although revolution in -omics approaches, such as metagenomics, metataxonomics, and metatranscriptomics, share common limitations[152]. (1) They must depend on reliable databases that provide information on the various genomes and their explanation; otherwise, the analysis will be challenging and may miss some crucial information[158]; (2) Studies must be carried out on purified RNA and DNA specimens, and occasionally, the yields are insufficient to cover poorly represented communities. In addition, residual host DNA and RNA molecules may persist in the sample after purification, leading to false outcomes[158]; (3) The sequencing depth must be very high to obtain accurate outcomes, particularly for metatranscriptomics, which may be expensive[163]; and (4) The present statistical method is constrained by the concept that the predictor variables are independent of one another and do not consider the complexity of the biological

ecosystem[158].

The use of more modern computational techniques, such as VIP and VirFinder, which offer workflows to map, filter, and detect viruses from metagenomic sequences[164,165], as well as METAVIR, an online library for identifying viral genes from metagenomic data[166], can make the understanding of human virome easier. Future gut virome investigations should include approaches like tracking viral protein exacerbation[167] or host DNA reduction, as well as high-throughput sequencing of the microbiome in patient samples[159]

COMMUNITY TYPING AS A NEW APPROACH TO DESCRIBING GUT VIROME

The idea of community typing, also known as "enterotyping" was first developed in bacterial studies to simplify the complexity and categorize the diversity of the gut microbiome[168]. The Dirichlet Multinomial Mixture approach is used for community typing, which is based on probability-based modeling and takes into account particular microbiome data properties such as relative scarcity[169]. With this technique, samples from the same community (those with comparable bacterial abundance patterns) are classified into microbial configurations without stating any assumption about the underlying separate character of the strata[169]. These techniques reliably divided the gut microbiome into the 4 enterotypes *Ruminococcus*, *Bacteroides* 1, *Bacteroides* 2 (Bact2), and *Prevotella* and found several connections to the abovementioned risk factors, including diet and illnesses[170-173].

Due to the massive insights and enterotyping helping in the understanding of the microbiome of the human gut[171, 174,175], it has been hypothesized that viral community typing might be a valuable method to pursue knowledge of the gut virome as well. Regarding this idea, Song *et al*[176] analyzed many published data and found that most people could be sorted into two viral community types depending on their gut virome; however, they were unable to identify their taxonomical makeup because of the elevated incidence of viral dark matter. Additionally, it has been demonstrated that the gut virome of patients with IBD existed in two viral community types: community type CrM, which includes either crAss-like phage and *Malgrandaviricetes*, or community type CA, which includes *Caudovirales* phages[177]. Moreover, the community type CA was linked to reduced virome diversity, dysbiosis in the Bact2-enterotype, and active illness, demonstrating the clinical potential of these community types[177,178].

In summary, viral community typing has great promise as a future strategy for discovering alterations in viral composition in health and illness.

CONCLUSION

IBD is a multifactorial chronic inflammatory disease involved in GIT. IBD is divided into two subtypes: UC and CD. The exact etiopathogenesis is still unknown, but the researchers are doing their best to remove this ambiguity. Most researchers focus on the role of gut bacteriome in the etiogenesis of IBD and ignore other microorganism communities as viruses. In 2015, Norman and partners conducted the first investigation revealing the role of gut virome dysbiosis in IBD. Since then, many studies have been conducted with evolution in novel approaches to describe virome dysbiosis and its role in disease and health conditions. In this review, we give an overview of gut virome and its role in normal health conditions. Further, we give deep insights into the implementation of gut virome in IBD pathogenesis regarding the role of both bacteriophages and eukaryotic viruses. Finally, we describe the challenges and limitations in describing gut virome and how the appearance of novel approaches as community typing opens the door for further research to understand the role of gut virome in disease states, including IBD.

FOOTNOTES

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MINIREVIEWS

Variations in quantifying patient reported outcome measures to estimate treatment effect

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Abstract

In the practice of healthcare, patient-reported outcomes (PROs) and PRO measures (PROMs) are used as an attempt to observe the changes in complex clinical situations. They guide us in making decisions based on the evidence regarding patient care by recording the change in outcomes for a particular treatment to a given condition and finally to understand whether a patient will benefit from a particular treatment and to quantify the treatment effect. For any PROM to be usable in health care, we need it to be reliable, encapsulating the points of interest with the potential to detect any real change. Using structured outcome measures routinely in clinical practice helps the physician to understand the functional limitation of a patient that would otherwise not be clear in an office interview, and this allows the physician and patient to have a meaningful conversation as well as a customized plan for each patient. Having mentioned the rationale and the benefits of PROMs, understanding the quantification process is crucial before embarking on management decisions. A better interpretation of change needs to identify the treatment effect based on clinical relevance for a given condition. There are a multiple set of measurement indices to serve this effect and most of them are used interchangeably without clear demarcation on their differences. This article details the various quantification metrics used to evaluate the treatment effect using PROMs, their limitations and the scope of usage and implementation in clinical practice.

Key Words: Patient-reported outcome measures; Treatment effect; Minimal clinical important difference; Patient-accepted symptom state; Minimum detectable change; Orthopedics

Core Tip: In health care, patient-reported outcomes and patient-reported outcome measures (PROMs) help track changes in complex clinical situations. They provide evidence-based guidance for patient care by showing how a treatment affects a specific condition and if the patient benefits from it. For PROMs to be useful, they must be reliable and able to detect real changes. Regular use of structured outcome measures helps doctors understand a patient's limitations better than just an office interview. This allows for meaningful discussions and personalized treatment plans. Understanding how to measure treatment effects with PROMs is crucial, as there are many different metrics, often used interchangeably. This article explains these metrics, their limitations, and their practical use in healthcare.

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INTRODUCTION

In the practice of healthcare, patient-reported outcomes (PROs) and PRO measures (PROMs) are used as an attempt to observe the changes in complex clinical situations. They guide us in making decision based on the evidence regarding patient care by recording the change in outcomes for a particular treatment to a given condition and finally to understand whether a patient will benefit from a particular treatment and to quantify the treatment effect[1]. According to the US Food and Drug Administration, PRO is any report coming directly from patients about a health condition and its treatment[2]. For any PROM to be usable in health care, we need it to be reliable, encapsulating the points of interest with a potential to detect any real change[3]. Using structured outcome measures routinely in clinical practice helps physicians to understand the functional limitation of patients, which would otherwise be not clear in an office interview, and this allows the physicians and patients to have a meaningful conversation as well as a customized plan for each patient. The importance of serially and routinely measuring outcomes is stressed by Codman, the father of modern-day outcome assessment[4] and the rationale behind collecting PROs is as follows: Better communication aids that also make the decision-making process shared between patients and providers; subjective assessment of health status and identification of treatment lacunae; quantifying the loss of function; distinguishing between problems due to physical, emotional and social reasons; identifying adverse effects of treatment methods; estimation of disease progression and treatment response; helping change treatment methods; and prognostication of disease course and treatment outcomes[5-7].

Having mentioned the rationale and the benefits of PROMs, understanding the quantification process is crucial before embarking on management decisions. Traditionally, statistical methods are used to measure the difference before and after an intervention. However, statistical significance may not relate to clinical improvement[8]. A better interpretation of change needs to identify the treatment effect based on clinical relevance for a given condition. Thresholds to measure the clinical relevance or significance of change can be of three types[8]. First, the minimum difference to understand the clinical relevance below which it cannot be distinguished from the random error; second, the difference between the scores pre- and postintervention, which can be perceived as good or bad by the patient; and finally, the difference that is perceived as clinically relevant or meaningful. There are several metrics to serve this purpose (Table 1)[8] and some of the most used are discussed in this review.

In a step towards understanding and standardizing the PROMs, Jaeschke *et al*[9] have described the concept called minimal clinically important difference (MCID) to aid in interpreting the questionnaire scores. Following MCID, other metrics to assess patients' perception of treatment effect were developed for interpreting PROMs, called "the alphabet soup" by Tashjian[4], including patient-acceptable symptomatic state (PASS), substantial clinical benefit (SCB) and maximal outcome improvement (MOI). This review analyses these commonly used evaluation metrics of PROMs to aid better comprehension and implementation of these measures in clinical practice.

MCID

According to Jaeschke *et al*[9], MCID is defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management." In this definition, three important things to note include patient perception; absence of excessive cost and troublesome side effects; and mandating change in management[10]. As shown in Table 1, there are multiple terms similar to MCID but they are different in their own definitions. MCID can be estimated for an

Table 1 Measurement indices to quantify patient-reported outcomes measures for clinical relevance

Measure of change	Satisfaction threshold
Minimal clinically important difference	Patient acceptable symptom state
Minimal important change	Substantial clinical benefit
Minimal clinically important change	
Minimal clinically important improvement	
Minimal clinically significant difference	
Minimal perceptible clinical improvement	
Clinically important difference	
Minimal important difference	
Minimum detectable change	
Minimal detectable difference	
Smallest detectable difference	

outcome measure by various methods[11,12]. We discuss the commonly used methods to estimate MCID for a given PROM. Consensus method, anchor-based method, distribution-based method and a combination of anchor-based and distribution-based method[13].

Consensus method

In this method of assessment of MCID, an expert panel is convened, discussed and consensus is reached on the proposed MCID for the outcome of interest. The main problem with this method is that the patients' perspective is not taken into consideration.

Anchor-based method

Outcome scores are compared with an independent, external face valid criterion called anchor to determine MCID of the particular outcome in question. Generally, anchor is a reliable and valid questionnaire for which patients respond based on their perspective[13]. Transition question, patient global impression change or patient global assessment of treatment effectiveness are some of the examples of the anchor questions. The threshold used to calculate MCID of an anchor question is minimally improved (it can be minimally deteriorated as well). Gum *et al*[14] have estimated MCID for back and leg pain for the numerical rating scale (NRS) 0–10 using better as threshold and concluded that a decrease in the score of ≥ 3.1 was considered as minimally improved[14]. The anchor-based method takes into account patients' perspective, for which these metrics were designed in the first place, unlike purely statistical approaches. Second, this method cannot be used in conditions where most patients get better and the ones who are unchanged are minimal. Third, anchor questions do not take into consideration the variability in the sample. Finally, the idea of MCID will only help in understanding whether there is an understandable improvement but not if that improvement is meaningful to the patient [15-18].

Distribution-based method

Paradoxically, this method uses statistical means to measure MCID. One such statistical means is to use standard error measurement (SEM) as it reflects the lack of precision in the measurement. Thus, any value below SEM cannot be MCID as this does not show any real change. Alternatively, the minimal detectable change (MDC) is calculated, which by definition is the smallest change that can be detected beyond the measurement error. In this method, MCID is considered as the upper value of the 95%confidence interval (CI) of the average score in nonresponders for a specific intervention. Usually MCID is shown to be on average similar to either 1 SEM or half the standard deviation[19]. Gum *et al*[14] and Carreon *et al*[20] assessed MCID in lumbar fusion surgery[14,20]. This method is also not without limitations. First, one can define MCID only based on the hope that change in the score is not due to the measurement error. Second, patient perspective is not accounted in this method.

Combination of distribution- and anchor-based methods

In this approach, an anchor question is used to differentiate between the responders and nonresponders, and then uses MDC to calculate the MCID as described above and uses the upper value of the 95%CI in nonresponders as MCID. Using this method, the MCID of visual analog scale (VAS) (0–10) was 2.1 for neck pain but on validation by receiver-operator characteristics (ROC) analysis, the cutoff was 4.1. However, for arm pain, both the methods, MCID and ROC, resulted in 4.1 and 4.0 as cutoff points, respectively. This method of assessing is more complex compared to the previously described methods. However, it is advantageous compared to the pure anchor-based method that is vulnerable to the sample variability.

Although MCID is useful to compare the efficacy of treatment in clinical trials and determine the efficacy of treatment in individual patients to inform treatment effect, there are some notable pitfalls. These include variability in the metric based on the quality of the data used, method used, anchor type, definition of improvement, population demographics, and their perception of symptoms and functional limitations. The weaknesses of using MCID involves the lack of universal fixed attribute that can be used across different patient populations. There is no consensus on the method to calculate, leading to extreme variability. Ostelo *et al*[21] found that depending on the method used to calculate MCID, Oswestry Disability Score for low back pain, on a scale of 0–100 varied between 2 and 8.6. Taking these data, Wright *et al* [3] explained how this could be disastrous in clinical practice.

There is no single value for MCID for any specific outcome measure as it can be influenced by type of patient population and the method used to estimate. MCID, if reported as single point estimate rather than a confidence interval, can be problematic because it can risk misclassifying the outcomes in patients as not improved even when they were improved. Rossi *et al*[22] concluded that the calculation of MCID is not as important as it seems. They reported MCID to be "a low bar" and recommended scientific studies to not only provide MCID but also mention PASS and SCB to be meaningful to both the scientific community and more importantly to the patient for whom a meaningful improvement makes more sense than a minimum one, as illustrated in Figure 1.

SCB

When assessing the clinical outcome of a patient, one does not reach a floor value like MCID but one would expect to see a substantial clinical improvement, which is the SCB; a concept introduced by Glassman *et al*[23]. SCB is the minimum amount of change in a PROM that allows a patient to feel sufficiently or substantially better after treatment. Generally, MCID is considered the lower limit of treatment effect and SCB is the upper limit of any meaningful outcomes of a treatment.

SCB is measured based on the anchor method as detailed for MCID. The commonly used anchor question is “Compared to the first evaluation, how is your physical condition now?” This question is usually answered using a Likert scale response[24]. Statistical analysis is done using various techniques to determine the SCB, but the most commonly used method is ROC curve analysis. SCB values are determined for every particular PROM and for every condition distinctively.

Depending on the type of anchor questions that are used, there can be an issue of recall bias in calculating SCB, as it is with MCID. Hubbard *et al*[24] used two anchor questions instead of one. While the first question was used to find out the improvement in the physical function since the first visit, the other was used to assess SCB. Similarly, Glassman *et al*[23] used five satisfaction statements in their study[23] to standardize the SCB determined. Although important, SCB is rarely reported in the published literature[25]. However, Wellington *et al*[26] showed that when patients were divided into those from different geographical locations or times, there was a high degree of variability in their SCB thresholds for total shoulder arthroplasty. Hence, SCB also suffers variability similar to MCID based on population characteristics.

PASS

Unlike MCID, which attempts to compare the pre- and postintervention scores for a given condition, PASS is a cross-sectional evaluation of how patients feel at a given point in time[27]. It is the magnitude of result that makes the patients feel fulfilled[4]. Several studies have proposed that overall improvement in health status is one of the crucial factors irrespective of the intervention for a given condition[28-30]. PASS is a holistic satisfaction score of the present health status of patients and not just related to the symptoms of a particular disease or intervention[31].

PASS cutoff point is estimated using an anchor question that has a binary response of yes or no. One of the most common question that is used is: "Taking into account your level of pain and also your functional impairment, if you were to remain for the next few months as you are today, would you consider that your current state is satisfactory?"[32]. Along with the anchor question, a 75th percentile method and ROC methods are used to reach a cutoff value for specific PROMs for a given condition[33,34]. MCID was called a low bar by Rossi *et al*[22]; however, PASS was called as “an ambitious target for disease management” by Maksymowych *et al*[35], thereby making it something to look forward to in PROMs[22,35] (Figure 1).

DISCUSSION

One of the most important thing that researchers and clinicians need to remember is that these metrics used to evaluate the treatment effect of interventions are not universal. They are usually specific for the condition that they are calculated for as well as the outcome measure that is used to calculate the change[36,37]. However, MCID does not differ with the treatment used when the same condition is assessed with the same outcome measure[13,38]. Katz *et al*[13] considered “improvement is improvement regardless of what produced it”. Farrar *et al*[38] demonstrated that pain intensity-NRS (PI-NRS), an 11-point pain measurement instrument (0-10), similar to MCID could be used among a host of conditions such as osteoarthritis, painful diabetic neuropathy, and low back pain. However, Stauffer *et al*[38,39] demonstrated that when a different version of VAS (0–100 mm) was used, MCID differed among different disease states such as knee and hip

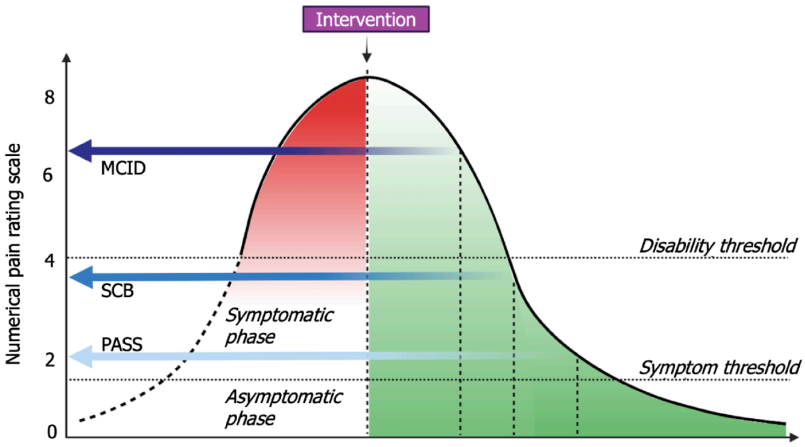

Figure 1 Illustration of the various quantification indices in the context of numerical pain rating scale for knee osteoarthritis. MCID: Minimal clinically important difference; SCB: Substantial clinical benefit; PASS: Patient acceptable symptomatic state.

osteoarthritis and back pain.

Disease severity is another variable that influences these metrics. Patients with lower preoperative scores find it easier to achieve MCID and SCB, whereas those with higher scores were better off to reach PASS[13,40]. Patients with a severe disease state have more room to reach the clinically important or significantly better state but those with a low severity have not enough room. Therefore, in patients with low disease severity, it is difficult to define MCID or SCB as they do not have sufficient room to become better. Hence, one can consider patients with low health status or a severe disease with significant functional limitations to have a higher chance of achieving MCID or SCB after an intervention, as the room for improvement is higher but the chances of reaching the PASS threshold remain unpredictable[40,41].

Use of MCID, SCB and PASS is not practical in daily clinical practice, because each individual patient may not perceive the change in their health status in a similar manner. For example, if PASS threshold on 11-point PI-NRS is 3 for a specific condition, a patient in with PI-NRS 2.5 might still not be able to accept the present condition as satisfied[4]. However, Goh *et al*[27] described the PASS thresholds for multiple PROMs following unicompartmental knee arthroplasty, and recommended these thresholds as the target to treat the condition in future studies.

As already described, patients with higher functional scores or less severe disease status pre-intervention may not be able to reach MCID or SCB owing to the lack of enough room for improvement. In this regard, Berglund *et al*[42] have proposed a new metric called MOI[42]. MOI is a threshold for an outcome measure normalized to the maximum possible outcome for each patient who considers to have achieved a satisfactory result. Tashjian in his editorial commentary claimed MOI as the threshold that can be used at an individual patient level in daily practice[4]. MCID, SCB and PASS are more meaningful when discussing the outcome of a group of patients than an individual patient. These metrics can also be used to assess the sample size, power of a study *etc*., as well in the statistical aspect of the research that usually takes into consideration only the numbers, but with these metrics, we are introducing the aspect of patient perception of change or satisfaction.

Comparison of these metrics among different studies remains difficult as there is a lack of consensus on their assessment methods[43,44]. Depending on the type of method that is used to assess the threshold, the value of these metrics can and will be different, making it a priority for researchers to come to a consensus on their estimation methods. The type of anchor, number of questions and responses to be used, and identification of responses that are chosen as no, minimal or substantial change need to be ascertained because they have a significant impact on the evaluation metric that is calculated. Considering the amount of variability, achieving universal threshold for the PROMs does not seem to be on the horizon currently. One of the ways in which this variability could be managed is to define a range of measurement as threshold for these evaluation metrics rather than a single cutoff value[45]. Standardization of the methods to estimate these threshold ranges needs to be developed to aid in universal acceptability and ease of use in both research as well as in daily clinical practice[46,47]. Table 2 gives the list of common orthopedic PROMs for hip, knee and shoulder ailments and their MCID and PASS cutoff values[48-77].

The findings of this study call for a unified approach in quantifying the PRO and its treatment effect measure for a given condition for the benefit of the readers and researchers. The concept of core outcome dataset (COD) is being developed to emphasize this concept[78,79]. However, they were not put into action as a standard practice due to the lack of necessary reporting guidelines. Authors suggest journals to facilitate the necessary COD for a given condition as a necessary publishing requirement. Although not possible for all study methods, studies of higher clinical impact such as randomized controlled trials should be mandated towards the same. Having tried to implement the COD concept and looking at its impracticality, the concept of minimum COD is now in development for various clinical conditions. The impracticality of the idea lies in the regional differences in the context of outcome measures utilized. The outcome measures and their treatment effect noted to be relevant in one part of the world may not be relevant to the other and making them mandatory only makes them impractical. Hence, the concept of minimum COD is in vogue to account for the regional, economic and cultural variations in outcome measurements[80]. Hence, the authors suggest that clinicians move towards a standard minimum COD for the condition with a standardized measure of treatment effect to make the

Table 2 Characteristics of patient-reported outcomes measures and their quantification metric cut-off values, *n* (%)

Patient population	PROM	Value range	MCID	PASS
Hip				
Arthroscopy patients[48,49]	mHHS	0-100	MDC 12	74
Measure of function in patients with hip disability[48,50-52]	HOS	0-100	MCID 9	87
Hip/groin disability[53-56]	HOOS	0-100	MDC 10	NR
Physically active patients with long standing hip/groin pain[57]	HAGOS	0-100	SDC 19	NR
Young (18-60 yr) active patients with hip disorders[58]	iHOT-12	0-100	NR	NR
Young (18-60 yr) active patients with hip disorders[59]	iHOT-33	0-100	MCID 6.1	NR
Young active nonarthritic patients with hip ailments[60]	NAHS	0-100	MDC 10	NR
Knee				
Patients with knee pain[61,62]	IKDC-SKF	0-100	MCID 6.3 (6 months); MCID 16.7 (12 months)	75.9
Patients with knee injury or osteoarthritis [63]	KOOS	0-100	SDC 16.6	88.9
Patients with knee injury/pain[64]	Lysholm	0-100	MDC 8.9	NR
Patients with knee pain due to any condition[62,65]	Cincinnati	0-100	MCID 14 (6 months); MCID 26 (12 months)	NR
Patients with knee pain due to any condition[66]	WOMAC	0-100	MCID 11.5	NR
Patients with osteoarthritis knee[64]	Tegner activity	0-10	MDC 1	NR
Shoulder				
Patients with shoulder instability[67]	WOSI	0-2100	MCID 220 (10.4)	NR
Patients with rotator cuff problems[68]	WORC	0-2100	MCID 245.25 (11.7)	NR
Patients with shoulder osteoarthritis[69]	WOOS	0-1900	NR	NR
Patients with shoulder pain due to instability, rotator cuff disease or arthritis [70]	ASES	0-100	MCID 6.4 MDC 9.7	NR
Patients with shoulder conditions including fracture, arthroplasty, cuff repair, adhesive capsulitis[71]	Constant	0-100	MCID 10.4	44
Patients with shoulder dysfunction[72]	SST	0-100	SDC 2.8	NR
Patients with upper limb disorders[73,74]	DASH	100-0	MCID 10.2; MDC 6.6-12.2	43
Patients with shoulder pathology from musculoskeletal, neurogenic, or other origin[75]	SPADI	0-100	MCID 8-13.2; MDC 18	41
Wrist and elbow				
Patients with wrist conditions, ulnar impaction, tendonitis, arthritis, or nerve compression syndrome from forearm to hand[76]	DASH	100-0	MCID: 10-13.5; MDC: 9.3	NR
Patients with wrist conditions, ulnar impaction, tendonitis, arthritis, or nerve compression syndrome from forearm to hand[76]	PRWE	100-0	MCID: 14-17; MDC: 7.7	NR
Ankle				
Patients with chronic ankle instability[76]	FAAM	0-84	MCID 8	NR

Patients with hallux valgus[77]	MOXFQ	100-0	MCID 12	NR

ASES: American Shoulder and Elbow Surgeons Score; DASH: Disabilities of the arm, shoulder and hand; FAAM: Functional Ankle Ability Measure; HAGOS: The Copenhagen Hip and Groin Outcome Score; HOOS: Hip dysfunction and osteoarthritis outcome score; HOS: Hip outcome score; iHOT-12: International Hip Outcome Tool-12; iHOT-33: International Hip Outcome Tool-33; IKDC-SKF: International Knee Documentation Committee Subjective Knee Form; KOOS: Knee injury and osteoarthritis outcome score; MCID: Minimal clinically important difference; MDC: Minimal detectable change; mHHS: Modified Harris Hip score; MIC: Minimal important change; MOXFQ: Manchester-Oxford Foot Questionnaire; NAHS: Nonarthritic hip score; NR: Not yet reported in the literature; PASS: Patient acceptable symptom state; PRWE: Patient-rated wrist evaluation; SDC: Smallest detectable change; SPADI: Shoulder Pain and Disability Index; SSS: Sport-specific subscore; SST: Simple shoulder test; WOMAC: Western Ontario and McMaster Universities Arthritis Index; WOOS: Western Ontario Osteoarthritis of the Shoulder Index; WORC: Western Ontario Rotator Cuff Index; WOSI: Western Ontario Shoulder Instability Index.

reported results meaningful to the readers and researchers in the present and future.

CONCLUSION

There is substantial variability in the estimation of treatment effect through indices such as MCID, SCB or PASS for a given intervention and patient population that prevents their generalizability. Hence, researchers and clinicians must exercise caution while utilizing these indices with their patient population to estimate the treatment effect for any given intervention. The author suggests utilization of minimum COD for outcome selection and their recommended estimation of treatment effect for the given conditions to establish a standardized reporting method beneficial to global readers and researchers.

FOOTNOTES

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MINIREVIEWS

Voices that matter: The impact of patient-reported outcome measures on clinical decision-making

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Abstract

The critical role of patient-reported outcome measures (PROMs) in enhancing clinical decision-making and promoting patient-centered care has gained a profound significance in scientific research. PROMs encapsulate a patient's health status directly from their perspective, encompassing various domains such as symptom severity, functional status, and overall quality of life. By integrating PROMs into routine clinical practice and research, healthcare providers can achieve a more nuanced understanding of patient experiences and tailor treatments accordingly. The deployment of PROMs supports dynamic patient-provider interactions, fostering better patient engagement and adherence to treatment plans. Moreover, PROMs are pivotal in clinical settings for monitoring disease progression and treatment efficacy, particularly in chronic and mental health conditions. However, challenges in implementing PROMs include data collection and management, integration into existing health systems, and acceptance by patients and providers. Overcoming these barriers necessitates technological advancements, policy development, and continuous education to enhance the acceptability and effectiveness of PROMs. The paper concludes with recommendations for future research and policy-making aimed at optimizing the use and impact of PROMs across healthcare settings.

Key Words: Patient-reported outcome measures; Clinical decision-making; Patient-centered care; Healthcare technology; Data management; Policy development

Core Tip: Patient-reported outcome measures (PROMs) are essential for patient-centered care, offering insights into patients' health status and treatment impact. Addressing technological, policy, and educational advancements to maximize PROMs' effectiveness in healthcare, future efforts should focus on optimizing PROMs' integration and utility in clinical practice and research.

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INTRODUCTION

Patient-reported outcome measures (PROMs) represent a significant evolution in healthcare, emphasizing the subjective experiences of patients alongside traditional clinical metrics[1]. The genesis of PROMs traces back to a growing acknowledgment that patient perspectives are crucial for a holistic understanding of health outcomes. These tools capture a range of patient experiences and outcomes, from physical symptoms and functional status to psychological well-being and life satisfaction, directly reported by patients themselves without interpretation by clinicians or others[2]. This direct feedback from patients helps to map out the impact of diseases and treatments on daily living, providing insights that purely clinical parameters might miss. The role of PROMs in healthcare extends beyond mere measurement. They are increasingly integrated into clinical practice as vital components of patient care and clinical decision-making. PROMs serve not only to monitor disease and treatment response but also to guide clinical interventions and ongoing management strategies[3]. This integration reflects a broader shift towards patient-centered care, where healthcare systems aim to align treatments more closely with patient preferences, enhancing both the effectiveness and acceptability of care.

The importance of PROMs lies in their ability to bring the patient's voice into the clinical arena, ensuring that the care provided aligns with what matters most to the patients themselves. By systematically capturing how patients feel and function, PROMs provide a richer, more nuanced picture of the patient experience than traditional clinical outcomes alone[4]. This enhancement in data collection helps clinicians to tailor treatments to individual needs, potentially leading to improved health outcomes. In clinical settings, PROMs have been pivotal in expanding the understanding of various health conditions. For instance, in mental health, PROMs are utilized to assess conditions like depression and anxiety, often influencing treatment decisions such as the choice of therapeutic interventions and the monitoring of patient progress over time. Similarly, in chronic conditions like arthritis or diabetes, PROMs help in monitoring disease progression and the impact of treatments on patient quality of life, thereby guiding adjustments in management plans. The integration of PROMs into clinical practice has encouraged a more dynamic interaction between patients and healthcare providers[5,6]. It facilitates a dialogue where patients can express concerns about their health, which may be overlooked in standard clinical assessments. For example, in oncology, PROMs have guided discussions about symptoms and side effects that are critically relevant to patients' quality of life but might not be routinely solicited during clinical visits[7]. This ongoing feedback loop not only enhances patient satisfaction and engagement but also fosters a therapeutic alliance that supports better health outcomes.

UNDERSTANDING PROMS

Definition and types

PROMs are standardized, validated questionnaires used by patients to report on aspects of their health status that matter most to them, such as symptoms, functionality, and quality of life, without interpretation by clinicians or anyone else[8]. The core intent of PROMs is to capture data that reflect patients' perceptions of their health conditions, providing a direct insight into the impact of diseases and treatments from the patient's perspective[9]. PROMs can be broadly categorized into several types based on the nature of the information they aim to collect.

Symptom scales: These are designed to measure the severity and frequency of symptoms associated with specific health conditions. For instance, the Beck Depression Inventory and the Asthma Symptom Utility Index provide insights into the mental and respiratory symptoms patients experience, respectively[10].

Functional scales: These assess the impact of a health condition on a patient's ability to perform daily activities. The Health Assessment Questionnaire used in rheumatology and the Stroke Impact Scale are examples where patients' functional abilities and limitations are evaluated[10].

Quality of life assessments: These encompass broader aspects of a patient's life, including physical, mental, and social health. Tools like the 36-Item Short-Form Health Survey and the European five-dimensional health questionnaire are used across various diseases to assess overall well-being and quality of life[10].

Each type of PROMs is tailored to capture specific information that is relevant to different therapeutic areas, disease states, or treatment responses, allowing for a comprehensive understanding of patient outcomes[11,12]. The summary of commonly used PROMs in various health conditions is tabulated in Table 1.

Development and validation

The development of PROMs is a rigorous process that involves multiple phases to ensure that the measures are both reliable and valid[13,14] as shown in Figure 1. Initially, the conceptual framework of the measure is established, which involves defining what the PROMs aims to measure and why. This phase often includes extensive literature reviews, expert consultations, and patient interviews to identify relevant items that should be included in the measure. Following the conceptualization, item development begins. This stage involves creating the actual content of the questionnaire, including the questions and the response options. The items are then subjected to cognitive interviewing with patients to ensure that the language is clear and reflects the intended dimensions of health. Once a draft version of the PROMs is assembled, it undergoes psychometric testing to evaluate its reliability and validity.

Reliability refers to the consistency of the results produced by the PROMs when used in similar conditions over time. This includes testing for internal consistency and test-retest reliability to ensure stable performance.

Validity involves several assessments to confirm that the PROMs accurately measures the constructs it is intended to measure. This includes content validity, construct validity, and criterion validity, among others.

Validation may also involve exploratory and confirmatory factor analysis to understand the underlying relationships between items and to refine the scale based on statistical data.

Applications

Clinical trials: In clinical trials, PROMs are increasingly used as primary or secondary endpoints to determine the effectiveness of interventions from the patient's perspective[15]. For example, in trials for new oncology drugs, PROMs can provide data on how treatment impacts patients' symptom severity and quality of life, which is vital for regulatory approval and clinical practice.

Routine care: In everyday healthcare settings, PROMs assist clinicians in monitoring disease progression and treatment response[16]. For instance, in the management of chronic diseases such as diabetes, PROMs help track patients' self-reported symptoms and functional status over time, guiding adjustments in treatment plans and enhancing patient engagement in their care.

Policy-making: At the policy level, PROMs inform health services research and quality improvement initiatives. They are used to evaluate the quality of care delivered across different healthcare systems and to benchmark outcomes for healthcare providers. PROMs data contribute to the development of performance indicators and standards that ultimately shape health policy and practice, ensuring that the systems are responsive to the needs of patients[17,18].

BENEFITS OF PROMS IN HEALTH CARE

Enhancing patient-centered care

Patient-centered care is a critical component of modern healthcare, emphasizing the importance of incorporating the patient's perspective into the medical care process. PROMs are instrumental in this paradigm, as they provide a structured way to capture how patients perceive their health status and the impact of their treatments on their daily lives [19,20]. This inclusion of patient voices facilitates a more comprehensive approach to care assessment and planning, fostering a healthcare environment that respects and responds to individual patient preferences, needs, and values. PROMs empower patients by involving them directly in their care. By regularly gathering data on how patients feel and function, healthcare providers can gain a clearer understanding of the benefits and downsides of treatments as experienced by the patients themselves. For example, PROMs can reveal issues that are not typically covered during routine medical examinations, such as the impact of a chronic condition on a patient's mental health or social life. This can lead to more meaningful conversations between patients and healthcare providers, where decisions about treatments can be jointly discussed and aligned with what is truly important to the patient. Moreover, PROMs enhance patient engagement and satisfaction by demonstrating that healthcare providers value the patient's input in the care process. Engaged patients are more likely to adhere to treatment plans, attend follow-up appointments, and engage in proactive health management-all of which are crucial for effective disease management and prevention[21]. By systematically integrating patient feedback through PROMs, healthcare systems can create a more dynamic, responsive, and patient-focused service delivery model (Table 2).

Table 1 Overview of commonly used patient-reported outcome measures in various health conditions

Disease category	PROMs Name	Focus of PROMs	Description and use case
Mental health	Beck depression inventory	Symptoms	Used to measure the severity of depression. Commonly used in both clinical settings and research to monitor treatment effects
Respiratory conditions	Asthma symptom utility index	Symptoms	Assesses the frequency and severity of asthma symptoms, guiding treatment adjustments
Chronic conditions	Health assessment questionnaire	Functionality	Evaluates functional ability in patients with rheumatoid arthritis, influencing therapy and patient management
General well-being	The 36-Item Short-Form Health Survey	Quality of life	Broad assessment of patient quality of life across physical and mental health domains, used widely in various chronic conditions
Cardiovascular	Stroke impact scale	Functionality and symptoms	Measures the impact of stroke on physical and emotional aspects, aiding in recovery management
Oncology	European organisation for research and treatment of cancer quality of life questionnaire-core 30	Quality of life and symptoms	Commonly used in clinical trials for cancer to assess the quality of life and symptom burden during treatments

PROMs: Patient-reported outcome measures.

Table 2 Benefits and challenges of implementing patient-reported outcome measures

Benefits	Description	Challenges	Description
Enhanced patient-centered care	PROMs empower patients, leading to tailored treatments and higher engagement, which are critical for effective care	Data collection and management	Managing large volumes of patient data securely and efficiently poses significant logistical challenges
Improved clinical outcomes	Real-time data from PROMs facilitate timely adjustments in treatment, improving health outcomes	Integration into clinical practice	Modifying existing systems and workflows to include PROMs can be costly and time-consuming
Increased patient safety	Early detection of adverse effects or complications through PROMs enhances patient safety	Patient and provider acceptance	Skepticism about the accuracy and utility of PROMs may hinder their adoption by clinicians
Supporting research and policy	PROMs data enrich health services research and inform policy-making, leading to improved care standards	Training needs	Adequate training is required for healthcare providers to effectively interpret and use PROMs data

PROMs: Patient-reported outcome measures.

Improving clinical outcomes

The utilization of PROMs in clinical settings has a profound impact on improving clinical outcomes. These tools provide real-time data that help clinicians monitor and adjust treatments in ways that are most beneficial to patients[22,23]. In the management of chronic diseases, for example, PROMs allow for the continuous monitoring of symptoms and functional statuses, helping clinicians tailor interventions more precisely and promptly. In conditions like rheumatoid arthritis or multiple sclerosis, where patient conditions can fluctuate significantly, PROMs offer insights into the daily experiences of patients, enabling adjustments in medications or therapies before acute issues arise[24]. In the realm of mental health, PROMs facilitate the early detection of deteriorations in patient conditions, such as increases in depression or anxiety levels, that might not yet be clinically apparent. This early detection enables timely intervention, potentially averting more severe health crises. PROMs also allow for the tracking of patient responses to medications or other treatments over time, providing a basis for ongoing adjustments to therapeutic approaches[25,26].

Moreover, the use of PROMs in guiding treatment decisions has significant implications for improving patient safety [26]. By providing a direct feedback loop from the patient to the provider, PROMs help identify adverse effects or complications associated with treatments earlier than traditional clinical indicators might. For instance, in oncology, PROMs can track the side effects experienced by patients undergoing chemotherapy, allowing for faster interventions to mitigate these effects and thus improving the patient's quality of life and potential treatment adherence[7]. PROMs also play a crucial role in surgical care, where postoperative recovery can vary widely among patients. By implementing PROMs, surgeons can follow up on patients' self-reported recovery trajectories, identify those who may be at risk of poor outcomes, and intervene accordingly. This approach not only improves individual patient outcomes but also contributes to broader efforts to standardize postoperative care and enhance recovery protocols based on patient-reported data (Table 2)[27].

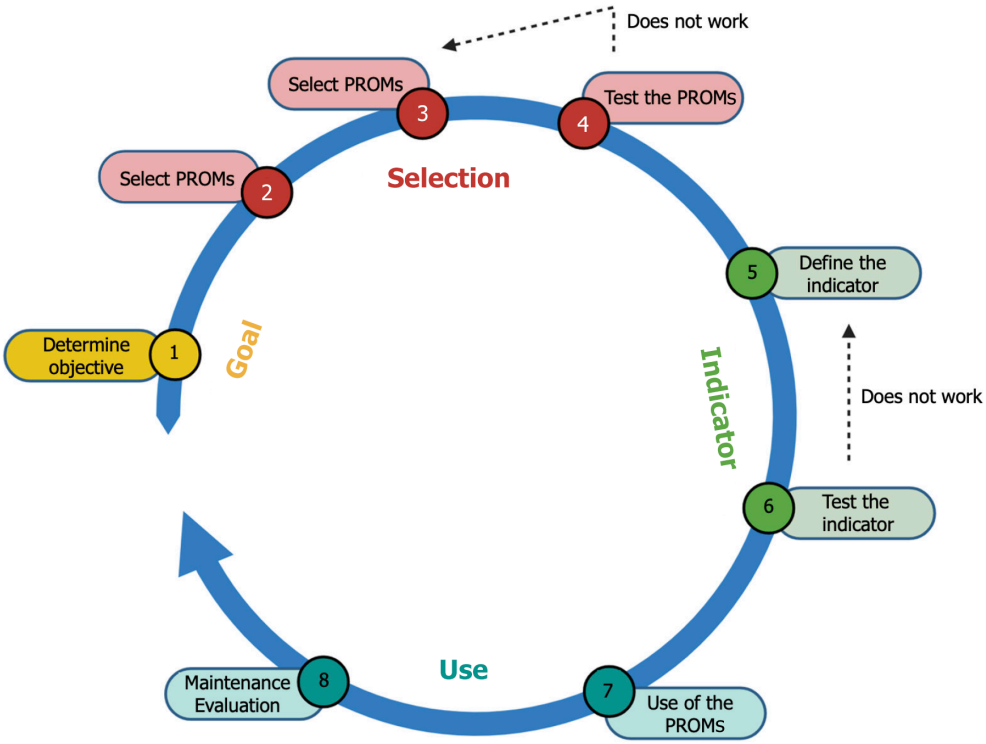

Figure 1 The patient-reported outcome measures cycle. PROMs: Patient-reported outcome measures.

CHALLENGES IN IMPLEMENTING PROMS

Data collection and management

The successful implementation of PROMs hinges significantly on the ability to efficiently collect, manage, and analyze large volumes of data. However, these processes come with several logistical challenges that can impede the effectiveness of PROMs. Firstly, the collection of PROMs data typically requires patients to complete questionnaires, which can be time-consuming and may lead to survey fatigue, particularly if surveys are lengthy or frequent. This fatigue can result in lower response rates or incomplete data, which diminish the reliability of the measures. Once collected, the management and analysis of PROMs data pose additional challenges. Healthcare organizations must ensure that data storage complies with privacy regulations such as the Health Insurance Portability and Accountability Act in the United States or the General Data Protection Regulation in Europe. Ensuring data security while maintaining easy access for authorized users requires sophisticated information technology systems, which can be costly and complex to implement[28]. Analyzing PROMs data also requires specialized statistical expertise. Health outcomes are often subjective and can vary significantly between patients, making it challenging to interpret results without advanced analytics techniques. Moreover, to be truly informative, PROMs data should be integrated with other clinical data, which involves additional layers of data management and analysis (Table 2)[27].

Integration into clinical practice

Integrating PROMs into routine clinical workflows presents its own set of barriers. One major challenge is the modification of existing electronic health records (EHR) systems to accommodate PROMs data. Many EHR systems are not initially designed to handle the free-text or varied format data provided by PROMs. Modifying these systems to integrate PROMs can be costly and time-intensive, and often requires ongoing maintenance and updates[16]. Furthermore, the integration of PROMs into clinical practice requires changes to the workflow of healthcare providers. Clinicians are often under significant time pressures, and adding the requirement to review PROMs data during patient visits can be seen as an additional burden. There is also the challenge of training staff to understand and effectively use PROMs data in their clinical decision-making processes. Without adequate training and perceived value in the PROMs, healthcare providers may be reluctant to adopt this practice fully (Table 2)[16].

Patient and provider acceptance

The acceptance and engagement of both patients and providers play critical roles in the successful implementation of PROMs. From the patient's perspective, the willingness to regularly complete PROMs can vary widely depending on factors such as the perceived relevance of the questions, the ease of completing the questionnaires, and the patient's overall engagement with their healthcare[29,30]. Some patients may also be concerned about privacy or skeptical about how their data will be used, which can further reduce their willingness to participate. Provider acceptance is equally crucial and similarly challenging. Some healthcare providers may doubt the reliability and validity of PROMs, particularly if the results contradict their clinical assessments or if they are unfamiliar with the use of PROMs in practice[31,

32]. There can also be a cultural barrier in healthcare organizations accustomed to prioritizing clinical over patient-reported data. Overcoming these barriers often requires demonstrating the value of PROMs through education and by showing evidence of their impact on patient outcomes (Table 2)[16].

FUTURE DIRECTIONS AND INNOVATIONS IN PROMS

Technological advances

The rapid evolution of digital technology has opened up new avenues for enhancing the capture and utility of PROMs. Digital health platforms and mobile applications are at the forefront of this transformation, providing innovative ways to collect, manage, and utilize PROMs data more efficiently and effectively[33,34]. Mobile apps, for example, can facilitate the regular collection of PROMs data by allowing patients to easily record their symptoms and quality of life in real-time, using their smartphones or other mobile devices. This real-time data collection can provide clinicians with more dynamic and timely insights into patient conditions, potentially leading to quicker adjustments in treatment plans. Moreover, these apps can be integrated with reminders and educational materials to enhance patient engagement and adherence to treatment protocols.

Digital health platforms that integrate PROMs data with EHR are another key innovation. These platforms can automate the flow of PROMs data into a patient's health record, making it immediately accessible to healthcare providers during clinical assessments[35,36]. Furthermore, advanced analytics can be applied to this integrated data to identify trends and patterns that might not be evident from manual analysis. For instance, machine learning algorithms can predict patient outcomes based on PROMs data, thereby informing more personalized and proactive care strategies[28].

Policy and standardization

As the use of PROMs expands across different health systems and disciplines, there is a growing need for comprehensive policy development and standardization. Standardization of PROMs is essential to ensure that data collected are comparable across different settings and populations, which is crucial for benchmarking and improving healthcare quality on a larger scale[30]. Policy development should focus on establishing clear guidelines for the selection, use, and interpretation of PROMs. These guidelines should address which PROMs are appropriate for different clinical conditions and care settings, how frequently they should be administered, and how the data should be interpreted and acted upon [37,38]. Furthermore, policies should ensure that PROMs are used ethically, protecting patient privacy and ensuring that data collection does not become burdensome or intrusive for patients[39,40]. Standardization efforts could also involve the development of universal PROMs that can be used globally across various health systems. This would facilitate international research and collaborations, enabling healthcare providers to learn from global best practices and innovations in patient-centered care[3].

Research opportunities

There are numerous areas for further research to improve the design, implementation, and interpretation of PROMs. One primary area is the development of more sophisticated measures that are sensitive enough to detect subtle changes in patient conditions but robust enough not to be affected by irrelevant factors. Research into patient psychology and behavior could inform the design of PROMs that better capture the nuances of patient experiences and expectations[24]. Another research opportunity lies in the integration of PROMs with other types of health data, such as physiological measurements and genomic data. This integration could lead to a deeper understanding of how patient-reported outcomes relate to other indicators of health and disease, potentially uncovering new insights into disease mechanisms and treatment effects[27].

Further research is also needed to explore the effectiveness of PROMs in different demographic groups, including those with varying levels of health literacy, language barriers, or cultural backgrounds. Studies could investigate how different populations interact with PROMs and how these tools can be adapted to meet diverse needs. This research would ensure that PROMs are inclusive and effective across all segments of the population[21]. There is a need for ongoing research into the use of artificial intelligence and machine learning to analyze PROMs data. These technologies have the potential to identify patterns and predict outcomes in ways that are not possible with traditional statistical methods, providing a more granular understanding of patient-reported outcomes and their implications for care[28].

CONCLUSION

PROMs are indispensable tools that enrich clinical decision-making and patient care by incorporating the patient's voice into health assessments. The integration of PROMs into clinical and research settings underlines a shift towards patient-centered healthcare, wherein the subjective experiences of patients are given weight comparable to traditional clinical indicators. While the implementation of PROMs presents challenges, including data management, integration into clinical practice, and acceptance by patients and providers, the benefits, notably in enhancing patient engagement and improving clinical outcomes, are profound. Recommendations for advancing the use of PROMs include investing in technological innovations to streamline data collection and analysis, developing comprehensive policies for the standardized use of PROMs, and continuous research to refine their validity and application. Further efforts should focus on training healthcare providers and educating patients to foster acceptance and maximize the utility of PROMs data in clinical and

policy-making contexts.

FOOTNOTES

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MINIREVIEWS

Surgical site soft tissue thickness as a predictor of complications following arthroplasty

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Abstract

Appreciation of soft-tissue thickness (STT) at surgical sites is an increasingly recognized aspect of arthroplasty procedures as it may potentially impacting postoperative outcomes. Recent research has focused on the predictive value of preoperative STT measurements for complications following various forms of arthroplasty, particularly infections, across procedures such as total knee, hip, shoulder, and ankle replacements. Several studies have indicated that increased STT is associated with a higher risk of complications, including infection and wound healing issues. The assessment of STT before surgery could play a crucial role in identifying patients at a higher risk of complications and may be instrumental in guiding preoperative planning to optimize outcomes in arthroplasty procedures. Standardized measurement techniques and further research are essential to enhance the reliability and clinical utility of STT assessment for arthroplasty surgery.

Key Words: Soft-tissue thickness; Arthroplasty; Surgical complications; Total knee arthroplasty; Total hip arthroplasty; Total shoulder arthroplasty; Total ankle arthroplasty; Preoperative assessment; Wound healing; Infection risk

Core Tip: This review examines the relationship between preoperative soft-tissue thickness (STT) and surgical complications in total knee arthroplasty, total hip arthroplasty, reverse shoulder arthroplasty, and total ankle arthroplasty. By synthesizing findings from multiple studies, we highlight the significant correlation between increased STT and higher complication rates. Our review underscores the importance of thorough preoperative assessment of STT to enhance surgical planning and patient outcomes in various arthroplasty procedures.

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INTRODUCTION

Total joint arthroplasty (TJA), which encompasses total hip arthroplasty (THA) and total knee arthroplasty (TKA) in addition to other forms of joint arthroplasty, is on the global rise due to its success in treating osteoarthritis (OA) and other debilitating joint conditions[1,2]. Along with an increase in OA in an aging population, comes an increase in arthroplasty procedures worldwide to restore mobility and help alleviate pain[3,4]. However, TJA, along with other surgical procedures, is not without risks and complications, which include surgical site and periprosthetic infection[5-9]. Infection can prolong hospital stay, increase costs, and even induce further surgeries or permanent disability[10]. Other complications include anesthetic-related issues, blood transfusion-related problems, and venous thromboembolism (VTE)[11]. These complications can be directly associated with increased morbidity and mortality. Therefore, understanding the risk factors for these complications must be understood to minimize risks and promote favorable outcomes.

Traditionally, body mass index (BMI) has been used to stratify patient risk before a TJA is performed due to its association with obesity, which has been a known risk factor for poorer surgical outcomes across a number of TJA procedure subtypes[12]. However, BMI can be a flawed measurement due to its poor ability to distinguish between muscle and fat within a body mass composition, and therefore lacks the ability to gauge for the presence of increased fatty soft tissue overlying the joint of interest[13-16]. Moreover, an individual with higher muscle compared to one with higher fat may have a lower risk for complications despite having a similar BMI. Alternative quantification methods, such as percent body fat and bioelectrical impedance analysis, correlate strongly with perioperative risks following TJA[17-19]. However, these measures require special testing that may not be easily accessible.

Soft-tissue thickness (STT) around the surgical site has shown relevance in predicting TJA outcomes and complications [20]. Increased STT can potentially complicate the arthroplasty surgery by requiring more dissection and retraction, which can lead to malalignment, component instability, longer operative duration, and post-operative infection and pain [21-24]. Advanced radiographic methods, such as magnetic resonance imaging (MRI) and computed tomography (CT) scans, can be used to further characterize the extent of the surgical site. Developing these radiographic measurements may offer precise measurements of STT and proved a representation of the local tissue geography. These measurements can provide anticipatory and management information regarding the complexity and complications of tissue retraction and alignment during the procedure. One study has indicated that increased STT, measured by preoperative MRI, is associated with a higher risk for wound complications after THA[25]. While STT shows promise as a marker for increased complications across various arthroplasty procedures, the use of this metric is not widespread and has not been reported across outcomes studies.

Thus, this review aims to examine and understand the effects of the extensivity of local periarticular STT on surgical outcomes following several varieties of TJA. By comparing the predictive value between STT and BMI, the review seeks to identify reliable yet accurate risk stratification methods. Understanding the application of STT could lead to improvements in surgical anticipation and management, therefore improving patient outcomes in TJA.

KNEE ARTHROPLASTY

The most prevalent TJA procedure is TKA, and the incidence of the procedure continues to increase. TKA is primarily performed in patients who have OA, rheumatoid arthritis (RA), and post-traumatic arthritis. Approximately seven studies investigated STT as a possible determinant of complication within TKA (Table 1). Of these seven studies, four found STT to be a significant determinant, while three of the studies did not find an association. The articles are summarized in Table 1.

Wagner *et al*[23] conducted a retrospective review in which the Patella-Femur Thickness Ratio (PFTR) was calculated to measure STT around the knee as a predictive measure to anticipate postoperative complications, specifically surgical site infection (SSI), after TKA[23]. This analysis of 528 patients indicated that those with a PFTR > 1 had a higher infection rate (5%) compared to patients with a PFTR < 1, indicating that PFTR may be a more reliable indicator of SSI risk than BMI, particularly in obese patients. The study included a small sample size of infections (n = 12), reducing the power of the statistical analysis. Moreover, the study was specific to the center of the patella, reducing a capacity to understand the implication of fatty deposition in other areas of the knee.

Table 1 Soft-tissue thickness in total knee arthroplasty

Ref.	Type of study	*n*	Mean BMI	Mean age	Indications for surgery	Approach	STT measurement definition	Outcomes studied	Results	Inter-rater reliabilities	Challenges
Wagner *et al*[23]	Retrospective	528	35.5	57.8	Osteoarthritis	Not specified	PFTR measured from radiographs	SSI, BMI, PFTR	Significant association between higher PFTR and increased risk of SSI	Strong agreement (r = 0.952; P < 0.001)	Small number of infections, limited generalizability to non-obese populations
Watts *et al*[24]	Case-control	116	44.8	62.7	Osteoarthritis	Not specified	PPT and PTT measured from radiographs	SSI, reoperation risk, PPT, PTT	Higher PPT and PTT associated with increased risk of reoperation	Excellent (Pearson coefficients: PPT 095, PTT 098)	Retrospective design, small sample size, potential unaccounted variables
Vahedi *et al*[22]	Case-control	824	32.5	63.9	Osteoarthritis	Not specified	Medial STT at joint line on AP radiograph; Anterior STT 8 cm above joint line on lateral radiograph	PJI, STT, BMI	Higher medial and anterior STT associated with increased risk of PJI	Excellent (ICC: Anterior STT 094, medial STT 096)	Retrospective design, potential unmeasured confounders, variability in surgical techniques
Shearer *et al*[28]	Retrospective	4745	32.1	68.3	Osteoarthritis	Not specified	PPT; KAI	PJI, surgical duration	BMI > 35 was strongly associated with PJI; local adipose measures were not significant	Excellent for KAI (inter: 0.94, intra: 0.99), moderate for PPT (inter: 0.75, intra: 0.99)	Variations in measurement techniques, low incidence of PJI, retrospective design
Yu *et al* [25]	Retrospective	376	30.9	66.2	Osteoarthritis	Not specified	PASTI using femoral and tibial measurements	Minor and major wound complications	High PASTI (> 3.0) associated with more minor complications (tibial OR: 3.89, femoral OR: 2.09); no significant difference in major complications	Excellent for both femoral and tibial PASTI (inter: 0.980/0.984, intra: 0.985/0.967)	Retrospective design, accuracy dependent on standardized X-ray technique, limited by proper lateral radiographs only
Gupta and Kejriwal [26]	Retrospective	494	30.6	71.3	Osteoarthritis	Medial parapatellar	PPT and PTT	Superficial wound complications	PTT ≥ 12 mm associated with lower risk of superficial wound complications (RR: 0.54); PPT not significantly associated	Measurement reliabilities not evaluated in this study, but previous study by Watts *et al*. noted high reliabilities (PPT: Intra 095, inter 0.92; PTT: Intra 098, inter 0.96)	Retrospective design, non-standardized surgical techniques, dressing types, and rehabilitation protocols, small sample size, no comparison group for BMI ≥ 40 kg/m^2
Secrist *et al*[27]	Retrospective	453	32.9	66	Osteoarthritis	Not specified	LEG ratio: Width of soft tissue envelope divided by bone width on lateral radiographs	90-day postoperative complications	No significant difference in LEG ratio between patients with/without complications; LEG ratio had no utility in predicting complications	Not specified	Retrospective design, novel measurement method not validated in previous studies, did not analyze intraoperative variables, limited to short-term complications

PFTR: Prepatellar fat thickness ratio; SSI: Surgical site infection; BMI: Body mass index; PTT: Pretubercular thickness; PPT: Prepatellar thickness; ICC: Intra-class correlation; PJI: Periprosthetic joint infection; STT: Soft-tissue thickness; KAI: Knee Adipose Index; PASTI: Preoperative Anterior Soft-Tissue Index; OR: Odds ratio; RR: Relative risk; LEG: Lower extremity girth.

Similarly, Yu *et al*[25] developed tibial and femoral Preoperative Anterior Soft-Tissue Index (PASTI) ratios that deviated from lateral knee radiographs to predict postoperative complications[25]. The study indicated that among 374 patients, those with high PAST (> 3.0) had significantly higher rates of minor complications for both tibial ($P < 0.001$) and femoral ($P < 0.013$) measurements, indicating a better predictor of complications of BMI. BMI indicated no significant correlation. The study was limited in its retrospective nature and dependency on accurate X-ray techniques for PASTI measurements.

Watts *et al*[24] used lateral knee radiographs to measure prepatellar thickness (PPT) and pretubercular thickness (PTT) to examine the relationship with early preoperative risk due to wound complication or infection after TKA in morbidly obese patients[24]. The study found that PPT and PTT are more predictive than BMI, indicating those with PPT ≥ 15 mm and PTT ≥ 25 mm had higher risks of reoperation (relative risks of 2.0 and 1.6, respectively). The study stated that BMI did not correspond with an increased preoperative risk. The study was limited in its retrospective design, possibly overlooking other surgical factors such as techniques and postoperative care.

Vahedi *et al*[22] investigated medial and anterior STT from AP and lateral radiographs to assess the association between STT and the risk of periprosthetic joint infection (PJI) following TKA[22]. The study indicated that patients with a higher prepatellar fat thickness ratio (PFTR) had an increased risk of infections. Those with a PFTR ≥ 1 had an infection rate of 5%, while those with PFTR < 1 had infection rates of 1.5% ($P < 0.05$). The study was limited in its retrospective design and relatively small number of infection cases ($n = 12$), limiting the generalizability of the study.

Gupta and Kejriwal assessed anterior subcutaneous fat thickness and superficial wound complications in nonmorbidly obese patients who underwent TKA[26]. Within the 494 patients, those with a PTT ≥ 12 mm had a significantly lower risk to develop superficial complications within 90 days of the operation (relative risk 0.54, $P = 0.028$). The results also indicated that PPT showed no significant association. The study was limited in its retrospective design and small sample size. Additionally, there were no comparison groups for patients with BMI ≥ 40. The inter-rater and intra-rater reliability was not discussed.

Secrist *et al*[27] investigated whether BMI or lower extremity growth (LEG) ratio is a better predictive measure for complications in TKA[27]. Within 453 patients, those with LEG ratios above or below 5 indicated no significant difference in postoperative complication rates. However, BMI > 35 was more predictive of complications ($P = 0.0637$). Moreover, the sensitivity and specificity of the LEG ratio as a predictive measure were poor. The study was limited in its retrospective design and unvalidated LEG ratio method. Intraoperative variables and comorbidities were not considered as well.

Shearer *et al*[28] investigated the predictive value of BMI and local knee adiposity measures for PJI and surgical duration after TKA[28]. The results indicated that those with a BMI > 35 were significantly associated with a higher risk for PJI (odds ratio = 2.9, 95%CI: 1.4-6.1). Conversely, knee adipose index (KAI) and prepatellar fat thickness did not correlate significantly with PJI. BMI and local adiposity measures correlated with higher surgical duration. The study was limited in its retrospective design and variability in X-ray techniques. Additionally, the infection rates were only captured within one year postoperatively, potentially not fully capturing the extensivity of possible infections.

Taken together, a growing number of studies have indicated that increased STT around the knee may correspond to higher complication risk and rates following TKA. Specific complications include SSI, PJI, and wound complications such as hematomas and wound dehiscence. Moreover, STT can lead to greater dead space, affecting wound healing in knee arthroplasty, resulting in prolonged operative times and more extensive soft tissue injury. Therefore, accurate preoperative assessment is imperative.

HIP ARTHROPLASTY

THA is most commonly indicated in patients with primary OA of the hip, osteonecrosis of the femoral head, and femoral neck fractures[29]. Pre-operative assessment and planning in THA patients is critical, just as in any arthroplasty or surgical procedure. Radiographs with quantified magnification of the hip are obtained to initiate pre-operative planning with assessing anatomical landmarks, establishing acetabular cup and femoral stem size, and anticipating intra- and post-operative challenges[30].

Obesity, defined as a BMI ≥ 30 kg/m^2, is a reducible risk factor that may be associated with some intra- and post-operative challenges. High BMI may pose an increased risk of superficial and deep infections, hip dislocations, re-operations, revisions, and readmissions[31,32] in THA. In one study regarding wound drainage in THA, obesity was shown to prolong wound healing, with morbidly obese patients having increased time to dry wounds. Furthermore, prolonged wound drainage was shown to be a significant predictor of wound infection[33]. Studies have shown that increased wound drainage time is associated with post-operative THA wound infection – both deep wound infections and superficial soft-tissue infection[34,35].

In addition, STT has been posed as another risk factor for complications in THA. There were eight articles examining the effect of STT on THA complications (Table 2). Measurement methodology of STT differed amongst studies, with two studies reporting thickness ratios, four studies reporting fat depth from greater trochanter to skin, and two studies using anterior superior iliac spine (ASIS) and pubic symphysis (PS) as measurement landmarks (Table 2). A variety of

Table 2 Soft-tissue thickness in total hip arthroplasty

Ref.	Type of study	Approach	STT measurement definition	Inter-rater and inter-observer reliabilities	Outcomes studied	Results
Bell *et al* [38]	Retrospective case-control analysis	Posterolateral	Skin tosourcil distance; tip of the GT to skin; lateral prominence of GT to skin	Inter-rater reliabilities: Skin to sourcil: 0.966; Tip of GT to skin: 0.958; lateral prominence of the GT to skin: 0.981	Compare interobserver reliability; peritrochanteric fat thickness association with increased wound complications and infection in early post-operative period	No association between peritrochanteric fat and infections/wound complications in primary THA patients
Hohmann *et al*[29]	Retrospective review	Lateral	Length from bilateral ASISs to the skin surface at a right angle to each ASIS as ASIS-thickness; Length from PS to skin surface at a right angle to the PS as PS-thickness	NR	Examine the relationship between postoperative acetabular cup angles and anterior pelvic STT overlying the anatomical landmarks; investigate the difference between obese patients and normal/overweight patients	No significant relationships between BMI, intraoperative cup placement, or final cup placement for both inclination and anteversion; No significant relationships between STT over either ASIS or pubic tubercle with respect to acetabular cup orientation; no association between inclination/anteversion angles and anterior pelvic soft tissues
Mayne *et al*[41]	Prospective series	Posterior	FD	NR	Post-THA complications: Dislocation, infection, periprosthetic fracture, wound dehiscence. Comparing with BMI and fat depth	Patients within upper quartile of FD were not at increased risk of developing complications, as compared to patients within lower quartile of FD; patients with highest BMI (≥ 40 kg/m^2) had significantly increased risk of complications, as compared to patients with lower BMI (< 40 kg/m^2); Patients with highest BMI had significantly greater proportion of post-operative infection, as compared to lower BMI; number of patients within upper quartile of FD was 311, higher than the 60 patients in the BMI ≥ 40 kg/m^2 category. Conclusions: Fat depth is not more useful in predicting complications and poor outcomes following THA
Rey Fernandez *et al*[36]	Case-control study	Posterolateral	Distance from the tip of the GT to the skin following a perpendicular line to the femoral diaphysis in post-operative AP hip radiographs	NR	APJI	Larger STT radiographic measurement associated with higher risk of APJI
Sezgin *et al*[37]	Retrospective cohort review	Anterolateral	Distance between most lateral point on the GT to the skin, on an axis perpendicular to the anatomical axis of the femur; HFTR: Subcutaneous fat tissue thickness divided by diameter of femoral diaphysis at level just inferior to minor trochanter	Pearson's coefficients: 0.981 (inter-observer), 0.965 (intra-observer)	Use HFTR and determine efficacy as a predictor of failure risk in 1-year post-operative period of primary THA	Increased peri-incisional subcutaneous fat tissue thickness associated with higher risk of failure of THA (*i.e.* reoperation, revision, death after 1 year)
Sprowls *et al*[40]	Retrospective cohort review	Anterolateral, posterior, lateral, direct anterior, hueter/smith-peterson	Thickness ratio (lateral/anterior): Lateral and anterior measurements of subcutaneous hip fat were obtained from CT, in slice where femoral head diameter was widest	NR	Compare thickness of subcutaneous fat in lateral hip incision (posterior, lateral, anterolateral approaches) with that of an approach using anterior incision (direct anterior and variations of Hueter or Smith-Peterson approach); examine relationship between BMI	Incision STT was greater for lateral hip incision approaches than for anterior incision; Greater BMI was associated with greater distribution of subcutaneous fat around the hip, based on sex and age; Lateral subcutaneous fat is greater in women, regardless of age or BMI

					and distribution of subcutaneous fat, based on sex and age	
Sprowls *et al*[38]	Retrospective cohort review	Direct anterior, posterior	Subcutaneous fat depth measurement obtained from superficial extent of fat layer, along lateral skin flap. Anterior and lateral thickness measurements were obtained	NR	Intraoperative thickness of subcutaneous fat at incision site for direct anterior *vs* posterior approaches; Examine relationship between fat thickness and 90-day post-operative complications	More soft tissue encountered with posterior than direct anterior approach; greater STT was associated with greater rates of re-operation; excess incisional fat was associated with higher rates of wound complications
Suzuki *et al*[43]	Retrospective observational study	Anterolateral	Length from bilateral ASISs to the skin surface at a right angle to each ASIS. Average of right and left used as the ASIS-thickness; length from PS to skin surface at a right angle to the PS as PS-thickness	Intra- and inter-observer reliabilities > 0.900 (high intraclass correlation coefficient)	Evaluate association between cup alignment errors and obese patients	PS-thickness and ASIS-thickness associated with radiographic anteversion and inclination errors, while BMI only associated with radiographic anteversion errors; PS-thickness and ASIS-thickness both risk factors for cup implantation error of acetabular component using HipCOMPASS technology

ASIS: Anterior superior iliac spine; CT: Computed tomography; FD: Fat depth; GT: Greater trochanter; HFTR: Hip fat thickness ratio; NR: Not reported; PS: Pubic symphysis; STT: Soft-tissue thickness; APJI: Acute periprosthetic joint infection; BMI: Body mass index; THA: Total hip arthroplasty.

approaches exist amongst studies, with anterior, anterolateral, and posterior being the most common. Association between STT and THA complications varied between studies, with some concluding that increased STT increases risk of wound and post-operative complications[36-38] and other studies noting no such association[39]. In one study looking at associated characteristics in patients with increased STT, it was found that STT was greater in lateral hip incision approaches as compared to the anterior approach[40]. In addition, a greater BMI was associated with a greater STT with predominance of lateral fat greater in women[40]. However, as noted by Mayne *et al*[41], BMI is a non-specific indicator of obesity and does not take into account anatomy such as fat distribution. Thus, STT and BMI are not necessarily interchangeable and STT may offer unique predictive value that BMI does not[41].

Some studies analyzed the effect of STT on post-operative acetabular cup positioning. Cup positioning in THA is critical, as malpositioning may lead to loosening of hardware, impingement, and increased rate of post-operative hardware dislocation. Increased STT is believed to obscure anatomical landmarks and increase rates of acetabular cup malpositioning[42]. Hohmann *et al*[29] reported no significant relationship between STT and acetabular cup placement [29], while Suzuki *et al*[43] reported that PS-thickness and ASIS-thickness were associated with cup implantation errors [43].

Limitations to the current literature on STT and complications of THA include the small sample size of patients that develop post-operative complications or re-operation. Another limitation is inherent in the imaging data available such as positioning of patients, calibration markers, and magnification which can all skew measurements[29,39,40]. Rey Fernández *et al*[36] has indicated that increased STT, measured by preoperative MRI, is associated with a higher risk for wound complications after THA[36].

SHOULDER ARTHROPLASTY

OA, RA, complex fractures of the proximal humerus, osteonecrosis of the humeral head, irreparable tears of the rotator cuff with or without arthropathy, and revisions of failed prosthesis are the most commonly indicated reasons to perform shoulder arthroplasty[44]. Shoulder arthroplasty can serve as a successful treatment option for this variety of pathologies once nonsurgical options have been exhausted[44-46]. Between 2011 and 2017, the number of primary shoulder arthroplasties increased by 103.7%, and reverse shoulder arthroplasties (RSA) increased by 191.3%. A linear projection model and Poisson model have predicted a 67.2% and 235.2% increase in shoulder arthroplasties, respectively, by 2025[46].

A meta-analysis from Bohsali *et al*[47], examined articles published between 2006 and 2015 pertaining to total shoulder arthroplasty (TSA) complications and RSA complications. The overall complication rate for both procedures was 11%. For TSA, common complications from highest to lowest incidence were component loosening, glenoid wear, instability, rotator cuff tear, periprosthetic fracture, neural injury, infection, hematoma, deltoid injury, and VTE. For RSA, common complications from highest to lowest incidence were instability, periprosthetic fracture, infection, component loosening, neural injury, acromial and/or scapular spine fracture, hematoma, deltoid injury, rotator cuff tear, and VTE[47].

To date, there is no literature evaluating the role of radiographic STT in predicting TSA complications. In RSA, increased radiographic STT has been identified as a significant predictor of operative and post-operative complications. In a retrospective chart review of patients who underwent RSA, a greater shoulder STT from measurements of the radius from the humeral head center to the skin, deltoid radius-to-humeral head radius ratio, deltoid size, and subcutaneous tissue size were demonstrated to be a strong predictor of operative time, length of stay, and postoperative infection rate (Table 3)[48]. Specifically, the distance from the humeral head center to the skin was shown to have the highest predictive

Table 3 Soft-tissue thickness and complications in shoulder arthroplasty

Ref.	Type of Study	Approach	Soft-tissue thickness measurement	Inter-rater and inter-observer reliabilities	Outcomes studied	Results
Wu *et al*[48] (2023)	Retrospective chart review	Reverse shoulder arthroplasties	Distance from the center of the humeral head to the skin. Ratio of the deltoid radius to the humeral head radius. Deltoid size. Subcutaneous tissue size	NR	Length of stay. Operative time. Infection	Greater shoulder soft-tissue thickness is a strong predictor of length of stay, operative time, and postoperative infection in primary reverse shoulder arthroplasties patients

NR: Not reported.

power for these outcomes[48]. Thus, indicating that greater STT poses a substantial challenge during RSA, leading to prolonged surgeries and increased postoperative complications.

STT can be obtained relatively easily from the preoperative radiograph, thus allowing for an estimation of adipose tissue distribution at the surgical site. Furthermore, prior operative shoulder surgical status and patient smoking status should be of particular interest. Orthopedic surgeons may use this assessment to plan for potential postoperative complications in patients with greater STT, prior shoulder arthroplasty, and a history of smoking with extended oral antibiotic prophylaxis or another suitable alternative[49,50].

Optimizing patients before surgery extends beyond just STT. Using a large dataset, Boddapati *et al*[51] prospectively collected 30-day outcomes to determine the relationship between revision TSA and primary TSA postoperative complications. From this, they identified wound infections to be significantly more common in revision TSA compared to primary TSA. Patients with a history of smoking served as a significant independent risk factor in the development of postoperative wound infections, which is supported by previous literature demonstrating increase in the risk of postoperative healing complications in both orthopedic and non-orthopedic procedures[49,50]. Boddapati *et al*[51], credited this increase in wound infections to the increased rate of *Propionibacterium* acne colonization of the shoulder, specifically mentioning that this bacterium is most commonly found in the pilosebaceous follicles of the upper body, such as the axilla, and that a prior prosthetic implant significantly increases the risk of infection[51].

ANKLE ARTHROPLASTY

Late-stage ankle arthritis is a disabling degenerative disease of the tibiotalar joint that inflicts significant pain and causes impaired function in patients[52-54]. After unsuccessful nonoperative conservative management, total ankle arthroplasty (TAA) and tibiotalar arthrodesis are the two most common surgical treatment options[55]. Over the past 30 years, TAA has become increasingly more popular with the development of newer implant designs and improved surgical techniques. Karzon *et al*[52] performed a retrospective database review and identified a total of 41060 TAAs performed from 2009-2019, where annual volumes increased by 136.1% from 2,180 in 2009 to 5147 in 2019[52]. From 2017-2030, the incidence of TAAs has been projected to increase from 110% to 796%[55]. A systematic review observed a mean complication rate of 23.7% for TAA, where the postoperative complications from highest to lowest incidence were aseptic loosening, intraoperative fracture, implant failure, and wound problems.

As evident from this review, preoperative radiographic STT has been suggested as a predictor outcome following hip, knee and shoulder arthroplasty. To date, only one study has explored radiographic STT as a predictive metric for identifying patients at risk of requiring revision surgery following primary TAA. Wu *et al*[56] performed a retrospective comparative study on 323 patients who underwent primary TAA between 2003 and 2019 (Table 4)[56]. Preoperative tibial tissue thickness was calculated as the distance from the posterior distal tibia to the anterior distal tibia, and preoperative talus tissue thickness was calculated as the distance from the lateral process of the talus to the head/neck junction of the talus. In patients who required revision surgery there was greater preoperative tibial and talus tissue compared to those not requiring revision. Furthermore, a multivariable logistic regression controlling for age, gender, BMI, American Society of Anesthesiologists classification, diabetes status, smoking status, primary diagnosis, and implant type demonstrated that both tibial tissue and talus tissue were significant predictors of revision surgery with tibial tissue thickness being the stronger of the two.

Implant malalignment may offer an explanation for STT being a predictor for revision following primary TAA. Implant malalignment can result in elevated edge loading, polyethylene wear, bearing subluxation, and premature failure of primary TAA. Additionally, malalignment can exacerbate any uneven distribution of force in the bone[57,58]. A retrospective study from Richter *et al*[59] examined primary TAA using a single-design three-component ankle implant in 1006 patients. The cumulative incidence of implant revision was 9.8%, and the most common indication for revision was instability at 34%. In this study, instability was defined as the progressive varus/valgus malalignment of the hindfoot and/or coronal malalignment of the talus in the ankle mortise[59]. Furthermore, a study from Clough *et al*[60] reported the clinical and radiological outcomes for 200 TAAs using the Scandinavian Total Ankle Replacement implant. Edge-loading of implants from coronal plane malalignment (varus or valgus) was the reason for revision surgery in 25% of patients. Three of their patients were required to have the polyethylene components exchanged due to excessive wear,

Table 4 Soft-tissue thickness and complications in ankle arthroplasty

Ref.	Type of study	Approach	Soft-tissue thickness measurement	Inter-rater and inter-observer reliabilities	Outcomes studied	Results
Wu *et al* [56] (2024)	Retrospective Study	Anterior	Posterior distal tibia to the anterior distal tibia (tibial tissue). Lateral process of talus to the head/neck junction of the talus (talus tissue)	Inter-observer Reliabilities: Tibial Tissue: 0.982; Talus Tissue: 0.935	Revision total ankle arthroplasty	Greater soft-tissue thickness was strong predictor of revision total ankle arthroplasty

and one patient was ultimately converted to an ankle fusion due to a late stress fracture that resulted in malalignment [60].

Increased STT could pose a challenge for proper alignment, as the increased thickness may result in orthopedic surgeons experiencing a higher degree of surgical complexity when properly positioning the implant within the ankle joint and performing soft tissue balancing. To this point, increased STT at the surgical site could impair visualization of the surgical field, further increasing surgical complexity when attempting to achieve proper alignment. A key limitation to address between the ankle joint in comparison to the hip and knee specifically, is the difference in soft-tissue coverage. Previous literature has underscored the importance of sufficient soft tissue coverage of the prosthesis in managing wound healing complication[61]. The ankle joint has significantly less soft tissue coverage compared to the hip and knee, and hence could affect the risk of complications following TAA. This reduced coverage means that while increased STT has been demonstrated to be predictive of complications in other lower-extremity arthroplasty, the specific anatomical characteristics of the ankle could alter these dynamics and warrants further research exploring this in greater depth. Overall, patients who experience greater STT may benefit from strategies aimed at managing the impact of STT on proper implant alignment through preoperative planning and intraoperative techniques[62].

MEASUREMENT CONSIDERATIONS

Inter-rater reliability pertains to consistency of measurements between multiple raters, and intra-rater reliability refers to consistency of measurements between an individual rater. Inter- and intra-rater reliability is important in the ability to replicate results and can be quantified using coefficients examples include intra-class correlation and Pearson (*r*)[63]. In pre-operative planning, this is important, as lower reliability may cause inaccurate mapping and registration of anatomical landmarks, and thus leading to improper positioning of prostheses[64].

The ability to make accurate and repeatable measurements is often limited by the radiographs obtained. As discussed in prior sections, positioning of patients may affect measurements. In addition, presence of inflammation and hematoma may affect STT and other metrics[36]. Standard positioning and calibration practices may mitigate some discrepancies in radiographs.

Due to the variation in measurement methodology of STT, a standardized measurement technique may prove beneficial. For THA, STT measurements that have been described encompass taking distances between two structures or using radiographic lines and various ratios. For TKA, measurements also vary across studies, ranging from measuring thicknesses (*i.e.* PPT, pre-tubercular thickness, anterior STT, medial STT) to ratios (*i.e.* prepatellar fat thickness ratio, KAI, periarticular soft-tissue index, lower extremity girth)[36].

FUTURE DIRECTIONS

STT has shown promise as a potential predictive tool for complications after TJA. However, accurately measuring the soft tissue is essential for respective validity and reliability. Accurate and consistent measures of STT allow for proper guidance in surgical planning and may help in understanding patient outcomes, allowing for enhanced preoperative patient counseling and expectation management. Measurements of STT have the potential to significantly enhance clinical decision-making by being integrated into existing clinical pathways. For example, incorporating STT indicators could help identify patients at higher risk for pressure ulcers or wound complications, allowing for early intervention and tailored management plans. Additionally, STT measurements could inform surgical planning by helping to customize treatment approaches based on individual soft tissue characteristics, improving outcomes and reducing complications. Overall, using STT data in risk assessment and patient management could lead to more personalized and effective care strategies.

Integrating artificial intelligence (AI) in preoperative assessment is a promising aspect for further research. Further resources and research with AI capability have shown its capabilities in analyzing image data at an accurate, reliable, and timely rate[65,66]. Therefore, AI can be a potential avenue to provide an accurate and precise way to deconstruct the complexity of the soft tissue envelope surrounding the joints. Additionally, redefining and standardizing current measurement techniques is essential for producing accurate and reproducible metrics. Additionally, developing ratios or indexes that account for individual baseline size in evaluating soft tissue distribution compared to simple measurements alone can make these metrics more accurate. Several ratios and indices have been proposed to account for variations in tissue distribution. In TKA patients, Wagner *et al*[23] examined a ratio comparing prepatellar fat to the patella itself to

account for patient size[23]. Similarly, Secrist *et al*[27] investigated the LEG ratio in TKA. In RSA, Wu *et al*[48] used a ratio comparing the size of the deltoid radius to the humeral head[48].

Several studies have explored the use of AI to evaluate various body parts including musculoskeletal structures[67,68]. Ning *et al*[69] employed a network model to accurately measure plantar STT in weight-bearing foot X-rays, demonstrating its potential for assessing foot health[69]. Additionally, foundation models have been explored as a possibility to address complex segmentation[67,68,70]. Foundation models are neural networks trained on vast data using creative learning objectives, enabling them to perform zero-shot learning on new data without traditional labels[68]. They have shown transformative abilities in natural language processing and demonstrated promising segmentation performance. For example, Gu *et al*[70] recently developed a deep-learning model using 8485 annotated slices to segment bone within MRI images[70]. These developments and models can be developed in the future to include STT and provide risk stratification.

Future studies should be implemented, ideally across multicenter samples, to fully enhance the clinical utility of measurements of STT and establish reliable and standardized protocols and thresholds. This additional research will optimally allow for confident and effective preoperative planning and risk stratification for TJA patients when STT is measured and used. Utilizing advanced imaging modalities can be a way to provide more detailed and consistent measurements. CT, already used in spine surgery to assess STT, can be further investigated for TJA[71]. CT scans can provide a more reproducible measurement of soft tissue around the joints. Future research must investigate whether CT scans can provide a better predictive measure for postoperative complications.

CONCLUSION

This comprehensive review highlights the significance of preoperative STT as a predictive measure for complications following arthroplasty procedures, including total knee, hip, shoulder, and ankle replacements. The findings across studies generally indicate that increased STT is often associated with higher risks of postoperative complications such as infections, wound healing issues, and SSI. These complications can lead to extended hospital stays, increased healthcare costs, and the need for further surgical interventions. While BMI has traditionally been used to assess patient risk, it falls short in accurately representing local tissue composition relevant to specific joints. In contrast, STT provides a more precise measure, particularly with advancements in radiographic techniques such as MRI and CT scanning that allow for detailed preoperative assessment. Several studies have demonstrated that STT is a reliable predictor of complications, offering valuable insights for preoperative planning and patient management. However, variability in measurement methodologies and the need for standardized techniques highlight the necessity for further research. The integration of AI in analyzing STT could revolutionize preoperative assessments by providing accurate and timely evaluations of the soft tissue envelope surrounding the joints. Continued research is essential to refine these methods and fully realize the potential of STT in guiding preoperative planning and optimizing arthroplasty results.

FOOTNOTES

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MINIREVIEWS

Magnification: The game changer in dentistry

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Abstract

During dental examinations and treatments, many dentists are using magnification to improve their vision. The dental operating microscope serves as the most effective tool for this purpose, enhancing the quality, longevity, and outcome of clinical work. This review will explore the latest research and data on the importance of magnification devices in dentistry, including diagnostic methods, treatment options and ergonomics in specialities such as restorative dentistry, endodontics, pedodontics, periodontics, and prosthodontics. This review aims to provide insights into the optimal magnification for different clinical situations, the specific benefits of dental operating microscopes for each dental branch, and their limitations.

Key Words: Magnification; Vision; Endodontics; Dentistry; Dental operating microscope

Core Tip: The primary purpose of using magnification devices in dentistry is to improve visibility and ergonomics. This is particularly crucial when treating obscure micro-anatomy for a prolonged amount of time. Nonetheless, the use of magnification in dentistry has yet to be widely accepted in general practice due to a variety of reasons in clinical practice.

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INTRODUCTION

People have always viewed magnification devices with a lack of confidence, which has sparked fascination and intense discussion. A variety of healthcare professions now commonly use magnification devices due to their significant benefits in identifying and treating certain diseases. Magnification alone can achieve the current goal of preventing as much healthy tooth structure as possible[1]. Nowadays, advanced dentistry strongly encourages the use of dental operating microscopes (Figure 1) and loupes (Figure 2), especially when treating endodontic procedures. Endodontics has created innovative procedures for root canal treatment that improve operative field visibility[2,3]. The small area of the operating field, insufficient lighting, and poor ergonomics encouraged the use of magnification advancements in clinical practice. Nowadays, there has been a rise in the use of magnification devices among practitioners of various specialisations, as well as the success of minimally invasive dental techniques[4].

A successful dentist must have two qualities: (1) Delicate skills and strong vision. Hard work and consistent training can refine controlled and very precise actions, which are not inherent but learned. The ability to see well is a natural characteristic of all eyes; and (2) Dentists should be aware of their visual abilities, as well as the numerous strategies for compensating for visual deficits[5].

The human eye can distinguish between two separate entities that are at least 0.2 mm away. A dental operating microscope offers a significant advantage: It can distinguish these entities at a distance of only 0.006 mm[6]. In other words, "the resolution of the human eye improves dramatically".

Dentists frequently perform treatments that need more resolution than a healthy eye can offer. Magnification enables the visualization of minute details in the operating field, enhancing their ability to identify and restore dental abnormalities[7].

HISTORY OF MAGNIFICATION DEVICES

The microsurgical technique began in 1960, Jacobson and Suarez developed the micro-surgical methods by joining tiny vessels using an operating microscope[8]. The literature[9] provides a history of microsurgical procedures in medicine. Following that, micro-surgical techniques underwent significant development and clinical application in many medical and dental specialities around the world. This would not have been possible without the development of the dental operating microscope, precise microinstruments, and microsutures.

Types of magnification devices

Dentists utilize a variety of magnification devices, including loupes and dental operating microscopes: There are several types of loupes available, depending on their optical construction.

Single-lens loupes: Basic and less expensive, but limited in magnification.

Galilean loupes: Typically offer 2.5 × magnification but can reach up to 3.2 ×.

Keplerian loupes: Provide a wider range of magnification, typically between 3.5 × and 4.5 ×, with improved depth of field.

Surgical microscopes: These provide higher magnification (up to 30 ×) and better control over the field of view, making them ideal for complex procedures in both restorative dentistry and endodontics. Modern surgical microscopes also allow for the integration of cameras to capture high-resolution images, aiding patient communication and documentation [33,34].

Magnification's ergonomic and clinical advantages

Magnification devices provide significant ergonomic advantages by encouraging better posture during procedures. Research has demonstrated that using loupes and microscopes helps to reduce musculoskeletal strain and prevent repetitive stress injuries. Improved posture not only enhances clinician comfort, but also prolongs career longevity by reducing the physical toll of dental practice[35].

Limitations of magnification devices

While magnification devices are invaluable tools, they come with certain limitations: (1) Cost: Magnification devices, especially surgical microscopes, can be expensive, making them a significant investment for dental professionals[2,9]; (2) Learning curve: Effective use of higher magnification devices requires training and experience[36]. There may be an initial adjustment period for clinicians learning to work with microscopes or advanced loupes; and (3) Field of view: As

Figure 1 Working with the dental operating microscope.

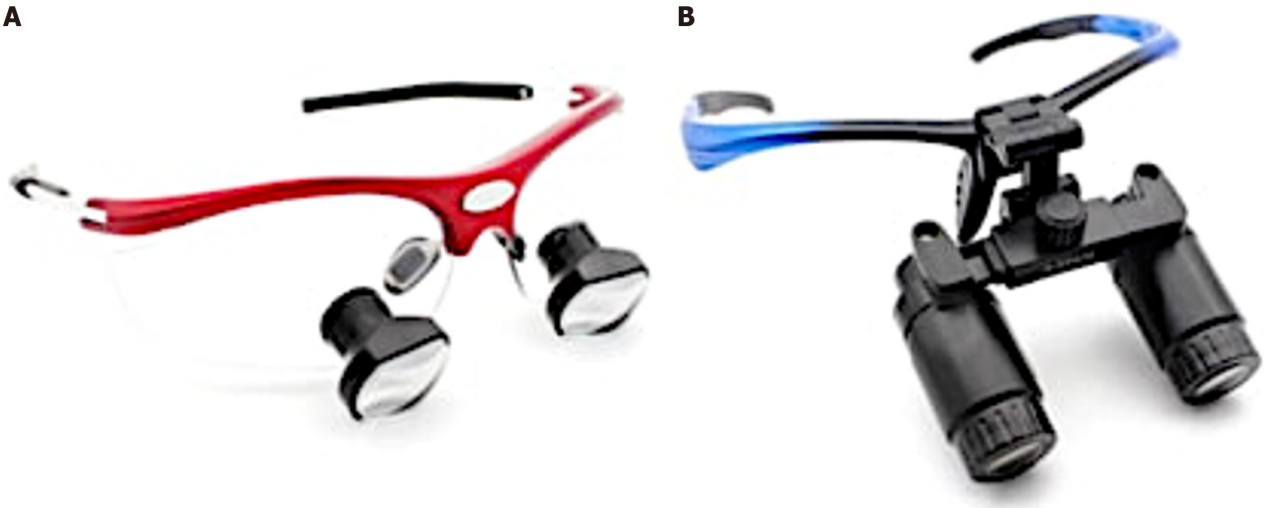


Figure 2 Different types of loupes.

magnification increases, the field of view narrows, which can make it challenging to maintain focus during procedures. This necessitates precise handling and a steady hand[37].

Research and clinical outcomes

Several studies have demonstrated the positive impact of magnification devices on clinical outcomes[11]. Research shows that clinicians using microscopes achieve better diagnostic accuracy, especially in detecting minute issues like cracks or cavities. Additionally, endodontic microsurgical procedures, such as osteotomies and retrograde fillings, benefit from the enhanced precision provided by high magnification[38].

Magnification devices, ranging from basic loupes to advanced surgical microscopes, play an essential role in modern restorative dentistry and endodontics. The ability to visualize fine anatomical details improves diagnostic accuracy,

procedural precision, and overall clinical outcomes. While there are challenges associated with cost and learning curve, the long-term benefits of magnification for patient care and practitioner ergonomics are undeniable[39]. Dental professionals should be aware of the different magnification options available and select the tools best suited to their clinical needs[40,41]. This version is more structured, ensuring clear sections for different magnification levels, applications in different dental specialties, and the benefits/limitations of each type of device.

Magnification in restorative dentistry and endodontics

Magnification is widely used in Restorative Dentistry and Endodontics. Magnification provides numerous benefits in dentistry, enhancing both diagnosis and treatment. It is important to remember that there is no ideal magnification level. The appropriate level of magnification depends on the type of procedure and its clinical purpose. Various levels of magnification-from low to high-offer different advantages depending on the treatment planning (Figure 3)[10].

Levels of magnification in dentistry

Low magnification (3X to 8X): For general examinations, burs orientation, and ultrasonic tip placement, low magnification is ideal. It provides a large field of vision, making it easier to compare nearby anatomical structures. For this level of magnification, dental loupes typically provide sufficient clarity for general procedures and diagnosis.

Medium magnification (8X to 16X): Commonly used for both surgical and non-surgical endodontic procedures, medium magnification offers an adequate field of view and depth of field. Procedures such as perforation repair, instrument retrieval, and complex canal treatments benefit from this level of magnification[2].

High magnification (16X to 30X): High magnification is essential for viewing minute anatomical details, such as calcified canal orifices and small cracks in teeth. While it provides superior visual detail, high magnification comes with a smaller field of view and requires precise control to avoid losing focus with small movements[11-13].

Applications of magnification in restorative dentistry

Magnification improves the precision of various procedures in restorative dentistry, including the following: (1) Identification of demineralized enamel tissue[14]; (2) Conservative removal of old restorations[15,16]; (3) Deep inspection of caries and remaining surrounding tissues[17-19]; (4) Enamel cracks and fissures identification[20]; (5) Assessment of sectional matrix adaptation and liner application[21-23]; (6) Preparation of small class III cavities with minimal invasion [24]; and (7) Evaluation of marginal gaps in restorations[25]. The process involves identifying any gaps or impurities present in the restorations. Clinicians can deliver more precise and conservative removal of pulp stones using magnification, resulting in improved clinical outcomes and long-term dental work durability (Figure 4)[27,28].

Applications of magnification in endodontics

Magnification devices have made significant advances in endodontics. The enhanced lighting and visual clarity provided by microscopes assist in: (1) Locating and accessing difficult anatomy (*e.g.*, sclerosed canals); and (2) Removing dystrophic calcifications like pulpal stones (Figure 4). Creating strong coronal seals repairing perforations and resorptive defects. Inspecting fractures and assessing microanatomy endodontic surgery, including periradicular and periodontal procedures, commonly employs operating microscopes. Microsurgical techniques allow for more precise tissue handling, resulting in reduced surgical morbidity, less scarring, quicker recovery times, and minimized postoperative pain[29-32].

Use of magnification in periodontology

Several symptoms associated with periodontal disease or gingival treatment necessitate a precise diagnosis. Dental operating microscopes and microsurgical instruments, together with conservative procedures, give the most effective remedies in such instances[42]. Such strategies can improve patient outcomes in terms of treatment relevance, healing time, pain reduction, and postoperative scarring[42,43]. The dental operating microscope makes it easier for the operator to see irritating substances that are still there, like calculus spicules or enamel pearls. This could help explain why epithelial attachment is lost or stays in one place[42].

The dental operating microscope, with its increased magnification and light, is useful in significant areas, such as furcations, and may be necessary to complete the work within. This also helps to provide a practical learning experience in how to use the instruments in the most efficient and least stressful manner feasible. Magnification devices have facilitated the development of various microsurgical procedures in periodontics (Figure 5), aiming to enhance patient satisfaction and improve outcomes[7]. These devices have increased the effectiveness of surgeons[5,6]. Microsurgical concepts have been established to enhance the visual acuity and accuracy of current surgical techniques, and to expand the field of periodontics by merging medical knowledge and technology.

Microperiodontal surgeries may offer more predictable outcomes, less invasive and more conservative procedures, less patient discomfort, faster healing, improved aesthetics, and more patient compliance[44,45]. Flap reflection and suturing have applied microsurgical principles and procedures, offering an excellent opportunity to accurately control the gingiva without undue tissue damage through stretching, twisting, or tearing[46]. In contrast to macro-surgery, micro-surgery involves training and experience using visual feedback rather than touch feedback[45].

Magnification is a topic of considerable interest and practical application for the advancement and future of periodontics[46]. With proper training, surgical operating microscopes have produced excellent results for periodontists[7]. Magnification offers significant promise for improving oral hygiene, clinical treatment, and dental hygienists' musculoskeletal wellness[47]. Studies have proven that magnification can help reduce the occurrence of musculoskeletal disorders among dental hygienists[14]. Microscope and microsurgical methods are effective approaches to keep our enthusiasm for

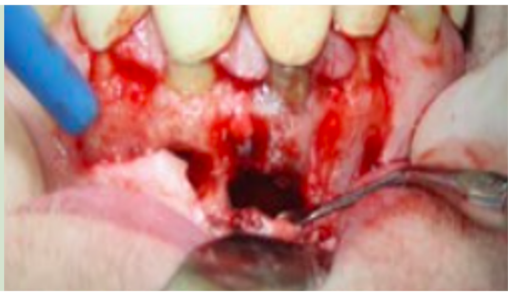
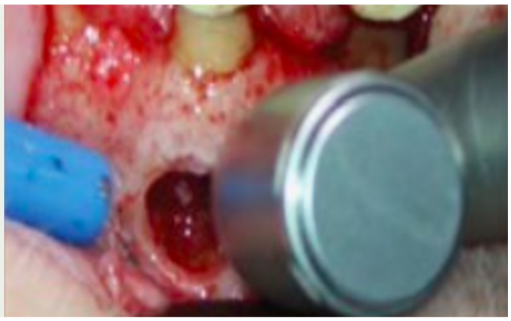
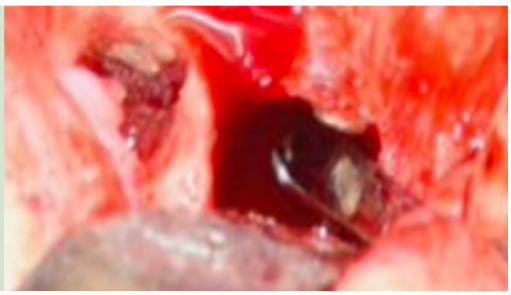
Magnification	Procedure	
Low (3X to 8X):	Orientation, inspection, osteotomy, apical preparation, suturing	
Medium (8X to 16X):	Full procedure	
High (16X to 30X):	Inspection of amputation, preparation and fillings	

Figure 3 Different stages of the procedure require different magnifications.

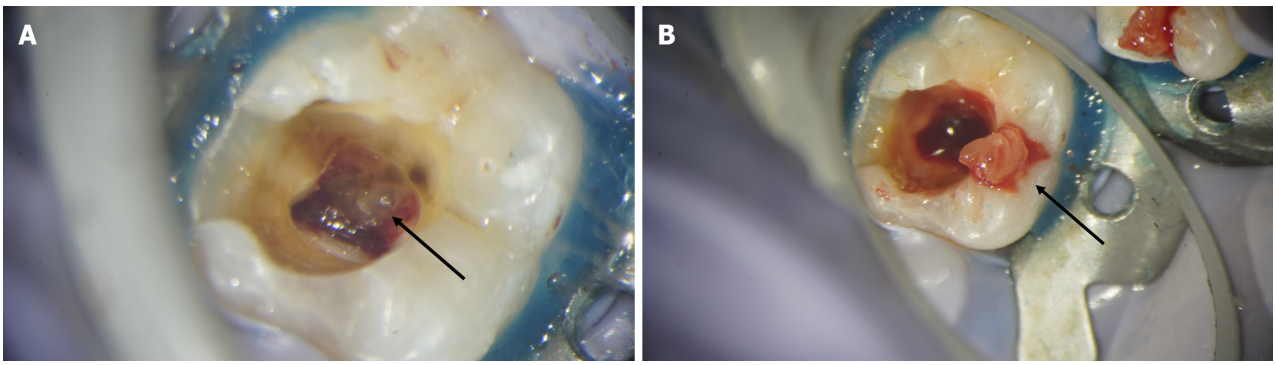


Figure 4 Conservative removal of pulp stone under magnification. A: Pulpal floor with embedded pulp stone; B: Pulpal floor after the removal of stone.

a more difficult career[47].

Use of magnification in prosthodontics

In prosthodontics practice, using a microscope or magnification device capable of increasing the surgical field by 6X to 8X simplifies several technically challenging tasks[48]. Coaxial lighting and magnification help identify a preliminary arch placement path for detachable partial dentures, minimizing long-term damage to abutment teeth[49]. In fixed prosthodontics, the vertical and horizontal marginal fit of dental prostheses impacts the restoration's outcome, longevity, and appearance (Figure 6). When dentists use a microscope, they can see tiny differences in the heights of marginal ridges or the fixed partial dentures margin above the abutment margin[50]. This allows for incremental improvements in indirect restoration seating[51].

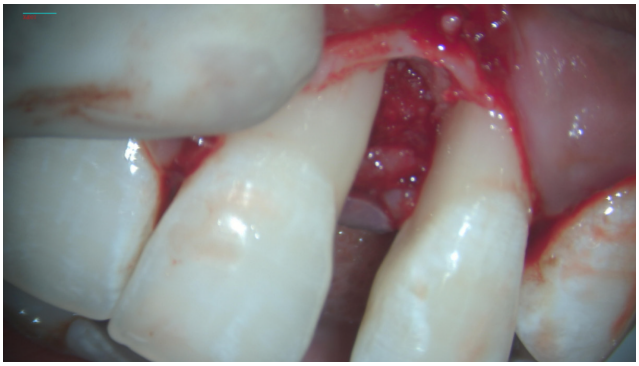


Figure 5 Microsurgical procedures in periodontics.

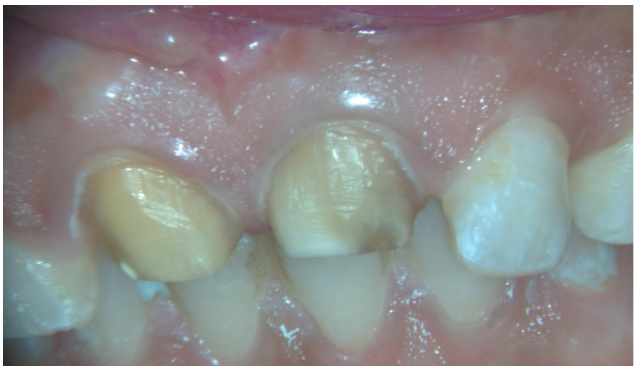


Figure 6 Crown preparations in prosthodontics.

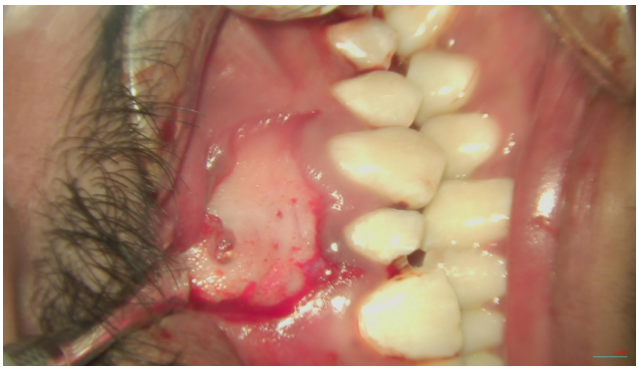


Figure 7 Micro-surgery under the dental operating microscope.

The ideal horizontal marginal separation between dental prostheses and abutments is 0 μm. Dental operating microscopes or loupes, accurate methods in the laboratory, and appropriate training are all easy ways to achieve this. The optimum vertical margin fit is 50 μm. The amount of vertical gap depends on the dental preparation, impression materials, and methods used. Tooth decay-causing bacteria are less than 1 μm in size. However, bacterial aggregations, not a single germ, cause caries. Reducing the marginal gap should lead to a significant reduction in the incidence of marginal caries[52], as well as an increase in patient comfort. Teeth and tongue proprioception detect variations in thickness or roughness of less than 20 μm[53]. Smooth surfaces achieved through proper implantation and polishing of fixed prostheses are critical for the patient's health and comfort[54].

Use of magnification in maxillofacial surgery

Magnification, laparoscopic, and endoscopic technologies reduce surgical morbidity by avoiding major incisions. Following the principles of microsurgery (Figure 7) significantly reduces the difficulties associated with fracture repair by creating micro incisions that only expose a limited amount of soft tissue[55]. Furthermore, minimally invasive approaches have progressed with the introduction of dental operating microscopes, which, are built with digital cameras, and aid in image acquisition during maxillofacial surgery procedures.

An endoscope, a valuable tool in this field, typically performs surgical operations on the maxillary sinus, salivary glands, or temporomandibular joint[56]. The microscope plays a crucial role in anastomosing blood vessels and nerve tissues after tumour removal.

Oral surgeons use the dental operating microscope to extract teeth. During surgery, surgeons successfully used it to inspect sockets for residual roots or oro-antral connections[57].

Use of magnification in orthodontics

So far, the magnification has seen minimal use in this speciality, necessitating further research. However, studies have shown that using a magnification system significantly increases bonding and cleaning procedures. The magnification of the finest features is very crucial to consider during the debonding technique to save as much enamel tissue as possible during adhesive removal[58].

Selection of magnification devices

Incorrectly adjusted magnification devices can lead to poor ergonomics, putting the operator at risk for muscular and skeletal issues[11]. "The working distance, depth of field, and optical declination angle of the selected system must all meet the clinician's musculoskeletal needs"[35,59]. Galilean loupes of 2.6 × or 3.25 × are commonly used, which provide a perfect blend of working distance, field of view, depth of focus, affordability, and comfort[15]. A clinician research assessment of over 1600 dentists, of whom more than 90% used loupes, showed that the majority of dentists advocated a longer working distance, with 18 inches being the most prevalent[60]. To avoid tiredness and headaches, the two eyepieces must have the same angle of convergence. It will help reduce eye strain, preventing double vision. Improper selection can lead to a shorter attention span throughout the clinical job. Dental specialists observed a high prevalence of coaxial misalignment among surgical loupes[61]. Prosthetics, orthodontics, and shade selection are just a few examples where magnification will provide little or no aid[62].

CONCLUSION

Magnification in dentistry offers numerous benefits and is poised to become a standard of care across all specialties. Clinical procedures, regardless of speciality, are inherently challenging, and enhanced vision through magnification can significantly improve both precision and comfort for the clinician. Loupes are currently the most commonly used magnification tool, and beyond just improved vision, they offer substantial ergonomic benefits that promote the long-term health of the practitioner. Clinicians using loupes often experience reduced musculoskeletal strain, leading to a higher quality of life and greater career longevity. While simple diopter lenses provide some magnification, compound and prismatic telescopic lenses offer superior clarity, depth of field, and a wider field of vision, making them more effective for complex dental procedures. Though magnification tools may have an initial learning curve, the long-term benefits far outweigh the drawbacks, including enhanced procedural accuracy and improved practitioner well-being. Dental institutions worldwide must incorporate the use of magnification, particularly loupes, into their curricula. Early exposure to magnification technology will help future dentists develop ergonomically sound practices and improve their clinical precision. Newly graduated clinicians, in particular, should start with low-magnification loupes to ease into their use, gradually building their skill set while reducing musculoskeletal stress over time. This version: Clarifies the benefits of magnification in terms of clinical outcomes and ergonomics. The text offers more precise comparisons between various types of lenses. It facilitates better transitions between ideas, such as moving from the benefits of magnification to the necessity of institutional adoption. The advice is tailored more clearly for different audiences, such as students and graduated clinicians.

FOOTNOTES

Author contributions: Chauhan S was responsible for conception design, literature review and critical review; Chauhan R was responsible for conception data collection; Chauhan S and Chauhan R were responsible for conception analysis and interpretation; Bhasin P was responsible for conception and supervision; Bhasin M was responsible for conception write; all of the authors read and approved the final version of the manuscript to be published.

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Abstract

Microorganisms such as bacteria, fungi, viruses, parasites living in the human intestine constitute the human intestinal microbiota. Dysbiosis refers to compositional and quantitative changes that negatively affect healthy gut microbiota. In recent years, with the demonstration that many diseases are associated with dysbiosis, treatment strategies targeting the correction of dysbiosis in the treatment of these diseases have begun to be investigated. Faecal microbiota transplantation (FMT) is the process of transferring faeces from a healthy donor to another recipient in order to restore the gut microbiota and provide a therapeutic benefit. FMT studies have gained popularity after probiotic, prebiotic, symbiotic studies in the treatment of dysbiosis and related diseases. FMT has emerged as a potential new therapy in the treatment of allergic diseases as it is associated with the maintenance of intestinal microbiota and immunological balance (T helper 1/T helper 2 cells) and thus suppression of allergic responses. In this article, the definition, application, safety and use of FMT in allergic diseases will be discussed with current data.

Key Words: Microbiota; Dysbiosis; Faecal microbiota transplantation; Allergic diseases

Core Tip: Fecal microbiota transplantation (FMT) studies have gained popularity after probiotic, prebiotic, symbiotic studies in the treatment of dysbiosis and related diseases. FMT is the process of transferring faeces from a healthy donor to another recipient in order to restore the gut microbiota and provide a therapeutic benefit.

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INTRODUCTION

The community formed by microorganisms such as bacteria, fungi, viruses and parasites living in the human intestine is called intestinal microbiota. Bacteria dominate the intestinal microbiota, which is a complex ecosystem[1]. Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria are the 4 main phyla that constitute 90% of the entire bacteriome in the intestine[2]. The intestinal microbiota of an adult human consists of approximately 40 × 10^{12} bacteria (approximately 0.2 kg)[3]. The composition of the human gut microbiota varies from region to region (anatomical part of the gut) and is highly dynamic. Differences such as mode of delivery (normal or caesarean section), postnatal food source (breast milk, formula), various diseases, diet, age, medications used, and gender are factors affecting the microbiota[4-7]. A healthy microbiota has immunomodulatory effects (increase in the number of T helper 1 and T regulatory cells) as well as effects such as protection of intestinal integrity by preventing invasion of pathogenic bacteria, synthesis of short-chain fatty acids (SCFAs) and vitamins required for intestinal metabolism, metabolism of drugs, hormones and carcinogens[8]. Compositional and functional disruption of the microbiota affected by many genetic and host-related factors is called dysbiosis[9]. In recent years, an increasing number of diseases (such as inflammatory bowel diseases, liver diseases, diabetes, atherosclerotic diseases, neurological diseases, autoimmune diseases, allergic diseases, psychiatric disorders) have been associated with dysbiosis[10-13]. Therefore, in recent years, many studies have been conducted to investigate the effect of microbiota and correction of dysbiosis in the treatment or prevention of these diseases. Probiotic studies constitute a large part of these studies.

Probiotics reduce intestinal permeability and systemic transmission of allergens by local action. Some of the systematic effects of probiotics are (Table 1): Induction of regulatory T cell (Treg) production, deflection of the response to allergens to T helper 1 (Th1) direction, and anti-inflammatory effect by Toll- like receptor stimulation[14]. In a systematic review conducted in 2014 in which 5 randomized controlled trial (RCT) were evaluated, it was found that probiotic use had no preventive role in allergic rhinitis (AR)[15]. Likewise, in the 2019 meta-analysis including 17 RCTs, it was observed that probiotic use in the perinatal and postnatal period was not effective in the prevention of AR[16]. According to a 2020 meta-analysis including 19 RCTs, taking probiotic supplements during pregnancy or early in life did not reduce the incidence of asthma or wheeze[17]. On the other hand, a meta-analysis by Chen *et al*[18] showed that the use of probiotics for respiratory allergies in children improved quality of life and reduced symptom severity[18]. In a study conducted by Amalia *et al*[19] in 2019, it was shown that a probiotic supplement mixture given to the mother while pregnant and continuing breastfeeding, as well as to the high-risk infant, is an effective strategy to reduce the risk of atopic dermatitis (AD) in children. Current studies with probiotics are not sufficient to routinely recommend the use of probiotics in the prevention and treatment of asthma, AR and AD. This may be explained by the heterogeneity of the studies in terms of factors such as probiotic type, duration of administration and dose.

On the other hand, FMT is thought to be more effective than probiotics in the restoration of altered intestinal microbiota. The reasons for this are that the number and diversity of microorganisms provided by FMT is higher than that provided by probiotics, and while there is a permanent change in the recipient microbiota after FMT, probiotics can colonize the intestinal lumen only temporarily[20-22]. In this article, FMT which is promising in the treatment of allergic diseases and the effect of FMT in allergic diseases will be discussed.

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) is the process of transferring faeces from a healthy donor into the gastrointestinal tract of the recipient in order to repair the intestinal microbiota and provide a therapeutic benefit[23]. The first FMT application was performed in China and dates back to 300-400 AD. The first applications were recorded as oral administration of human faecal suspension to patients with food poisoning or severe diarrhoea[24]. The first introduction of FMT into the medical literature was in 1958 reported FMT administered *via* enema as a highly effective treatment in the treatment of severe pseudomembranous enterocolitis[25]. In 2013, in a randomized controlled trial conducted by van Nood *et al*[26], FMT was found to be 81% successful in the treatment of recurrent C. difficile (rCDI) infection compared to 31% with standard antibiotic treatment and the Food and Drug Administration (FDA) approved the use of FMT in humans in the same year[26,27]. This significant success of FMT in the treatment of rCDI has created great excitement for its use in the treatment of other diseases associated with dysbiosis.

Potential effect mechanisms of FMT in allergic diseases

The main objective is to rebuild the gut microbiota by normalizing immune and inflammatory responses, the amount and activity of neurotransmitters/vasoactive substances and intestinal energy metabolism. This main objective is realized through the following mechanisms (Table 1): (1) The main goal of FMT is to restore the "normal" bacterial population in a dysbiotic colonic environment[25]; (2) A change in the bacterial population in the intestine occurs that mirrors the donor feces[25]; (3) An increase in Firmicutes and Bacteroidetes and a decrease in Proteobacteria and Actinobacteria[25]; (4) It may reduce intestinal permeability and maintain the integrity of the epithelial barrier by increasing the production of SCFAs[23]; (5) It inhibits the secretion of proinflammatory cytokines[23]; (6) It promotes Th1 cell differentiation, T cell activity, leukocyte adhesion and immunostimulating factors[23]; and (7) It lowers intestinal pH and inhibits the transport of pathogenic microorganisms by increasing bacterial adhesion to H_2O_2[23].

FMT procedure, safety and side effects

There is no standard protocol for the preparation of FMT. The recommended and commonly used method of FMT preparation for rCDI is as follows: 50-60 g of faeces and 200-300 mL of diluent (water, saline or milk) are homogenized and suspended. The suspension is left to settle for 5 minutes. Then it is passed through gauze and then through a syringe

Table 1 Potential roles of probiotics and fecal microbiota transplantation in alleviating or preventing allergic diseases[99]

Probiotics and FMT	Potential roles
Probiotics	Epithelial integrity ↑
	Tight junction protein expression ↑
	Bacterial translocation ↓
	Inflammatory cytokines such as IL-6, IL-8 and TNF-α ↓
	Restoration of Th1/Th2 balance
	Treg cell numbers and function, IL-10 and TGF-β ↑
	SCFAs production (especially butyrate) ↑
FMT	Pro-inflammatory cytokine secretion ↓
	Restoration of Th1/Th2 balance
	Stimulates T cell activity and leukocyte adhesion
	Change in intestinal bacterial diversity (Firmicutes, Bacteroidetes ↑/Proteobacteria, Actinobacteria ↓)
	Intestinal permeability ↓
	Epithelial integrity ↑
	SCFAs production ↑
	Intestinal pH ↓
	Bacterial adhesion to H_2O_2 ↑

SCFA: Short chain fatty acid; FMT: Fecal microbiota transplantation; TNF-α: Tumor necrosis factor-alpha; IFN-γ: Interferon-gamma; IL: Interleukin.

with filter. The resulting filtrate is ready for FMT[28]. There are routes of administration of FMT such as oral administration in the form of capsules, nasal administration, administration into the upper gastrointestinal tract with the help of nasogastric or nasoduodenal tube, rectal administration *via* colonoscopy or enema[29].

Although FMT is generally considered safe, the adverse event rate was reported as 28.5% in a systematic review. However, most of these side effects were self-limiting and included abdominal pain, gas, increased stool frequency, vomiting and fever. Serious adverse events were more rare and occurred in 5%. Although more serious side effects such as aspiration and intestinal perforation have been reported after FMT, these risks are mostly related to the route of administration[30]. Administration of FMT *via* capsules is a less invasive approach and can be used to overcome complications related with the route of administration[31,32]. FMT also has reported side effects including sepsis, peritonitis and toxic megacolon[30]. To prevent disease transmission from donor to recipient, it should be ensured that the donor is completely healthy. The donor is examined for the presence of human immunodeficiency virus, syphilis, hepatitis A, B, C, autoimmune and atopic diseases. The donor's faecal material is also examined for the presence of parasites, helminth eggs and pathogenic bacterial toxins. The donor should be free of tumors, inflammation, diabetes, infectious diseases and metabolic syndrome and the donor should not be obese. In addition, the donor should not be using immunosuppressants, steroids, probiotics, aspirin, proton pump inhibitors and antibiotics[33]. FDA has recently recommended additional donor screening and testing protocols to reduce the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and monkeypox transmission with FMT[34].

FMT in disease treatments

As mentioned above, FMT is a method applied to restore the gut microbiota and provide a therapeutic benefit and dates back to 300-400 AD and China[23]. The first clinical applications were oral administration of human fecal suspension to patients with food poisoning or severe diarrhea[24]. Studies conducted in the last decade have demonstrated the potential efficacy of FMT in conditions such as ulcerative colitis (UC), Crohn's disease, epilepsy, autism and recurrent urinary tract infections (UTIs)[20-24].

FMT has also been proven to be highly effective in the treatment of rCDI (approximately 90% cure rate) and FMT has become an undisputed treatment modality for rCDI[35,36]. A recent systematic review revealed that FMT can treat 85 specific diseases. When evaluated according to the number of cases treated using FMT, the diseases such as intestinal infections (rDCI), UC, irritable bowel syndrome, constipation, hypertension, fatty liver disease, autism spectrum disorders, radiation enteritis are the leading diseases[35]. In addition to these diseases, FMT has also been found to be effective in diseases such as hepatic encephalopathy, epilepsy, depression, metabolic syndrome, obesity, primary sclerosing cholangitis, anorexia and recurrent UTI[37-45]. Various animal studies and human case reports for Parkinson's disease, Alzheimer's disease, multiple sclerosis and stroke show the positive effect of FMT in these diseases[46-50].

FMT in allergy and allergic diseases

The increase in the prevalence of allergic diseases in modern societies over the last 50-60 years is remarkable. This allergy pandemic is explained by 2 hypotheses: Hygiene hypothesis[51] and microbiota hypothesis[52]. T helper 2 (Th 2) response is dominant in humans during pregnancy and the first years of life[53]. Microbial agents encountered in the early period of life cause interleukin (IL) 12 production from macrophages, the innate cells of the immune system. IL-12 plays a key role in the progression of the immune system towards Th 1. According to the hygiene hypothesis, if IL-12 production does not occur in the early stages of childhood, Th 2 cells will predominate and as a result, atopy will develop in genetically predisposed children[54]. A healthy gut microbiota helps to maintain intestinal integrity by preventing the invasion of pathogenic bacteria and to prevent the development of allergies through immunomodulatory effects (increase in the number of Th 1 and Treg cells)[8]. Today, factors such as excessive use of antibiotics, consumption of more germ-free foods, better personal hygiene, and smaller family size are held responsible for changes in intestinal microbiota and allergy risk[55-57]. Many studies have shown that traditional agriculture has a preventive effect on the prevalence and incidence of asthma in childhood; exposure to farm animals and their feed and consumption of unpasteurized cow's milk have a protective effect on asthma. Higher microbial exposure is hypothesized to have a protective effect on allergy development[58,59]. Decreased microbiotal diversity in the gastrointestinal tract has been found to be associated with diseases such as atopy, asthma and eczema[60-63]. For all these reasons, the effect of FMT in allergic diseases has started to be investigated more recently (Table 2). In the following sections of this article, the use of FMT in allergic diseases will be emphasized.

Food allergy and FMT

Low microbial diversity in the intestines and high Enterobacteriaceae/Bacteroidaceae ratio have been associated with the development of food sensitivity in children[64]. Similarly, the risk of allergic diseases was found to be higher in children born after caesarean section who did not receive vaginal microbiota from their mothers[65]. In the absence of healthy microbiota, the decrease in SCFA, which are also involved in the recovery of epithelial barrier integrity, will lead to increased sensitivity to food allergens[66,67]. The first studies with germ-free mice showed the importance of gut microbiota in modulating food allergy and revealed that germ-free mice could not develop tolerance against food allergens[68]. Recent studies with germ-free mice demonstrated the importance of gut microbiota in modulating food allergy and revealed that germ-free mice without healthy gut microbiota could not develop tolerance to food allergens[69, 70]. These findings obtained with FMT in mouse models have formed the basis of new studies to be conducted in humans. A Phase 1 study with 10 adult subjects to monitor the safety and tolerability of oral capsule FMT administered for 2 days in the treatment of peanut allergy has been completed but the data have not yet been published[71]. A phase II randomized double-blind placebo-controlled phase II randomized double-blind placebo-controlled study to evaluate the safety and tolerability of oral encapsulated FMT in 24 patients with peanut allergy is still ongoing[72].

Eosinophilic gastroenteritis, allergic colitis and FMT

Eosinophilic gastrointestinal disorders are a group of rare disorders characterized by pathological eosinophilic infiltration of the gastrointestinal tract with symptoms such as dysphagia, abdominal pain, nausea, vomiting, early satiety, diarrhoea and weight loss. These Th 2 -mediated disorders include eosinophilic oesophagitis, eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), eosinophilic enteritis (EE) and eosinophilic colitis. Symptoms of the disease vary according to the site of involvement and depth of involvement (mucosa, submucosa, serosa)[73-75]. Although there is no consensus on the treatment of EGE so far, steroid treatment forms the basis of treatment. In the literature, there is a case report in which the combination of FMT and steroid treatment improved the symptoms of a 35-year-old patient with EG who did not respond to steroid treatment alone[76].

Allergic colitis, also known as food protein-induced allergic proctocolitis (FPIAP), is a clinical entity characterized by inflammatory changes developing in the distal colon in response to one or more food proteins. Although the underlying mechanism in allergic colitis is not known, IgE is thought not to play a role[77]. Symptoms in infants with FPIAP usually start in the first months of life. Patients present with red blood and mucus mixed with stools with or without diarrhoea [78]. The most common trigger for FPIAP is cow's milk and elimination diet, which involves the removal of the responsible food from the diet, is the mainstay of treatment of allergic enteritis[79]. In a 2017 study, 19 infants with proctocolitis who had severe diarrhoea/haematochezia and who did not recover completely with routine treatment were treated with FMT *via* rectal tube and clinical results were followed up. In 17 infants, allergic colitis symptoms were alleviated within 2 days after FMT and no recurrence was observed during the following 15 months. According to 16S rDNA analysis performed in 10 of these babies, an increase in microbiota diversity was observed in most of these babies after FMT[80].

AD and FMT

AD (eczema) is a condition that causes dry, itchy and inflamed skin. Atopic dermatitis is one of the chronic inflammatory skin diseases affecting 15%-30% of children and 10% of adults in which impaired barrier function, immune response and microbial factors play a role in its pathogenesis[81,82]. In recent years, as in many diseases, the treatment of AD has focused on gut microbiota in relation to immune modulation. Different results have been reported in various studies investigating the effects of probiotic treatment on AD and the efficacy of probiotics in AD treatment has not been proven [83-85]. In recent years, studies on the effects of FMT in the treatment of AD have started to be carried out because of the reconstitution of the intestinal microbiota and the long-term change of the recipient microbiome. In a study conducted with mice with and without AD, an increase in SCFA levels was found in recipient mice after FMT. As a result of the measurement of cytokine levels before and after FMT in mice with AD, Th-2 cytokines (IL-4, IL-5, IL-13) decreased and

Table 2 Impact of fecal microbiota transplantation on allergic diseases

Disease	Species	Main result	Ref.
Food allergy	Mice	Food allergy protection was achieved in food allergy-prone recipient mice receiving FMT from a healthy donor	[69]
	Mice	It has been shown that recipient germ-free mice after FMT from healthy and cow's milk allergy-free donors are protected against anaphylactic reactions to cow's milk allergen	[70]
	Human	Phase 1 and phase 2 study investigating the efficacy of oral capsule FMT in people with peanut allergy is ongoing	[71, 72]
Eosinophilic gastritis	Human	Combination of FMT and steroid therapy in a patient with steroid-resistant eosinophilic gastritis improved the patient's symptoms	[76]
Allergic proctocolitis (FPIAP)	Human	After 2 days after administration of FMT *via* rectal tube to 19 infants with FPIAP, 17 infants showed symptomatic regression	[80]
Atopic dermatitis	Mice	In recipient mice after FMT administered from non-atopic dermatitis patients to atopic dermatitis patients: SCFA ↑, Th1 cytokines (IL-12, IFN-γ, TNF-α) ↑, Th2 cytokines (IL-4, IL-5, IL-13) ↓, Total IgE ↓, SCORAD ↓	[86, 87]
	Human	After FMT in patients with moderate to severe AD: SCORAD ↓, need for topical corticosteroids ↓	[88]
Allergic rhinitis	Mice	In recipient mice after FMT: nasal symptoms ↓, Total IgE ↓, histopathological recovery (decrease in eosinophilia)	[91]

SCFA: Short chain fatty acid; FMT: Fecal microbiota transplantation; FPIAP: Food protein-induced allergic proctocolitis; SCORAD: Scoring atopic dermatitis; TNF-α: Tumor necrosis factor-alpha; IFN-γ: Interferon-gamma; IL: Interleukin.

Th1 cytokines (IL-12, IFN-γ and TNF-α) increased, total IgE level decreased and dermatitis scores decreased after FMT [86]. Similar results were found in another mouse study conducted in 2023[87]. In a human study conducted with 9 patients with moderate to severe AD, a significant improvement in AD SCORAD (SCORing Atopic Dermatitis) scores and a decrease in the frequency of weekly topical corticosteroid use were observed in 7 patients after FMT. No side effects were reported during the study[88]. These studies show that FMT may be effective through immune modulation by gut microbiota and are promising for the future of AD treatment, but more clinical studies are needed.

AR and FMT

AR is an IgE-mediated inflammatory disease of the upper airway induced by inhaled allergens affecting 10-30% of the world population[89,90]. In an experimental mouse model investigating the effect of FMT on AR, it was found that nasal symptoms were significantly alleviated in recipient mice after transplantation of normal mouse faecal microbiota into AR mice. In contrast, it was observed that AR symptoms developed in healthy mice that received FMT from allergic mice. In the study, it was found that total IgE levels decreased in AR mice treated with FMT. In addition, histopathological evaluation of the nasal mucosa was performed after FMT and a decrease in eosinophil levels was observed in the recipient group after FMT[91]. Although there is no human study on the effect of FMT in the treatment of AR, improvement in AR symptoms was found incidentally in a patient with AR who received FMT for UC and reported on a case basis[92]. These studies show promise that FMT may be an effective treatment in the treatment of AR.

Asthma and FMT

Asthma is one of the most common chronic diseases thought to affect more than 300 million people worldwide[93]. Asthma is related with the predominance of the immune response in the Th2 direction and its etiology has not yet been fully elucidated. Genetic and environmental factors are also thought to contribute to the pathogenesis of asthma[94,95]. Intestinal microbial triggers are an important environmental factor associated with asthma. Recent studies have shown that gut microbiota plays a role in the etiology of asthma through its effects on innate and adaptive immunity[96,97]. In line with this information, FMT represents a possible treatment modality to improve asthma. However, scientific studies in this field have only recently begun[98].

CONCLUSION

After the high success rate of FMT, especially in the treatment of rCDI, and the increase in data proving the relationship between disorders in the intestinal microbiota and many diseases in recent years, the number of studies investigating the effects of FMT in these diseases has increased. Until this time, studies targeting microbiota in disease treatment have mostly been probiotic studies. The most important limitation of probiotic treatment in the treatment of diseases is that the variety of microorganisms given in probiotic treatment is limited and the duration of action is short. FMT is thought to be more successful in the treatment of diseases because it contains more and various microorganisms and can provide a more permanent microbial environment. Studies on the efficacy of FMT in the treatment of allergic diseases have only recently started and the first results are promising for the use of FMT in the treatment of allergic diseases in the future. However, more clinical studies are needed to recommend the routine use of FMT in the treatment of diseases.

FOOTNOTES

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MINIREVIEWS

Optimizing bone marrow harvesting sites for enhanced mesenchymal stem cell yield and efficacy in knee osteoarthritis treatment

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Abstract

Knee osteoarthritis (OA) is a debilitating condition with limited long-term treatment options. The therapeutic potential of mesenchymal stem cells (MSCs), particularly those derived from bone marrow aspirate concentrate, has garnered attention for cartilage repair in OA. While the iliac crest is the traditional site for bone marrow harvesting (BMH), associated morbidity has prompted the exploration of alternative sites such as the proximal tibia, distal femur, and proximal humerus. This paper reviews the impact of different harvesting sites on mesenchymal stem cell (MSC) yield, viability, and regenerative potential, emphasizing their relevance in knee OA treatment. The iliac crest consistently offers the highest MSC yield, but alternative sites within the surgical field of knee procedures offer comparable MSC characteristics with reduced morbidity. The integration of harvesting techniques into existing knee surgeries, such as total knee arthroplasty, provides a less invasive approach while maintaining therapeutic efficacy. However, variability in MSC yield from these alternative sites underscores the need for further research to standardize techniques and optimize

clinical outcomes. Future directions include large-scale comparative studies, advanced characterization of MSCs, and the development of personalized harvesting strategies. Ultimately, the findings suggest that optimizing the site of BMH can significantly influence the quality of MSC-based therapies for knee OA, enhancing their clinical utility and patient outcomes.

Key Words: Knee; Osteoarthritis; Mesenchymal stem cells; Bone marrow harvest; Regenerative medicine

Core Tip: Knee osteoarthritis (OA) has limited long-term treatments. Mesenchymal stem cells from bone marrow aspirate concentrate show promise for cartilage repair. However, variability in mesenchymal stem cell (MSC) yield from the sites necessitates further research to standardize techniques and optimize outcomes. Future directions include large-scale studies and personalized harvesting strategies to enhance MSC-based therapies for knee OA.

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INTRODUCTION

Knee osteoarthritis (OA) is a prevalent and debilitating condition, contributing significantly to the global burden of disease and affecting millions of individuals worldwide[1,2]. As one of the leading causes of disability, knee OA is associated with chronic pain, reduced mobility, and a diminished quality of life. Current treatment modalities, including pharmacological interventions, physical therapy, and surgical procedures, such as total knee arthroplasty, often provide only temporary relief or are limited in their effectiveness, especially in the long term[3,4]. The limitations of these treatments have driven the exploration of regenerative medicine, particularly the use of mesenchymal stem cells (MSCs), as a promising alternative for cartilage repair and the management of OA[5]. Mesenchymal stem cell (MSC)-based therapies have garnered attention due to the cells' ability to differentiate into chondrocytes, their immune-modulatory properties, and their potential to release trophic factors that promote tissue regeneration. Bone marrow aspirate concentrate (BMAC), which contains a high concentration of MSCs, is commonly harvested from the iliac crest and is considered the gold standard for regenerative procedures[6]. However, the procedure is associated with significant donor-site morbidity, which has prompted research into alternative bone marrow harvesting (BMH) sites that could provide an adequate yield of MSCs with reduced morbidity[7].

Emerging evidence suggests that bone marrow harvested from sites such as the proximal humerus, tibia, and femur could offer similar or even superior yields of MSCs compared to the iliac crest[8]. This is particularly relevant in knee OA treatments, where local harvesting sites within the surgical field could not only reduce morbidity but also enhance the efficiency of the procedure by eliminating the need for a secondary harvest site. Despite these potential benefits, there remains a paucity of comprehensive studies comparing the yield, viability, and regenerative potential of MSCs obtained from different anatomical sites within the same patient. While the iliac crest remains the most commonly utilized source for MSCs due to its well-documented efficacy in providing a high yield of progenitor cells, the associated morbidity of this harvest site necessitates the exploration of alternative sites[8]. The potential of other anatomical locations, such as the femur, tibia, and proximal humerus, to provide MSCs with comparable regenerative capacity is yet to be fully understood. Although some studies have investigated the yield and characteristics of MSCs from these alternative sites, results have been inconsistent and often limited by small sample sizes or the lack of intra-subject comparisons.

The impact of anatomical variability on MSC yield and the functional abilities of these cells across different harvesting sites is not well established. The current understanding of MSC functionality, particularly about their chondrogenic potential and the expression of surface markers, is primarily based on studies using cells from the iliac crest, with limited comparative data from other bone marrow sites[9]. Moreover, the clinical outcomes of using MSCs from alternative harvest sites in regenerative procedures for knee OA remain underexplored, highlighting the need for rigorous, standardized studies that evaluate the efficacy and safety of these approaches[10]. This review aims to discuss the optimal BMH site for obtaining MSCs with the highest yield and regenerative potential for use in knee OA treatment.

PATIENT POSITIONING

Patient positioning is a crucial aspect of BMH techniques, particularly in procedures intended to optimize the characteristics and purity of the harvested cells for use in knee OA treatment. Proper positioning not only enhances the efficacy of

the procedure but also minimizes complications, thereby improving patient outcomes. This section discusses the various aspects of patient positioning relevant to BMH, drawing on insights from multiple studies and technical guidelines (Figure 1).

Importance of patient positioning

The correct positioning of the patient during BMH is vital for several reasons. Firstly, it ensures that the harvesting needle is accurately guided to the optimal site, such as the iliac crest or other accessible locations like the proximal tibia or humerus. Secondly, it helps in reducing the risk of injury to surrounding tissues, nerves, and blood vessels. Thirdly, proper positioning facilitates the ease and efficiency of the procedure, which is crucial when large volumes of bone marrow are required for concentration and subsequent therapeutic use[11]. Patient comfort and safety are also paramount considerations during positioning. Incorrect positioning can lead to complications such as nerve damage, excessive bleeding, or suboptimal cell yield, which can compromise the effectiveness of the treatment. Therefore, a thorough understanding of anatomical landmarks and the patient's specific anatomy is essential for optimal positioning.

Common positions used in BMH

Supine position: The supine position is one of the most commonly used positions in BMH, especially when the anterior superior iliac spine or proximal tibia is the site of aspiration[5]. This position is favored for its accessibility and ease of patient monitoring during the procedure. It is particularly useful in procedures where the bone marrow needs to be harvested from the anterior iliac crest or proximal tibia, adjacent to the knee joint. In the supine position, the patient lies flat on their back with their legs extended. For harvesting from the proximal tibia, the knee may be slightly flexed, and a leg holder can be used to stabilize the limb. The tibial tuberosity and posteromedial border of the tibia serve as important landmarks, and the needle is inserted at an angle directed toward the fibular head. This position provides a stable and secure access point, which is crucial for the successful aspiration of bone marrow.

Prone position: The prone position is typically used when accessing the posterior iliac crest, which is considered one of the gold standard sites for BMH due to its high yield of cell-dense marrow[12]. In this position, the patient lies face down on the operating table, with their hips slightly elevated and the area around the iliac crest exposed. Pillows or foam pads are often placed under the patient's abdomen and pelvis to reduce pressure on the chest and abdomen, thus minimizing discomfort and facilitating respiration during the procedure. The prone position allows for a more direct approach to the posterior iliac crest, which can result in a higher quality and quantity of bone marrow aspirate. The use of this position, however, requires careful consideration of the patient's overall condition, particularly in those with respiratory or cardiovascular issues, as lying face down for an extended period can exacerbate these conditions.

Lateral decubitus position: In some cases, particularly when accessing the posterior iliac spine, the lateral decubitus position may be employed[11]. In this position, the patient lies on their side, with the side of interest facing up. The legs are often bent at the knees, and pillows are placed between them to maintain spinal alignment and reduce pressure on the lower back. This position provides good access to the posterior iliac crest while allowing for easier patient breathing compared to the prone position. The lateral decubitus position is advantageous in situations where the prone position is contraindicated, such as in patients with respiratory compromise. It also allows for simultaneous access to both the anterior and posterior aspects of the iliac crest if needed, thereby increasing the flexibility and efficiency of the procedure.

Beach-chair position: For procedures involving the proximal humerus, particularly in shoulder-related harvesting, the beach-chair position is commonly used[6]. This position involves the patient sitting in a semi-reclined position, with the backrest of the operating table elevated to about 45-60 degrees. The arms are positioned at the sides or slightly abducted to allow access to the humeral head. The beach chair position is particularly useful for harvesting bone marrow for shoulder-related conditions. It allows for easy access to the proximal humerus, where the lateral acromial border and the greater tuberosity serve as important anatomical landmarks. The position also facilitates the surgeon's ability to rotate and manipulate the limb as needed to optimize needle placement and marrow extraction.

Positioning aids and techniques

The use of positioning aids such as leg holders, foam pads, and pillows is critical in maintaining the correct posture and stability of the patient throughout the BMH procedure. These aids help minimize movement, reducing patient discomfort, and ensuring that the anatomical landmarks are consistently accessible during the procedure.

Leg holders: In procedures involving the lower extremities, such as those targeting the proximal tibia, leg holders are often used to stabilize the limb and maintain the desired flexion or extension angle[13]. This stability is crucial for ensuring that the needle is accurately positioned and that the harvesting process is efficient.

Pillows and foam pads: Pillows and foam pads are commonly used to provide additional support and comfort, particularly in the prone and lateral decubitus positions[14]. These aids help in relieving pressure on certain body parts, thus reducing the risk of pressure sores and enhancing overall patient comfort.

Intraoperative imaging: Intraoperative imaging techniques such as fluoroscopy or ultrasound can also be employed to guide needle placement, particularly in challenging cases where anatomical variations or previous surgical interventions might obscure standard landmarks[15]. These imaging techniques can help in confirming the correct needle placement within the bone marrow cavity, thus optimizing the yield and quality of the aspirate.

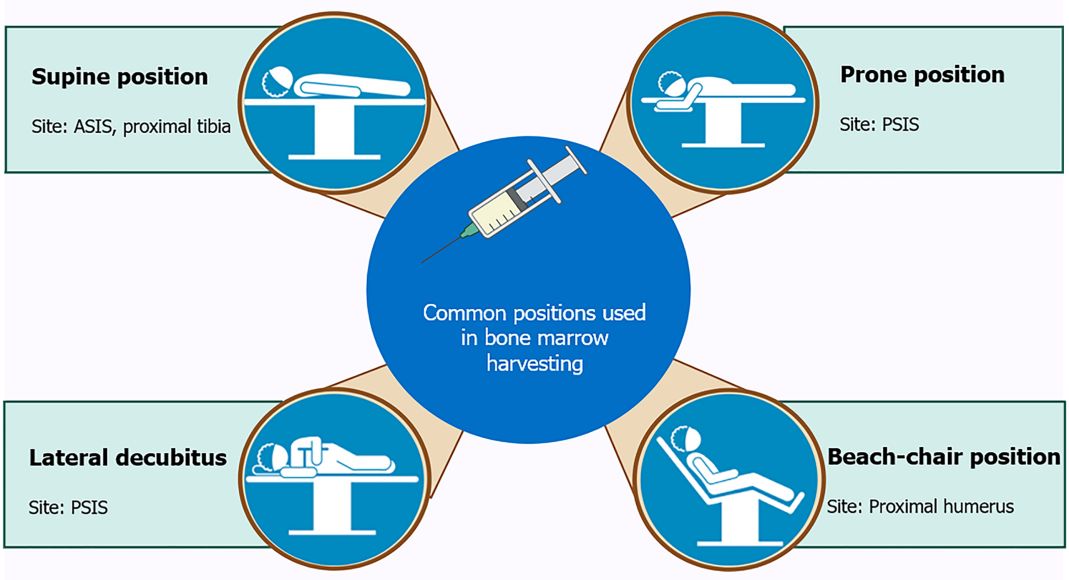

Figure 1 Various positions used in bone marrow harvesting. ASIS: Anterior superior iliac spine; PSIS: Posterior superior iliac spine.

Positioning and anesthesia considerations

The choice of patient positioning must also take into account the type of anesthesia being used[7]. General anesthesia is commonly employed for BMH, particularly when larger volumes are required, as it allows for complete muscle relaxation and patient immobility[16]. However, in cases where local or regional anesthesia is used, positioning becomes even more critical, as the patient may still have some degree of muscle tone or reflex movement. Under general anesthesia, the patient's position must be carefully monitored to avoid complications such as nerve compression or impaired circulation. For example, in the prone position, care must be taken to ensure that the head and neck are properly aligned to prevent airway obstruction or cervical spine injury. Similarly, in the supine position, attention must be paid to the patient's lower back and sacrum, areas that are prone to pressure-related injuries if not adequately supported.

PROCEDURE, TECHNIQUES, AND REQUIREMENTS

Procedure

The procedure for bone marrow aspiration (BMA) typically involves the extraction of bone marrow from the iliac crest, a common site due to its accessibility and the richness of the marrow. The process begins with the identification and preparation of the aspiration site, usually the posterior superior iliac spine (PSIS), under sterile conditions. Local anesthesia is administered to minimize patient discomfort during the procedure.

Two primary techniques are utilized for BMA: (1) Single-site aspiration; and (2) Multiple-site aspiration. Each technique has its implications for cell yield and patient outcomes. For instance, in single-site aspiration, a larger volume is drawn from one puncture site, which may result in a higher yield of MSCs from that specific location but can also lead to increased contamination with peripheral blood[17]. Conversely, multiple-site aspiration involves collecting smaller volumes from several sites, potentially reducing peripheral blood dilution and improving the overall purity and quality of the MSCs obtained[17].

TECHNIQUES

Aspiration volume management

Optimal aspiration volumes: The volume of marrow aspirated during each pull is a critical determinant of the yield and purity of MSCs. Research indicates that larger aspiration volumes tend to dilute the marrow with peripheral blood, which contains significantly fewer MSCs and can lower the overall cellular concentration of the aspirate[18]. Studies recommend limiting each aspiration to approximately 5-8 mL to maintain a higher concentration of MSCs and minimize peripheral blood contamination[19]. When more bone marrow is needed for therapeutic purposes, instead of increasing the volume from a single site, which risks excessive dilution, it is advisable to perform multiple small-volume aspirations from different sites. This approach, often referred to as "multi-site small volume aspiration" or "re-orientation technique" ensures that each pull is less contaminated and remains rich in MSCs, which are essential for subsequent therapeutic applications[20–22].

Single *vs* multiple site aspiration: Single-site aspiration involves drawing a larger volume of marrow from one site, which can lead to higher MSC yields initially but also increases the risk of peripheral blood contamination as the marrow cavity becomes depleted[17]. In contrast, multiple-site aspiration, where smaller volumes are drawn from different sites, can reduce this risk[17]. This technique ensures that the marrow drawn is less likely to be diluted with peripheral blood, thus maintaining a higher purity of MSCs across the samples. The choice between these techniques often depends on the specific clinical requirements, including the volume of MSCs needed and the patient's tolerance to multiple puncture sites [17].

Needle selection and insertion techniques

Needle types: The choice of needle for bone marrow aspiration significantly impacts both the quantity and quality of the aspirated material. The traditional Jamshidi needle is commonly used due to its reliability and effectiveness[23]. However, more advanced needles, such as the Marrow Cellution™ (AMC) needle[21,24], have been developed to optimize the process further. The AMC needle features a unique design with multiple lateral openings along its shaft. These openings allow the needle to aspirate marrow from various points within the bone cavity, rather than from a single location, reducing the likelihood of peripheral blood contamination. Additionally, the needle is designed to be gradually retracted during aspiration, which increases the number of marrow pockets accessed and improves the yield of MSCs. This design innovation represents a significant improvement over traditional needles, particularly in its ability to enhance the purity and quantity of MSCs without requiring additional punctures.

Needle insertion techniques: The technique used to insert the needle into the bone marrow cavity is another crucial factor. A commonly used method is the perpendicular or vertical insertion, which directly targets the marrow cavity[12,25]. However, this method might limit the area of marrow accessed and could lead to quicker depletion of the local marrow, increasing the risk of peripheral blood contamination in subsequent aspirations. An alternative approach is the divergent or angled insertion technique[26]. In this method, the needle is inserted at an angle, allowing it to traverse a broader area of the marrow cavity. This technique can access multiple inter-trabecular spaces, which are rich in MSCs, thereby increasing the heterogeneity and overall yield of the aspirated cells. Divergent insertion also minimizes the depletion of any single marrow pocket, maintaining a more consistent cellular concentration throughout the procedure.

Aspiration rate and pressure control

Aspiration rate: The rate at which bone marrow is aspirated plays a pivotal role in the quality of the sample obtained. Rapid aspiration, which involves quickly drawing the marrow into the syringe, creates a high differential pressure that can inadvertently increase the amount of peripheral blood in the sample[27]. This rapid influx of peripheral blood not only dilutes the MSC concentration but may also cause discomfort to the patient due to the sudden change in pressure. In contrast, a slower aspiration technique involves gently drawing the marrow at a controlled pace, typically over 5 seconds to 15 seconds. This method reduces the likelihood of peripheral blood mixing with the marrow, thereby enhancing the purity and concentration of MSCs. Slow aspiration is particularly beneficial in procedures where high-quality cellular material is critical, such as in regenerative therapies for knee OA[27].

Pressure control mechanisms: Controlling the pressure during aspiration is another important consideration. Manual aspiration techniques, where the operator controls the syringe pressure, can vary significantly depending on the practitioner's experience and technique[28]. This variability can affect the consistency of the aspirate's quality. To address this, some advanced systems include mechanisms that maintain a consistent differential pressure, regardless of the operator's manual input. These systems can help standardize the procedure, reducing the variability in MSC yield and improving overall sample quality.

Advances in aspiration techniques

Rotational aspiration devices: Recent innovations include the development of rotational aspiration devices, which use a powered mechanism to rotate the needle during aspiration. This rotation helps the needle traverse more marrow spaces, potentially increasing the volume and quality of the cells collected[28,29]. These devices can reduce the time required for the procedure and may improve patient comfort by decreasing the manual effort needed during aspiration.

OnControl powered bone marrow biopsy system: The OnControl system is one such device that has shown promise in clinical settings. It combines a powered rotary drill with a biopsy needle, which can be used to both aspirate marrow and obtain a core biopsy. Studies have shown that the OnControl system can increase the yield of bone marrow cells while reducing the procedure time[30]. Moreover, the device's ability to minimize patient discomfort, particularly in challenging cases where manual aspiration might be difficult, makes it an attractive option in clinical practice.

Slow suction techniques: Another innovative approach is the use of slow suction techniques with controlled pressure systems, such as the ones studied in the randomized controlled trials mentioned earlier. These systems are designed to optimize the balance between sufficient pressure to draw marrow and minimizing peripheral blood contamination. In clinical trials, such as those conducted by Grønkjær *et al*[27], slow suction techniques have demonstrated superior sample quality compared to rapid suction, with the added benefit of being less painful for the patient.

Aspiration technique and cell viability

Impact of technique on MSC viability: The techniques employed during bone marrow aspiration can also influence the viability of the MSCs harvested. High shear forces, which may occur during rapid aspiration or improper needle

handling, can damage cell membranes, reducing the viability of the cells and their subsequent proliferative and differentiation capacities[31]. Therefore, it is crucial that the aspiration technique not only focuses on maximizing yield but also preserves the functional integrity of the MSCs. To enhance cell viability, techniques that reduce mechanical stress on the cells are preferred. These include slow aspiration, which minimizes shear forces, and the use of specially designed needles that reduce turbulence within the syringe[22,32]. Additionally, maintaining the sample at physiological temperatures and processing it promptly post-aspiration are essential steps in preserving cell viability.

Post-aspiration handling: Once the bone marrow is aspirated, the sample must be handled with care to maintain the viability of the MSCs. This includes avoiding excessive agitation, which can induce apoptosis or necrosis in sensitive cell populations[11]. Immediate cooling of the sample and quick processing in a controlled environment are recommended to ensure that the cells retain their functional characteristics for therapeutic use.

Patient selection criteria

Age and health status: The selection of patients for BMA plays a critical role in the success of the procedure, particularly in the context of regenerative therapies for knee OA. Age is a significant factor, as the quantity and quality of MSCs in bone marrow tend to decrease with age[33]. Studies have shown that older patients, especially those over the age of 60 years, often have a lower density of MSCs in their bone marrow, which can affect the therapeutic efficacy of the harvested cells[34]. Therefore, when selecting patients, clinicians must consider the patient's age and overall health status. Moreover, the presence of comorbid conditions such as osteoporosis or other bone-related diseases can further complicate BMA[35]. In patients with osteoporosis, for instance, the bone marrow cavity may be less dense, potentially leading to a lower yield of MSCs. Pre-procedure assessments, including bone density scans and possibly magnetic resonance imaging (MRI) or computed tomography (CT) imaging, are essential to evaluate the suitability of the bone marrow site for aspiration. These assessments help in identifying the best possible site for marrow extraction, maximizing the likelihood of obtaining a high-quality sample.

Exclusion criteria: Certain conditions may contraindicate BMA or reduce its effectiveness. Patients with hematological disorders that affect bone marrow quality, such as leukemia or myelodysplastic syndromes, are typically excluded from MSC harvesting procedures unless the bone marrow is being specifically assessed or treated for these conditions[36]. Additionally, patients with active infections, especially in the area of the aspiration site, should not undergo BMA due to the risk of spreading infection and contaminating the sample[37]. Patients on anticoagulant therapy or those with coagulation disorders also require careful consideration. These individuals are at an increased risk of bleeding during and after the procedure, which can lead to complications. For such patients, it may be necessary to adjust or temporarily discontinue anticoagulation therapy under close medical supervision before proceeding with BMA[38].

Recommendations for specific patient populations

In older adults, the decline in MSC quantity and regenerative capacity requires modifications in harvesting strategies. To maximize MSC yield, employing multiple small-volume aspirations from different sites can enhance concentration while reducing peripheral blood contamination[7]. Harvesting from alternative sites, such as the proximal tibia or distal femur during knee surgeries, can also minimize morbidity associated with iliac crest aspiration[7]. Advanced aspiration devices, like the Marrow Cellution™ needle, may help optimize cell harvest with minimal manipulation[24]. For patients with osteoporosis, considerations related to bone density are crucial. Pre-procedural imaging, including DEXA scan and MRI, helps assess bone quality and determine optimal harvesting sites[39]. Using needles specifically designed for osteoporotic bone, such as those with sharper tips and adjustable depths, minimizes fracture risk[7]. Gentle aspiration techniques, applying controlled pressure, further reduce the chances of cortical breaches. In patients with comorbid conditions such as diabetes or vascular disease, a comprehensive evaluation of how these conditions impact MSC function and healing potential is needed[35]. Anesthesia and sedation protocols should be tailored to the patient's cardiovascular or metabolic status to reduce procedural risks[7]. Collaborative care, involving specialists like endocrinologists and cardiologists, helps in optimizing patient outcomes. Optimizing aspiration techniques, such as using slow aspiration rates and limiting the volume per pull, can improve MSC purity[7]. Ensuring strict aseptic conditions throughout the procedure is crucial to prevent contamination and maintain cell viability. Educating patients regarding the procedure, its risks, benefits, and post-procedural care can significantly enhance compliance and overall satisfaction.

Personalized approaches based on patient-specific factors are essential for tailoring BMH and MSC therapy. Age-related factors, such as reduced proliferative capacity and differentiation potential of MSCs in older patients, should be considered[7]. While the iliac crest often provides the highest MSC yield, alternative sites like the proximal tibia may be preferred to reduce morbidity during specific surgeries. Adjunct therapies, such as combining MSCs with growth factors or scaffolds, can be used to boost efficacy in older populations. In patients with decreased bone density, imaging modalities help evaluate bone integrity and determine suitable harvesting sites. Adjustments in needle insertion angles and aspiration pressures can reduce the risk of fractures[7]. For individuals with severe osteoporosis, alternative MSC sources like adipose-derived stem cells may be considered. Comorbid conditions, such as diabetes, necessitate customized protocols to address impaired MSC function and delayed healing[35,36]. Holistic care plans that encompass the management of underlying conditions along with MSC therapy are essential. Engaging patients in decision-making ensures that treatment strategies align with their preferences and expectations. An interdisciplinary approach, collaborating with specialists across different fields, addresses the broad needs of each patient. Adaptive treatment strategies should be implemented based on patient response, new data, and evolving best practices. Incorporating patient-specific factors into harvesting site selection and treatment planning enhances the safety and effectiveness of MSC therapies, leading to improved outcomes.

PROCEDURAL ENVIRONMENT AND EQUIPMENT

Sterile environment

Maintaining a sterile environment during the BMA procedure is crucial to prevent infections, which can have severe consequences for both the patient and the quality of the harvested MSCs[40]. The procedure should be performed in a controlled, sterile environment, such as an operating room or a dedicated procedure room equipped with appropriate facilities for sterilization. All equipment, including needles, syringes, and aspiration devices, must be sterile. The skin at the aspiration site should be thoroughly disinfected using antiseptic solutions like chlorhexidine or iodine. Sterile drapes should be used to isolate the procedure area from potential contaminants. Additionally, the clinician performing the aspiration should wear sterile gloves, gowns, and masks to minimize the risk of contamination.

Equipment requirements

The choice of equipment for BMA is integral to the success of the procedure. High-quality needles, such as the Jamshidi [23] or AMC[21] needles, should be used to ensure effective penetration of the bone and optimal aspiration of marrow. These needles are designed to minimize trauma to the bone and surrounding tissues, reducing patient discomfort and improving the yield of MSCs. Advanced aspiration devices that control the pressure and rate of aspiration are also recommended. These devices can help standardize the procedure, ensuring consistent results across different patients and operators. For example, powered bone marrow aspiration devices like the OnControl system provide a more controlled and efficient method of marrow extraction, which can enhance the quality and quantity of the harvested cells [30]. In addition to the aspiration equipment, facilities for immediate processing of the bone marrow sample are necessary. This includes centrifuges for separating MSCs from other cellular components and flow cytometry equipment for assessing cell viability and concentration. In regions where regulatory requirements permit, in-room processing of the aspirate may be performed to concentrate the MSCs before they are used in therapy.

Pre-procedure preparations

Informed consent and patient education: Obtaining informed consent is a legal and ethical requirement before performing BMA[6]. The patient must be fully informed about the procedure, including its purpose, risks, benefits, and potential complications. This discussion should also cover what the patient can expect during and after the procedure, including the possibility of pain or discomfort, the time required for recovery, and any specific post-procedure care instructions. Patient education is also critical. Educating patients about the procedure helps to alleviate anxiety, which can significantly impact their overall experience and even the physiological outcomes of the procedure. Patients should be informed about the importance of following pre-procedure instructions, such as fasting or avoiding certain medications, to ensure the best possible outcome.

Pre-procedural medications: Depending on the patient's condition and the expected level of discomfort, pre-procedural medications may be administered[6]. Local anesthesia is typically used to numb the aspiration site, reducing pain during the procedure. In some cases, especially in patients with high anxiety or those undergoing multiple aspirations, additional anxiolytics or mild sedatives may be administered to help the patient relax. For patients with a history of significant pain during previous BMAs, or those who express considerable concern about pain, stronger analgesics or even conscious sedation may be considered. However, these decisions must be made on a case-by-case basis, weighing the benefits of pain control against the risks of sedation.

Imaging and site selection: Pre-procedural imaging can be beneficial in selecting the optimal site for marrow aspiration. While the PSIS is the most common site for BMA, alternative sites may be considered based on the patient's anatomy and bone density[25]. Imaging techniques such as MRI or CT scans provide detailed views of the bone and marrow cavity, allowing for more precise targeting of rich marrow areas and avoiding areas with poor cellularity or high-fat content[41, 42].

Post-aspiration handling and processing

Sample transport and handling: After the bone marrow is aspirated, the sample must be handled with utmost care to maintain the viability and quality of the MSCs. The sample should be immediately transferred to a sterile, pre-chilled container to minimize cell degradation. Rapid transport to the processing laboratory is essential, especially if the aspirate is being used for immediate therapeutic purposes. During transport, the sample should be kept at a controlled temperature, ideally between 2 °C and 8 °C, to preserve cell viability[43,44]. It is also crucial to minimize agitation during transport, as excessive movement can damage the delicate MSCs.

PROCESSING

After the successful aspiration of bone marrow, the handling and processing of the BMA are crucial steps that determine the quality, concentration, and efficacy of the BMAC. This section provides a detailed overview of the best practices and critical considerations involved in the post-aspiration handling and processing of BMAC. Once the bone marrow has been aspirated, it must be promptly handled to prevent cellular degradation and clot formation, which could compromise the viability of the stem cells and other bioactive components. The aspirate is typically collected in syringes preloaded with anticoagulants such as heparin to prevent clotting[5]. Anticoagulation is essential because the formation of clots within

the aspirate can significantly reduce the yield of viable cells and other critical components necessary for therapeutic use [7]. The aspirated bone marrow should be immediately filtered through a sterile, mesh filter (typically 200-micron) to remove bone fragments and other debris[12]. This filtration step is critical to ensure that the aspirate is free from particulate matter that could interfere with subsequent processing or introduce complications during the injection phase.

Centrifugation process

Centrifugation is the cornerstone of BMAC processing, allowing for the concentration of stem cells, platelets, and growth factors while removing unwanted components such as red blood cells and plasma. The process typically involves a two-step centrifugation protocol.

First centrifugation (separation step): The filtered bone marrow aspirate is transferred into sterile 50 mL conical tubes and subjected to an initial centrifugation at approximately 3200 rpm for 15 minutes[5]. This step separates the blood components into distinct layers, with the buffy coat (containing mononuclear cells, including MSCs) situated between the red blood cell layer and the plasma.

Buffy coat isolation: After the first centrifugation, the buffy coat layer, which is rich in MSCs and platelets, is carefully extracted. This layer is crucial as it contains the highest concentration of the desired therapeutic cells and factors. The buffy coat is typically transferred into new conical tubes for further processing.

Second centrifugation (concentration step): The isolated buffy coat undergoes a second round of centrifugation at a higher speed, typically around 4800 rpm for 15 minutes[5]. This step further concentrates the mononuclear cells and platelets, resulting in a denser pellet at the bottom of the tube. The supernatant, which contains platelet-poor plasma, is carefully removed, leaving the concentrated BMAC.

Resuspension of the concentrate: The final step in the centrifugation process involves resuspending the concentrated cell pellet in a small volume of platelet-poor plasma or another suitable carrier solution. This resuspension is essential to achieve a consistent and injectable BMAC product, ensuring that the stem cells and growth factors are evenly distributed throughout the solution.

Quality control and analysis

Following centrifugation, it is imperative to perform quality control checks on the BMAC to ensure its suitability for clinical use. This typically involves performing a complete blood count with differential and a hemacytometer analysis to assess the concentration and viability of the MSCs and other mononuclear cells within the BMAC[35,45,46]. The analysis includes the following parameters.

Total nucleated cell count: A higher total nucleated cell count indicates a more concentrated BMAC, which is generally desirable for therapeutic applications.

Mononuclear cell count: This specific cell count is crucial as it includes MSCs, which are the primary therapeutic agents in BMAC.

Cell viability: Assessing cell viability is essential to ensure that the BMAC contains a high proportion of live, functional cells capable of contributing to tissue repair and regeneration.

The results of these analyses guide the decision-making process regarding the adequacy of the BMAC for clinical application. If the cell counts or viability are below acceptable thresholds, additional processing steps or adjustments may be required.

Considerations for optimal processing

Several factors can influence the quality and therapeutic efficacy of BMAC, and careful attention must be paid to these during the processing phase.

Temperature control: Maintaining the aspirate and BMAC at appropriate temperatures (typically around 4 °C to 8 °C) throughout the processing is crucial to preserving cell viability. Prolonged exposure to suboptimal temperatures can lead to cellular apoptosis or necrosis, reducing the efficacy of the BMAC.

Minimizing mechanical stress: The handling of BMAC during processing should be done gently to avoid mechanical stress that could damage the cells. Excessive agitation or forceful pipetting can result in cell lysis, decreasing the overall cell count and viability.

Processing time: The time between aspiration and final processing should be minimized. Prolonged delays can lead to cell death and reduced growth factor activity, ultimately compromising the therapeutic potential of the BMAC.

Sterility: Throughout the handling and processing of BMAC, maintaining a sterile environment is paramount to prevent contamination. This includes using sterile equipment, working within a laminar flow hood when possible, and employing aseptic techniques at all stages.

The cellular characteristics of bone marrow from various anatomical locations are tabulated in Table 1[5,6,46] and Figure 2. The clinical application of bone marrow from various anatomical locations are tabulated in Table 2. The merits and de-merits of bone marrow from various anatomical locations are tabulated in Table 3. The factors influencing the

Table 1 Cell characteristics of bone marrow from various anatomical locations

Anatomical site	Common use	MSC characteristics	Differentiation potential	Homing and engraftment potential	Therapeutic use
Iliac crest[5]	Most commonly used site for bone marrow harvesting due to its high yield and easy access	Robust proliferative capacity, multi-lineage differentiation potential. High expression of CD105, CD73, CD90, CD146, and CD271	Potent osteogenic differentiation; suitable for bone regeneration. High expression of alkaline phosphatase and osteocalcin	Higher due to the high expression of adhesion molecules like CD146 and CD271	Ideal for bone regeneration due to osteogenic potential may support hematopoiesis
Tibial bone marrow[6]	Alternative site for MSC harvesting, especially for knee OA treatment	Potentially enhanced chondrogenic differentiation. Higher expression of chondrogenic markers like Sox9 and aggrecan	Enhanced chondrogenic potential; produces glycosaminoglycans and type II collagen. Suited for cartilage repair	Potentially higher chondrogenic activity due to enhanced niche for cartilage repair	Better suited for cartilage regeneration in OA due to chondrogenic differentiation potential
Femoral bone marrow[46]	Commonly accessed during orthopedic procedures such as total knee arthroplasty	High osteogenic potential, expressed higher levels of Runt-related transcription factor-2 and bone sialoprotein but lower proliferation rates compared to iliac crest	Superior osteogenic potential, higher mineralization capacity. High calcium deposition during osteogenic differentiation	Lower proliferation rates but high osteogenic commitment	Best suited for bone repair applications like non-union fractures or large bone defects

MSC: Mesenchymal stem cell; OA: Osteoarthritis.

Table 2 Clinical application of bone marrow from various anatomical locations

Anatomical site	Clinical application	Advantages	Drawbacks	Clinical considerations
Iliac crest	Gold standard site for BMAC harvesting, widely used in regenerative therapies for knee OA due to high progenitor cell yield. High culture success rate for MSCs	High nucleated cell and clone forming unit yield, extensive clinical experience, and literature supporting efficacy. MSC yield is superior and the culture success rate can reach up to 90%	Associated with donor-site morbidity, including pain, hematoma, and nerve injury. Requires a secondary surgical site, increasing invasiveness	Preferred in cases where maximum progenitor cell yield is critical. Established protocols and extensive use in knee OA treatment. Potential for postoperative complications
Proximal humerus	Emerging alternative, commonly used in shoulder surgeries such as rotator cuff repair. Offers high-quality BMAC without a secondary incision	No need for separate incisions during shoulder procedures, and high progenitor cell yield even after large volume aspirations. Reliable across patient age groups	Primarily useful in shoulder surgeries, less studied compared to the iliac crest, though efficacy is promising	Best for minimizing patient morbidity in shoulder surgeries, with comparable efficacy to iliac crest BMAC. Convenient for combined procedures
Acetabulum	Primarily used in hip surgeries, where BMAC harvesting can occur within the same surgical field, offering dual-purpose potential. Useful for hip-related therapies	Convenient for hip-related procedures, high progenitor cell counts comparable to the iliac crest. Single-session harvesting and BMAC preparation	Limited to hip-related procedures, indirect application in knee OA treatment	Suited for scenarios where a dual-purpose approach is needed, particularly in hip surgeries. Produces high-quality BMAC but is limited to specific surgeries
Distal femur	Anatomically accessible during knee surgeries, particularly TKA. Can be seamlessly integrated with the procedure for autologous therapies	Easy anatomical access during knee surgeries, minimally invasive, lower complication risk, and integrated into surgical workflow. MSCs show similar differentiation potential to those from the iliac crest	Lower MSC yield compared to iliac crest (0.67 million cells/mL *vs* 10.05 million cells/mL). Slightly lower MSC culture success rate	A viable alternative when iliac crest access is limited or undesirable. Moderate MSC culture success rate (approximately 71%) but lower yield. Beneficial in knee OA treatments integrated with TKA
Proximal tibia	Similar to the distal femur, the proximal tibia can be harvested during knee surgeries like TKA. Lower MSC yield compared to the iliac crest but viable for knee OA therapy	Reduces invasiveness, less risk of complications. Easier access in knee surgeries. MSCs exhibit robust differentiation capacity, although yield is lower than iliac crest	Lower MSC yield than iliac crest (1.70 million cells/mL *vs* 10.05 million cells/mL). MSC culture success rate is around 47%	Suitable alternative for patients contraindicated for iliac crest harvesting. Moderate MSC yield and culture success rate (approximately 47%). Useful in knee-focused procedures

BMAC: Bone marrow aspirate concentrate; MSC: Mesenchymal stem cell; OA: Osteoarthritis; TKA: Total knee arthroplasty.

Table 3 Merits and de-merits of bone marrow from various anatomical locations

Anatomical site	Merits	Demerits
Anterior superior iliac spine	Ease of access: Superficially located and easy to palpate, facilitating quicker and less invasive procedures	Lower cell purity: Increased risk of blood dilution due to fatty tissue, potentially reducing MSC concentration
	Adequate yield: Provides a good volume of aspirate with acceptable TNC and CFU-f yields	Variable CFU-f yield: Typically lower CFU-f counts compared to the posterior superior iliac spine, which may affect the therapeutic potential of the aspirate
	Lower complication rate: Reduced risk of neurovascular injury and other complications when performed with proper technique	Patient discomfort: Proximity to muscle attachments can cause discomfort during and after the procedure
	High culture success rate: High success rate in MSC culture, indicating reliable cell viability and expansion potential	Postoperative pain: Potential for significant postoperative pain and hematoma formation
Posterior superior iliac spine	High cell yield: Provides a high concentration of TNCs and CFU-fs, making it the preferred site for harvesting high-quality aspirates	Increased technical difficulty: Less accessible, particularly in patients with high BMI or anatomical variations, requiring more complex positioning and technique
	Reduced blood dilution: Lower fatty infiltration results in higher cell purity and reduced blood contamination	Higher risk of complications: Proximity to the sacroiliac joint and gluteal neurovascular bundle increases the risk of neurovascular injury
	Consistency in results: Yields consistent results with less variability in cell counts across different patients	Patient discomfort: A deeper location and the need to traverse more tissue can cause significant post-procedural pain
	Gold standard for MSC yield: Considered the gold standard for bone marrow harvesting due to its high MSC yield and well-established protocols	Donor-site morbidity: Associated with significant morbidity, including pain, hematoma, and nerve injury, which may deter its use in certain populations
Proximal tibia	Convenience in certain surgeries: Proximity to the knee joint makes it convenient during knee-related surgeries, reducing procedure time	Lower MSC concentration: Typically provides a lower concentration of MSCs compared to the iliac crest, which may limit its effectiveness in regenerative therapies
	Adequate cell yield in some cases: Can produce a reasonable volume of aspirate, especially when large volumes are needed	Greater variability in yield: High variability in cell yield depending on factors such as patient age, BMI, and bone density, leading to inconsistent results
	Reduced risk of major complications: Stable site with a lower risk of major complications like neurovascular injury, making it a safer choice in some contexts	Difficulty in aspiration technique: Requires careful technique to avoid complications such as cortical bone fracture, particularly in osteoporotic patients
	Integrated into knee surgeries: Easily integrated into knee surgeries like TKA, adding minimal additional risk and reducing invasiveness	Lower culture success rate: MSC culture success rate is lower compared to the iliac crest, which may limit its utility in certain therapeutic applications
Proximal humerus	Convenience in shoulder surgeries: Located within the surgical field during shoulder procedures, reducing the need for an additional surgical site	Limited data: While promising, there is limited data compared to the iliac crest, and long-term outcomes need further study
	High MSC yield: Can yield a comparable number of progenitor cells to the iliac crest, making it a viable alternative for bone marrow aspirate concentrate preparation	Variability with age: Potential variability in MSC yield with age, although studies suggest this site may still be reliable across different age groups
	Reduced morbidity: Less invasive compared to iliac crest harvesting, with a lower risk of complications and patient discomfort	Not standard practice: Not as widely used or studied as the iliac crest, leading to less familiarity and potentially greater variability in outcomes
Distal femur	Ease of access during knee surgeries: Easily accessible during knee surgeries such as TKA, reducing the need for additional procedures	Lower MSC concentration: Significantly lower MSC concentration compared to the iliac crest, potentially limiting its effectiveness in high-demand applications
	Lower postoperative complications: Reduced invasiveness with potentially fewer postoperative complications, particularly in patients with previous pelvic surgeries	Lower culture success rate: The culture success rate for MSCs is lower than that of the iliac crest, which may affect the feasibility of its use in large-scale therapeutic applications
	Potential for integration into existing surgeries: Can be seamlessly integrated into existing knee procedures, adding minimal risk and enhancing therapeutic options	Inconsistent yield: Variability in cell yield can lead to inconsistent outcomes, which may affect the reliability of the site for routine use in MSC harvesting
Acetabulum	Dual-purpose during hip surgeries: Accessible during hip surgeries, allowing simultaneous bone marrow harvesting without additional surgical risks	Limited to hip procedures: Primarily applicable in the context of hip surgeries, limiting its broader use in other orthopedic applications such as knee OA
	Comparable yield to iliac crest: Studies suggest a comparable progenitor cell yield to the iliac crest, making it a feasible alternative in certain contexts	Not a primary choice for knee OA: While effective for hip procedures, its role in knee OA treatment is more indirect and not commonly pursued as a first choice

BMI: Body mass index; CFU: Clone forming unit; MSC: Mesenchymal stem cell; OA: Osteoarthritis; TKA: Total knee arthroplasty; TNC: Total nucleated

cell count.

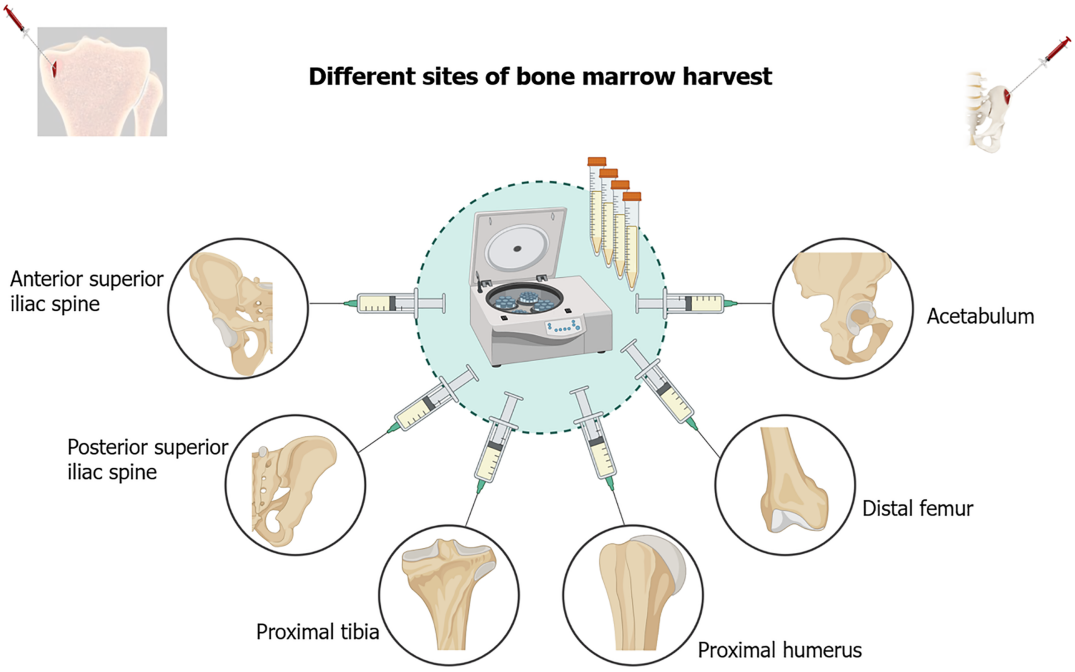

Figure 2 Depiction of different sites of bone marrow harvest.

quality of BMAC is depicted in Figure 3.

LIMITATIONS AND FUTURE DIRECTIONS

BMH from alternative sites, such as the distal femur and proximal tibia, presents notable limitations, primarily due to lower MSC yields compared to the gold standard iliac crest. This lower yield often necessitates the use of larger bone marrow volumes or *in vitro* cell expansion, increasing both time and cost. Additionally, MSC yields are highly variable due to factors like patient age, bone quality, and harvesting techniques, which further complicate the process. The absence of standardized protocols for bone marrow aspiration across different sites adds to this challenge, resulting in inconsistent outcomes and difficulties in comparing clinical studies. Moreover, donor-site morbidity, especially at the iliac crest, raises concerns about postoperative complications such as pain, hematomas, or nerve damage, prompting the exploration of alternative sites. However, these alternatives also carry risks, such as cortical bone fractures during harvesting from the tibia or femur. Personalized approaches, considering patient-specific factors like age, comorbidities, and bone health, are becoming more relevant to optimizing therapeutic outcomes. Future research should focus on improving aspiration techniques, refining tools for harvesting, and developing standardized protocols for various anatomical sites. Large-scale, comparative studies are needed to evaluate the yield and functionality of MSCs from different sites. Integrating new technologies like three-dimensional (3D) bioprinting, bioengineered scaffolds, and gene editing holds promise for improving the efficacy and safety of MSC-based therapies, particularly in regenerative applications like knee OA. The summary of challenges and limitations in isolation and characterization of bone marrow is summarized in Table 4.

Despite the potential of alternative harvesting sites, several limitations hinder the widespread adoption of these techniques. Many existing studies have small sample sizes and lack statistical power, which limits the generalizability of their findings. The heterogeneity in study designs, including variations in aspiration volumes, needle types, and processing methods, complicates comparisons and meta-analyses. The inconsistency in MSC yields from alternative sites is also a significant concern. Factors such as patient age, bone quality, and comorbidities contribute to this variability[35]. Without standardized protocols, it is challenging to determine whether differences in outcomes are due to the harvesting site or procedural inconsistencies. Most studies focus on short-term outcomes, with limited data on the long-term efficacy and safety of MSC therapies derived from alternative sites. This gap makes it difficult to assess the sustained benefits and potential risks associated with these approaches. To address these limitations, future research should conduct large-scale, multicenter trials to increase sample sizes and include diverse populations, thereby enhancing the robustness of findings and their applicability. Standardizing protocols by developing consensus guidelines on harvesting techniques, processing methods, and outcome measures will facilitate comparability across studies. Stratifying patients based on age, bone density, and comorbidities can help isolate the effects of these variables on MSC yield and therapeutic outcomes. Longit-

Table 4 Challenges and limitations in isolation and characterization of bone marrow

Challenges/limitations	Proposed solutions	Research gaps	Future directions
Lower MSC yield from alternative sites (distal femur, proximal tibia)	Optimize harvesting techniques at alternative sites to enhance MSC yield and viability	Lack of comprehensive comparative studies of MSC yield from different anatomical sites	Prioritize large-scale, randomized controlled trials across multiple anatomical sites
Necessity of larger volumes or *in vitro* expansion due to low yield	Refinements in aspiration technique and improvements in instruments	Limited data on long-term efficacy and safety of MSC-based therapies	Focus on personalized harvesting strategies based on biomarkers and patient characteristics
Influence of patient-specific factors (age and bone quality)	Develop protocols that combine cells from multiple sites for therapeutic dose	The absence of standardized protocols leads to variability in outcomes	Explore the integration of bone marrow harvesting techniques with emerging technologies (three-dimensional bioprinting, gene editing)
Variability in MSC yield and success rates across patients	Conduct large-scale comparative studies evaluating MSC yield, viability, and regenerative potential	Insufficient exploration of alternative harvesting sites for applications beyond knee osteoarthritis	Develop bioengineered scaffolds to enhance MSC survival and differentiation
Absence of standardized aspiration protocols for different sites	Establish standardized bone marrow aspiration protocols	Limited understanding of MSC functional heterogeneity from different sites	Investigate pre-operative and post-operative strategies to minimize complications
Complications at alternative sites (*e.g.*, cortical bone fracture)	Explore less invasive harvesting techniques to reduce morbidity	Lack of personalized strategies considering genetic background, age, and disease state	Use advanced techniques (single-cell RNA sequencing, proteomics) to assess MSC characteristics
Donor-site morbidity from iliac crest harvesting	Innovate with rotational aspiration devices and powered biopsy systems		
Age and health-related limitations (osteoporosis, lower MSC density)	Investigate personalized approaches based on patient-specific factors		
Long-term efficacy and safety of MSC therapies not fully studied	Include extended follow-up in studies to assess long-term efficacy and safety		

MSC: Mesenchymal stem cell.

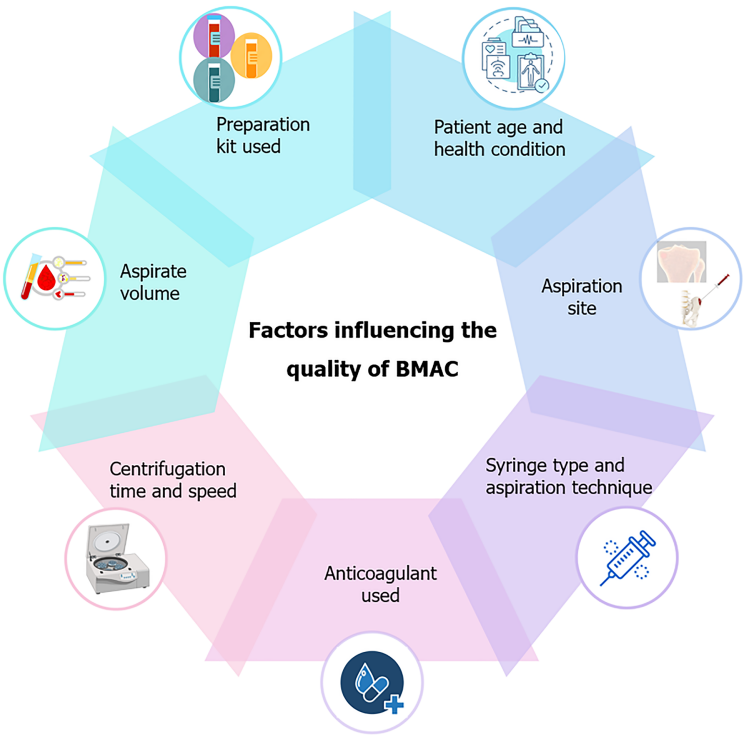

Figure 3 Depiction of the factors influencing the quality of bone marrow aspirate concentrate. BMAC: Bone marrow aspirate concentrate.

udinal follow-up studies, incorporating extended periods of observation, are needed to provide insights into the durability of treatment effects and potential late-onset complications. By critically analyzing current limitations and outlining strategies to overcome them, the field can advance towards more effective and reliable MSC-based therapies for knee OA.

Integration of emerging technologies in MSC therapies

The incorporation of emerging technologies has the potential to significantly enhance BMH techniques and MSC therapies for knee OA.

Single-cell sequencing: Single-cell RNA sequencing enables the detailed analysis of individual MSCs, revealing heterogeneity within cell populations[47]. By identifying subpopulations with superior regenerative potential or specific differentiation capabilities, clinicians can select or enrich for MSCs most likely to contribute to cartilage repair. This precision can improve therapeutic efficacy and allow for the development of customized MSC products tailored to patient needs.

Advanced imaging techniques: Utilizing advanced imaging modalities such as high-resolution MRI, micro-CT, and ultrasound elastography can assist in assessing bone quality and marrow composition before harvesting. These techniques can identify areas with higher MSC concentrations or better bone integrity, guiding needle placement to optimize cell yield. Intraoperative imaging can also enhance the accuracy of needle insertion, reducing procedural complications[48].

Artificial intelligence and machine learning: Artificial intelligence (AI) and machine learning algorithms can analyze large datasets to predict MSC yield, viability, and differentiation potential based on patient-specific variables. By integrating demographic data, imaging findings, and procedural parameters, AI can assist in personalizing harvesting protocols and predicting therapeutic outcomes. Machine learning models can also optimize processing techniques by identifying patterns that correlate with higher MSC viability and potency[49].

Intraoperative guidance systems: The development of AI-driven intraoperative guidance systems can improve the precision of bone marrow aspiration. Real-time feedback on needle positioning and aspiration parameters can enhance MSC yield while minimizing patient discomfort and procedural risks. Such systems can be particularly beneficial in patients with anatomical variations or compromised bone quality[50].

3D bioprinting and tissue engineering: Advancements in 3D bioprinting allow for the creation of custom scaffolds that can be seeded with MSCs to generate tissue constructs mimicking native cartilage. By integrating patient-specific imaging data, personalized implants can be designed to fit precisely within cartilage defects, enhancing integration and functional recovery[50].

Integrating these emerging technologies into clinical practice requires interdisciplinary collaboration and adherence to regulatory standards. Continued research and development in these areas hold promise for optimizing MSC harvesting and therapies, ultimately improving outcomes for patients with knee OA.

INNOVATIVE RESEARCH DIRECTIONS AND THEORETICAL MODELS

Advancing MSC-based therapies for knee OA necessitates exploring innovative research directions and developing theoretical models that can shape future studies. One promising avenue is the utilization of computational modeling to predict MSC yield and viability based on patient-specific factors such as age, bone density, and comorbidities[51,52]. By integrating patient data into predictive algorithms, clinicians can tailor harvesting strategies to optimize both the quantity and quality of MSCs obtained from individual patients. Systems biology approaches can be employed to unravel the complex interactions between MSCs and the osteoarthritic joint environment. By constructing computational models of signaling pathways and gene networks, researchers can identify key regulatory nodes that influence MSC differentiation and cartilage regeneration. This holistic understanding can inform the development of targeted therapies that modulate specific molecular pathways to enhance therapeutic outcomes.

Investigating the MSC secretome, particularly extracellular vesicles (EVs) and exosomes, represents another innovative direction. These vesicles carry bioactive molecules that can modulate inflammation and promote tissue repair. Exploring the therapeutic potential of MSC-derived EVs may lead to cell-free therapies that mitigate the risks associated with cell transplantation while harnessing the regenerative capabilities of MSCs[53,54]. Combining MSC therapies with biomaterials and scaffold technologies also holds significant promise. Developing bioengineered scaffolds that mimic the native extracellular matrix can provide structural support and enhance MSC survival, proliferation, and differentiation within the joint. Such scaffolds can be designed to deliver MSCs in a controlled manner, improving their integration and functional contribution to cartilage repair[55]. Utilising gene-editing technologies like CRISPR/Cas9 allows for the genetic modification of MSCs to enhance their regenerative properties[56-58]. By upregulating genes associated with chondrogenesis or downregulating inhibitory pathways, engineered MSCs can exhibit improved efficacy in cartilage repair. These innovative research directions and theoretical models offer valuable pathways for optimizing MSC-based therapies and warrant further exploration in future studies.

CONCLUSION

The exploration of alternative BMH sites, such as the proximal tibia, distal femur, and proximal humerus, offers promising avenues for optimizing MSC yield and minimizing donor-site morbidity, particularly in the context of knee OA treatment. While the iliac crest remains the gold standard due to its high MSC concentration, the emerging evidence suggests that alternative sites may provide viable MSCs with significant therapeutic potential, albeit with some limitations in yield and consistency. To fully harness the regenerative capabilities of MSCs, further research is essential to standardize harvesting techniques, improve cell viability, and refine clinical applications. As the field advances, personalized approaches, tailored to patient-specific factors and optimized harvesting strategies, will be crucial in enhancing the efficacy of MSC-based therapies for OA and other degenerative joint conditions, ultimately improving patient outcomes and quality of life.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Immunohistochemical expression of matrix metalloproteinase-9 and 13 in oral squamous cell carcinoma and their role in predicting lymph node metastasis

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Abstract

BACKGROUND

One of the main characteristics of oral squamous cell carcinoma (OSCC) is that it metastasizes to cervical lymph nodes frequently with a high degree of local invasiveness. A primary feature of malignant tumors is their penetration of neighboring tissues, such as lymphatic and blood arteries, due to the tumor cells' capacity to break down the extracellular matrix (ECM). Matrix metalloproteinases (MMPs) constitute a family of proteolytic enzymes that facilitate tissue remodeling and the degradation of the ECM. MMP-9 and MMP-13 belong to the group of extracellular matrix degrading enzymes and their expression has been studied in OSCC because of their specific functions. MMP-13, a collagenase family member, is thought to play an essential role in the MMP activation cascade by breaking down the fibrillar collagens, whereas MMP-9 is thought to accelerate the growth of tumors. Elevated MMP-13 expression has been associated with tumor behavior and patient prognosis in a number of malignant cases.

AIM
To assess the immunohistochemical expression of MMP-9 and MMP-13 in OSCC.

METHODS
A total of 40 cases with histologically confirmed OSCC by incisional biopsy were included in this cross-sectional retrospective study. The protocols for both MMP-9 and MMP-13 immunohistochemical staining were performed according to the manufacturer's recommendations along with the normal gingival epithelium as a positive control. All the observations were recorded and Pearson's χ^2 test with Fisher exact test was used for statistical analysis.

RESULTS
Our study showed no significant correlation between MMP-9 and MMP-13 staining intensity and tumor size. The majority of the patients were in advanced TNM stages (III and IV), and showed intense expression of MMP-9 and MMP-13.

CONCLUSION
The present study suggests that both MMP-9 and MMP-13 play an important and independent role in OSCC progression and invasiveness. Intense expression of MMP-9 and MMP-13, irrespective of histological grade of OSCC, correlates well with TNM stage. Consequently, it is evident that MMP-9 and MMP-13 are important for the invasiveness and progression of tumors. The findings may facilitate the development of new approaches for evaluating lymph node metastases and interventional therapy techniques, hence enhancing the prognosis of patients diagnosed with OSCC.

Key Words: Matrix metalloproteinases; Oral squamous cell carcinoma; Tumor staging; Immunohistochemistry; Invasion; Lymph node metastasis; TNM stage

Core Tip: The most prevalent type head and neck cancer is oral cavity squamous cell carcinoma (OCSCC). The major cause of the poor prognosis is extensive local invasion that spreads to the lymph nodes. Degradation of the matrix and spread of cancer cells are major characteristics of malignant tumors. Hence, in the present study, matrix metalloproteinase (MMP)-9 and 13 expression was investigated to understand and interpret the invasion and metastasis in OSCC. Most of the cases showed various degrees of staining intensity for MMP-9 and MMP-13. MMP-9 and MMP-13 staining intensity had no significant correlation with tumor size, though a significant relationship ($P = 0.000$) was observed with metastasis.

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is characterized by significant local invasiveness and a strong propensity for cervical lymph node metastasis. Cancer-related mortality often stems from either local recurrence or regional and systemic metastasis[1]. Understanding and predicting metastasis, as well as enhancing prognosis, are major areas of direct and indirect oral cancer research attention. There have been significant efforts in the past few years to investigate the cellular and molecular pathways involved in metastasis[2].

In this regard, matrix metalloproteinases (MMPs) are one notable category of variables that show promise in predicting invasion and metastasis in OSCC. MMPs are a large family of calcium-dependent zinc-containing endopeptidases that belong to the extracellular matrix (ECM) degrading enzyme family[1]. The ECM, which is made up of proteins like proteoglycans, collagens, elastins, and gelatin, is remodeled and broken down by enzymes of this family[1,3]. MMP-9 and MMP-13, as two members of this family, have drawn interest in OSCC because of their unique roles.

A zinc-dependent proteinase called MMP-9 is essential in breaking down type IV collagen, which is a significant part of the basement membrane, and it is believed to significantly contribute to tumor invasion by facilitating tumor cell migration and the release of cytokines and other factors within the tumor environment, thereby promoting tumor growth and development[3-6].

Another member of the collagenase family, MMP-13, assumes a critical role in the MMP activation cascade by degrading various fibrillar collagens (types I, II, III, IV, X, and XIV), tenascin, fibronectin, aggrecan, versican, and fibrillin-I. MMP-13's involvement in oral cancer lies in its influence on metastasis through the formation of focal adhesions, protein synthesis during the G1 phase, and induction of cell cycle arrest in the G2 phase leading to the accumulation and

activation of transcription factors like P53 and cyclin B1/CDK1.

During the breakdown of the ECM, collagen type II is more efficiently cleaved than collagen types I and III[7-9]. MMP-13 expression is elevated in several malignancies and is linked to tumor behavior and patient prognosis. Hence, this study aimed to evaluate the immunohistochemical expression of MMP-9 and MMP-13 in tissue specimens of OSCC and their correlation with clinical and histopathological grades.

MATERIALS AND METHODS

Approvals

Approval from the local Institutional Ethics Committee was obtained under the reference SVIEC/ON/DENT/BN-PG12//D12102, and written informed consent was obtained from each participant. The participants' demographic information, clinical presentation, and radiological findings, including size, location, lymph node status, and clinical stage, were documented in the provided format.

Case selection

This retrospective study involved a total of 40 cases of OSCC which were previously histologically confirmed by incisional biopsy.

The exclusion criteria included having other systemic disorders, refusing to provide informed consent, or having received OSCC treatment in the past.

Sectioning and staining procedures

Paraffin-embedded blocks were used to prepare four sections measuring 4 to 5 microns each. Hematoxylin and eosin (HE) staining was applied to two of these sections, and immunohistochemistry (LSAB) expression of MMP-9 and MMP-13 (DAKO Corporation, Denmark, Clone-DCS-6) was detected on the remaining two sections that were mounted on slides coated with silane.

Tissue sections after deparaffinization in xylene were rehydrated through a descending ethanol series (100%, 95%, 90%, 80%, and 70%) at room temperature for 5 min. Antigen retrieval was done using a microwave, followed by a wash in distilled water after allowing it to cool for 10 min. Endogenous peroxidase activity was blocked with hydrogen peroxide for 5 min. Incubation with the prediluted primary rabbit monoclonal MMP-9 antibody (DAKO Corporation, Denmark, Clone-DCS-6) was then done for 30 min at room temperature. The slides were then rinsed with Tris buffered saline (TBS) three times and incubated with the secondary antibody reagent: A labeled secondary antibody (biotinylated anti-mouse, anti-rabbit, anti-goat immunoglobulin) in phosphate buffered saline (PBS) with carrier protein and sodium azide, streptavidin peroxidase (streptavidin conjugated to horseradish in PBS with carrier protein and an antimicrobial agent), and buffered substrate containing hydrogenperoxide (H_2O_2) and a preservative (pH 7.5) for 15-30 min at room temperature. 3'3-diaminobenzidine (DAB) was then applied for minutes. For counterstaining, the slides were rinsed with deionized water, incubated for 5 min with hematoxylin, and rinsed with PBS for 1 min.

Evaluation of staining

Using the Bryne's grading scheme, the HE stained areas were evaluated and categorized as grade I, grade II, or grade III [10]. Both markers were processed following the manufacturer's instructions. Positive immunoreactivity was indicated at the target antigen site by the presence of a brown-colored end product. Normal gingival epithelial tissue sections were used as positive controls, while the absence of staining was used as a negative control. MMP-9 immunopositivity was detected in the cytoplasm of tumor cells, and Table 1 provides an assessment of its intensity. MMP-13 exhibited predominantly positive staining in the cell nucleus, occasionally in the cytoplasm, and its intensity was assessed as indicated in Table 2[11].

In order to reduce observer bias, all observations were recorded by three separate observers. The surgically removed lymph node samples were subjected to histological examination to ascertain whether tumor cells were present in the lymph nodes.

Statistical analysis

Pearson's χ^2 test was used to establish a relationship between two variables.

RESULTS

Case demographics

This study examined a sample of 40 people, of whom 25 were male and 15 were female (Table 3). The majority of the 40 participants were in their fifth or sixth decade, and there was a noticeable male predominance.

The most frequently implicated areas were the vestibule and the buccal mucosa, followed by the tongue; the least frequently involved site was the hard palate (Table 4).

The majority of patients used tobacco, primarily in non-smoking forms. Histopathologically, according to the Bryne's grading system, the majority of cases, as shown in Table 5, were grade I (62.5%) lesions, followed by grade II (30%) and grade III (7.5%).

Table 1 Staining intensity and grading of matrix metalloproteinase-9 expression

Grade	Interpretation
0	No positivity
Mild	Up to 10% of positive tumor cells
Moderate	11%-50% of positive tumor cells
Intense	Above 50% of positive tumor cells

Table 2 Staining and grading of matrix metalloproteinase-13

Grade	Interpretation
0	No staining of the tumor or stromal cells
1+	Mildly (< 50%) positive staining of the tumor cells and/or weak staining of stromal cells
2+	Moderately (> 50%) positive staining of the tumor cells and/or moderate staining of stromal cells
3+	Intense staining of the tumor cells and/or strong staining of stromal cells. No normal epithelial cells were stained

Table 3 Gender frequency distribution of cases

	Male	Female	Total
Cases	25	15	40

Table 4 Site distribution of cases

Site	No of cases	Percentage
Buccal mucosa	20	50
Buccal vestibule	01	2.5
Tongue	16	40
Hard palate	03	7.5
Total	40	100.0

Table 5 Bryne's histological grading of oral squamous cell carcinoma cases

Grade	No of cases	Percentage
I	12	30.0
II	25	62.5
III	3	7.5
Total	40	100.0

Staining analysis and interpretation

Details of different MMP-9 and MMP-13 staining intensities are displayed in Table 6. All the cases were positive for MMP-9, with the majority showing intense expression. Important details of the associations between tumor size and MMP-9 and MMP-13 expression are given in Table 7. For MMP-13, categorized by expression intensity ('None', 'Mild', 'Moderate', and 'Intense'), a χ^2 analysis revealed a non-significant association (P = 0.27) with tumor size. Comparably, categorized MMP-9 exhibited a non-significant association (P = 0.80) with tumor size. Table 7 displays MMP expression patterns in relation to tumor size, even though no statistical significance was found. 'Intense' MMP-9 and MMP-13 expression was frequently associated with greater tumor sizes.

Table 8 presents the results, which indicate a significant (P = 0.000) correlation between MMP-9 expression (classified as 'Mild', 'Moderate', and 'Intense') and lymph node involvement. Notably, 'Intense' MMP-9 expression predominated in cases with nearby lymph nodes (19 cases). Similarly, MMP-13 exhibited a strong association (P = 0.000) with lymph node

Table 6 Comparison of matrix metalloproteinase-9 and matrix metalloproteinase-13 expression

Metastasis	MMP-9			MMP-13			Intense
	Mild	Moderate	Intense	Nil	Mild	Moderate	
Absent	1	5	12	2	2	6	8
	5.6%	27.8%	66.7%	11.1%	11.1%	33.3%	44.4%
Present	0	6	16	1	7	5	9
	0.0%	27.3%	72.7%	4.5%	31.8%	22.7%	40.9%
Total	1	11	28	3	9	11	17
	2.5%	27.5%	70.0%	7.5%	22.5%	27.5%	42.5%

MMP: Matrix metalloproteinase.

Table 7 Association between tumor size with matrix metalloproteinase-9 and matrix metalloproteinase-13 expression

MMP-13					MMP-9			
Tumor size	T1	T2	T3	T4	T1	T2	T3	T4
None	1	3	0	0				
Mild	5	6	0	0	5	5	0	0
Moderate	1	11	1	0	2	6	0	0
Intense	1	8	2	1	1	17	3	1
χ^2 (P) value				11.02 (0.27)				11.26 (0.80)

MMP: Matrix metalloproteinase.

Table 8 Association between node involvement and matrix metalloproteinase-9 and matrix metalloproteinase-13 expression

		MMP-9			MMP-13		
		Mild	Moderate	Intense	Mild	Moderate	Intense
Node involvement	No involvement	9	6	1	10	2	0
	Nodes nearby	1	2	19	1	10	11
	Distant nodes	0	0	2	0	1	1
χ^2 (P) value		26.17 (0.000)			29.18 (0.000)		

MMP: Matrix metalloproteinase.

involvement, with the highest frequency of "Moderate" expression in cases with nearby nodes (10 cases). The results highlight the clinical importance of MMP-9 and MMP-13 in the advancement of OSCC, irrespective of the histological grade. Table 9 indicates the striking connections between the formation of metastasis and the expression of MMP-9 and MMP-13 in our study. MMP-9 expression, categorized as 'Mild', 'Moderate', and 'Intense', displayed a significant relationship (P = 0.000) with metastasis. Notably, 'Intense' MMP-9 expression was predominantly seen in cases where metastasis was present (21 cases). MMP-13, categorized as 'None', 'Mild', 'Moderate', and 'Intense', also displayed a strong association (P = 0.000) with metastasis. 'Intense' MMP-13 expression was most prevalent in cases with metastasis (12 cases).

Tumor size and grade of node involvement

Table 10 sheds light on the relationships between tumor size, grade of mode involvement, and the presence of metastasis. Tumor size T1 was associated with 'Good' involvement (2 cases) and 'Moderate' involvement (6 cases), while no cases were observed in the 'Poor' involvement category (χ^2 = 4.31, P = 0.63). For tumor size T2, 10 cases exhibited 'Good' involvement, 15 cases exhibited 'Moderate' involvement, and 3 cases exhibited 'Poor' involvement. Tumor sizes T3 and T4 did not exhibit any cases of 'Poor' involvement.

Table 9 Association of presence of metastasis with matrix metalloproteinase-9 and matrix metalloproteinase-13 expression

		MMP9			MMP13			
		Mild	Moderate	Intense	None	Mild	Moderate	Intense
Presence of metastasis	Presence	1	2	21	0	1	11	12
	Absence	9	6	1	4	10	2	0
χ^2 (*P*) value		26.03 (0.000)			29.16 (0.000)			

MMP: Matrix proteinase.

Table 10 Association between tumor size, grade of node involvement, and presence of metastasis

Tumor size	Good	Moderate	Poor	χ^2 (*P*) value
T1	2	6	0	4.31 (0.63)
T2	10	15	3	
T3	0	3	0	
T4	0	1	0	
Node involvement				
No involvement	4	12	0	3.55 (0.47)
Nodes nearby	7	12	3	
Distant node	1	1	0	
Presence of metastasis				
Presence	8	13	3	2.88 (0.23)
Absence	4	12	0	

Node involvement and grade

Among cases with 'No Involvement' of nearby nodes, 4 cases were categorized as 'Good' involvement and 12 cases as 'Moderate' involvement, with no cases in the 'Poor' category ($\chi^2 = 3.55$, $P = 0.47$). In cases with 'Nodes Nearby', 7 cases had 'Good' involvement, 12 cases had 'Moderate' involvement, and 3 cases had 'Poor' involvement. In the 'Distant Node' category, 1 case each exhibited 'Good' and 'Moderate' involvement, with no cases of 'Poor' involvement observed.

Presence of metastasis and grade

'Presence' of metastasis was associated with 8 cases of 'Good' involvement, 13 cases of 'Moderate' involvement, and 3 cases of 'Poor' involvement ($\chi^2 = 2.88$, $P = 0.23$). 'Absence' of metastasis was associated with 4 cases of 'Good' involvement and 12 cases of 'Moderate' involvement, with no cases of 'Poor' involvement.

DISCUSSION

OSCC stand as the most common type of cancer affecting the head and neck region, and it frequently involves lymph nodes and has a predisposition toward substantial local infiltration, which generally translate into a bad prognosis. One of its most distinguishing characteristics is the ability to penetrate surrounding tissues, such as blood and lymphatic vessels, though the ability depends on the tumor's ability to degrade the ECM. Several studies have identified a connection between a high level of enzymatic degradation of the ECM, tumor invasion, metastasis, and elevated expression of MMPs[2,5-7,12].

Malignant cells go through a number of complex stages during their invasion and metastasis, including adhesion to the ECM, disintegration of matrix elements, cell separation, and migration through the deteriorated matrix[13]. Numerous proteases are necessary for this intricate process, and it is vital to keep a local equilibrium between these proteases and protease inhibitors[14].

Among the family of degrading proteases, MMPs are an important group involved in ECM degradation and tissue remodeling[15,16]. More than 20 membrane-type MMPs, collagenases, gelatinases, stromelysins, matrilysins, and other structurally related but genetically distinct MMPs have been found and classified into several families[13,17]. MMP-13, classified as a collagenase, has been linked to the formation and invasion of OSCC and is involved in the regulation of cell proliferation and survival. Its expression can be triggered by various cytokines and growth factors such as tumour

necrosis factor-alpha and transforming growth factor-beta[9]. Notably, tumour necrosis factor-alpha can also stimulate the metastatic pathway by attracting factors conducive to metastasis to the cell surface[1-4,18].

However, MMP-9, also referred to as gelatinase B, is involved in the breakdown of collagen in the basement membrane and connective tissue. This role is essential for promoting the invasion of tumor cells and the metastatic process[17,19,20].

The present study aimed to assess the expression of MMP-9 and MMP-13 and their association with different tumor characteristics. The results revealed that the expression increased with tumor size. Also, MMP-13 expression intensified with respect to the presence of metastasis and grade. Nonetheless, it was observed that the expression had a significant association with the existence of metastases. A similar observation was made regarding nodal involvement, demonstrating a strong association between the intensity of MMP-9 and MMP-13 expression and nodal involvement[21-23]. A recent study witnessed that MMP-13 expression was associated with poor tumour differentiation and malignancy in patients at younger age, indicating tumour aggressiveness[24]. Elahi *et al*[25] in their study, observed that MMP-9 expression remained independent of the stage/grade of the tumor. Nevertheless, when taking into account different histological grades, the clinical significance of MMP-9 overexpression was noteworthy, indicating its potential function in promoting tumor cell infiltration. Champatyray *et al*[23] reported a contrasting finding, indicating that MMP-9 expression displayed a significant correlation with different histological grades of oral cancer. In this study, MMP-9 expression levels increased from well-differentiated to poorly differentiated OSCC[23]. A similar study observed that higher expression of MMP-9 was correlated with greater possibilities of lymph node metastases and tumor stage[26]. Comparable results in concurrence to these studies were noted in the present study. Thus, the expression of MMP-9 may help clinicians with better management of this malignancy. In a separate investigation conducted by Xia *et al*[5], they identified MMP-9 as a promoter of metastasis in OSCC by regulating the mRNA stability of the parental gene. This finding implies that targeting circular MMP-9 could be a potential treatment strategy for metastatic OSCC[5].

It was found that MMP-9 and MMP-13 were both overexpressed during the early phases of OSCC, suggesting that these two MMPs might function together. It is hypothesized that MMP-9 and MMP-13, *via* different mechanisms, each contribute significantly, albeit independently, to the invasiveness and advancement of OSCC.

Remarkably, high levels of MMP-9 and MMP-13 expression showed a strong link with TNM stage but no association with the histological grade of OSCC. This result draws attention to possible subjectivity in the grading scheme, which may have been brought about by an unequal distribution of cases across grades and a small sample size. Furthermore, differences in their expression patterns may be attributed to the intricate and multifactorial nature of metastasis in squamous cell carcinoma, which involves the activity of numerous MMPs.

This observation further emphasizes the need for a thorough understanding of the pathogenesis of OSCC by highlighting the possibility that some well-differentiated OSCCs may display clinical aggressiveness, which is defined by regional invasion and metastasis.

The subjectivity in this study will be greatly reduced by a larger sample size. Additionally, a sample that is evenly distributed based on histological grading will facilitate improved comparison and correlation between various variables. Although the current study provides evidence in support of the role of tumor tissue MMP-9 and MMP-13 in lymph node metastasis, other MMPs have also been proposed.

CONCLUSION

OSCC is the most prevalent type of cancer in the world. MMPs change the way that cells behave and accelerate the progression of the disease, leading to invasion and metastasis. MMP-9 has prognostic significance in OSCC due to its overexpression, which facilitates metastasis and advances tumor growth.

The current study provides insight into the roles played by MMP-9 and MMP-13 in tumor invasiveness and progression. It may also aid in the creation of novel methods for evaluating lymph node metastasis, which could enhance patient outcomes and treatment options for those with OSCC. Further research and investigation into MMP-9 and MMP-13 in OSCC can use it as a template. Further research is needed on this to establish the correlation and interdependence of MMP-9 and MMP-13 with other MMPs in early stages of OSCC. This could make it easier to create new interventional therapy strategies that could enhance the prognosis and available treatment modalities for OSCC.

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FOOTNOTES

Author contributions: Manjunatha BS, Handge KT, and Shah VS were responsible for research concept, design, and writing the article; Handge KT, Shah VS, and Pateel DGS were responsible for collection and/or assembly of the data; Manjunatha BS, Handge KT, and Al-Thobaiti YE were responsible for data analysis and interpretation; Shah VS and Al-Thobaiti YE were responsible for critical revision of the article; Manjunatha BS, Handge KT, Shah VS, Al-Thobaiti YE, and Pateel DGS were responsible for final approval of the article; all of the authors read and approved the final version of the manuscript to be published.

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Informed consent statement: The study did not use any individual's personal data. All the cases were retrieved from the archives of Department of Oral Pathology and Microbiology, KM Shah Dental College and Hospital, Vadodara, India.

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ORIGINAL ARTICLE

Prospective Study

Prognostic factors for acute central retinal artery occlusion treated with hyperbaric oxygen: The Hong Kong study report number five

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Abstract

BACKGROUND

Central retinal artery occlusion (CRAO) is a potentially blinding disease, and hyperbaric oxygen therapy (HBOT) is becoming increasingly popular with the support of scientific evidence. Despite the presence of various acute management measures, there is no clear evidence on the gold standard treatment for CRAO.

AIM

To identify factors and imaging parameters associated with good visual outcome, which guide ophthalmologists in the triage of CRAO patients for HBOT.

METHODS

Patients who suffered from CRAO and had a symptom onset ≤ 6 h were recruited for a course of HBOT in a tertiary hospital after failing bedside treatment. Patient demographics, onset time, CRAO eye parameters, and past medical history were prospectively collected. Visual outcomes after HBOT were also analyzed.

RESULTS

A total of 26 patients were included; the female-to-male ratio was 1:1.6, and the mean age was 67.5 years ± 13.3 years (range 44–89 years). The mean duration of follow-up and mean visual acuity (VA) improvement were 10.0 mo ± 5.3 mo and 0.48 logarithm of minimal angle of resolution (logMAR) ± 0.57 logMAR (approximately 9 letters in ETDRS) (P = 0.0001, Z = -3.67), respectively. The 1 mm zone of central macular thickness (CMT) on optical coherence tomography was not associated with VA changes (P = 0.119); however, the 1-to-3 mm circular rim of CMT was fairly associated (P = 0.02, Spearman's coefficient = 0.45). Complete retinal perfusion time during fundus fluorescein angiography (FFA) was moderately associated (P = 0.01, Spearman's coefficient = 0.58) with visual outcome.

CONCLUSION
A thinner 1-to-3 mm circular rim of CMT, but not the central 1 mm zone, is associated with better visual outcome. A shorter perfusion delay on FFA is also associated with better visual outcome.

Key Words: Central retinal artery occlusion; Fundus fluorescein angiography; Hyperbaric oxygen therapy; Optical coherence tomography; Stroke

Core Tip: Patients' eyes with central retinal artery occlusion demonstrated a mean visual acuity improvement of 0.48 logarithm of minimal angle of resolution (logMAR) ± 0.57 logMAR (approximately 9 letters in ETDRS) after hyperbaric oxygen therapy. A thinner 1-to-3 mm zone of central macular thickness, but not the central 1 mm zone, was associated with better visual outcome. A shorter perfusion delay on fundus fluorescein angiography was also associated with better visual outcome.

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INTRODUCTION

Central retinal artery occlusion (CRAO) is a potentially blinding ophthalmic emergency[1], also known as ocular stroke [2]. Despite the presence of various acute management measures, including breathing into a paper bag, carbogen inhalation[3], topical and/or systemic medical treatment for lowering intraocular pressures, ocular massage, anterior chamber paracentesis[4], or even thrombolytic therapy[5], there is no clear evidence on the gold standard treatment for CRAO[6].

With the support of scientific evidence[7,8], hyperbaric oxygen therapy (HBOT) for CRAO was started in Hong Kong in November 2018[9]. This HBOT center is situated in a tertiary hospital that receives referrals from both public and private practitioners 24 h every day on a territory-wide basis. During the coronavirus disease 2019 (COVID-19) pandemic, the HBOT service is still continuously serving more than 7 million people in the city[10,11]. A study on the outcome of this novel treatment in Hong Kong was established, which is called the HBOT for CRAO (HORA) study[12]. Previously we reported the absence of severe acute respiratory syndrome coronavirus 2 among our cohort, and delayed hospital presentation of CRAO patients during the local COVID-19 crisis[12,13]. This study aimed to identify prognostic factors associated with visual outcome, which might guide ophthalmologists in the triage of CRAO patients for HBOT.

MATERIALS AND METHODS

The management of patients in this prospective study adhered firmly to the tenets of the Declaration of Helsinki, and the research ethics committee approval number was HKECREC-2020-116. CRAO patients with ≤ 6 h of symptom onset were first given emergency bedside treatments, such as ocular massage, topical and systemic intraocular pressure lowering medications, rebreathing into paper bags, *etc.* In addition, if all possible means failed to reverse the CRAO, they were recruited for a course of HBOT at a tertiary hospital[9]. The first session of HBOT would follow the United States Navy Treatment Table (USNTT) 5. The protocol started with slow pressurization to a maximum pressure of 2.8 atmospheres absolute (ATA), which was maintained for 45 min, followed by slow depressurization to 1.9 ATA, which lasted for 30 min. The total treatment time was approximately 141 min. The subsequent planned 9 HBOT sessions (twice daily) followed the USNTT 9. A protocol with a maximum pressure of up to 2.4 ATA was used for 100 min with slow depressurization to level ground pressure lasting for 14 min. The total treatment time was approximately 124 min. HBOT might be terminated early if the patient could not tolerate treatment, refused further treatment, or was complicated with other medical conditions such as seizure and further cerebral stroke *etc.* Basic ophthalmic examinations including visual acuity (VA), intraocular pressure, slit lamp and dilated fundus examinations, were performed by ophthalmology specialists recognized by the College of Ophthalmologists of Hong Kong to confirm the diagnosis[14]. Eyes with pathologies other than CRAO were excluded from the HBOT and HORA study. Eyes with concurrent retinal vein occlusion, diabetic macular edema, age-related macular degeneration, pigment epithelial detachment, central serous chorioretinopathy, retinal detachment, hereditary retinal or macular dystrophy, epiretinal membrane, vitreomacular traction, lamella hole, macular hole, giant cell arteritis patients, or CRAO cases with cilioretinal artery spared were all excluded. Optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) were performed by vitreoretinal practitioners to evaluate the severity of CRAO. Each CRAO patient was managed using a multidisciplinary approach together with

internal medicine and emergency department HBOT practitioners.

Patient data were retrieved from the electronic health records system held by the Hospital Authority[15,16]. Patient demographic information (age, gender, ethnicity), follow-up duration, onset-to-attendance time, symptom-to-HBOT time, diseased eye characteristics (laterality, best corrected VA, OCT parameters, FFA perfusion time in seconds), past ophthalmic history, and past medical and drug history (any brands of anti-platelet/anti-coagulant use) were retrieved. The best corrected VA was measured using Snellen's charts and converted to the logarithm of minimal angle of resolution (logMAR) unit for analysis[17]. The following logMAR denotations were used for non-numerical VA measurements: (1) Finger count = 1.7 logMAR; (2) Hand movement = 2.0 logMAR; (3) Light perception (LP) = 2.3 logMAR; and (4) No LP = 3.0 logMAR.

OCT and FFA were performed with images captured by Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany), and a central macular thickness (CMT) map was generated from 19 horizontal line scans (Figure 1A). The central 1 mm zone of CMT data in micron was directly extracted from the printout (Figure 1B), whereas the circular rim of 1-to-3 mm circular rim of CMT was calculated by averaging the numerical data shown for each quadrant (superior, temporal, inferior, nasal) of the circle (Figure 1C).

FFA was stopped 15 min after the injection of dye if retinal artery perfusion was still not observed, and in such cases, the perfusion time would be marked as > 900 s. Post-HBOT VA outcomes and HBOT-related adverse events and complications were reviewed. Normal distribution of the data was tested by the Shapiro-Wilk test given the small sample size, and statistical analyses for the non-parametric data were conducted using Wilcoxon, Fisher's exact, and Spearman's correlation tests *via* Statistical Package for the Social Sciences version 27 (IBM, Armonk, NY, United States)

RESULTS

A total of 37 CRAO patients attended our hospital during the study period, of which 11 were out of our treatment timeframe of 6 h (Figure 2). Eventually, 26 patients were included, and the female-to-male ratio was 1:1.6, with a mean age 67.5 years ± 13.3 years (range 44–89 years). Only one patient was not Chinese. There were no patients lost to follow-up. Only 7 patients were too ill to undergo FFA, or refused FFA; otherwise there were no missing data for other parameters. The mean follow-up period and mean best corrected VA improvement were 10.0 mo ± 5.3 mo and 0.48 logMAR ± 0.57 logMAR (approximately equal to 9 letters of improvement in ETDRS, details in Table 1) (P = 0.0001, Z = -3.67), respectively. The data were not normally distributed; hence, non-parametric tests were used. Age (P = 0.49), pre-HBOT VA (P = 0.42), anti-platelet/anti-coagulant medication history (P = 0.42), onset-to-attendance time (P = 0.36), and symptom-to-HBOT time (P = 0.42) were not correlated with VA outcomes. The mean, SD, and median of each parameter are listed in Table 1.

Concerning OCT parameters, there were no failed scans, and thickness maps were successfully generated for all patients. The 1 mm zone of CMT (334 μm ± 64 μm) was not associated with VA changes (P = 0.119), but the 1-to-3 mm circular rim of CMT (430 μm ± 51 μm) was fairly associated (P = 0.02, Spearman's coefficient = 0.45) with a positive correlation, *i.e.*, the thicker the CMT was, the less negative the logMAR VA change. By categorizing the VA changes into two groups, "responder" for those with VA improvement after HBOT and "non-responder" for those without any VA improvement, 18 responders and 8 non-responders were identified. The mean 1 mm zone of CMT for responders and non-responders was 332 μm ± 70 μm and 338 μm ± 51 μm, respectively. For the 1-to-3 mm circular rim of the CMT, the means for responders and non-responders were 423 μm ± 59 μm and 447 μm ± 24 μm, respectively. A full dose of 5 mL of 10% Fluorescite (Alcon Laboratories, Fort Worth, TX, United States) was given to each patient who underwent FFA, and the complete retinal perfusion time (221 s ± 212 s, range 44–710 s) was moderately associated (P = 0.01, Spearman's coefficient 0.58) with visual outcome.

One patient experienced cerebrovascular stroke shortly after being diagnosed with CRAO, and HBOT had to be terminated after 2 sessions for the treatment of stroke. No other ischemic cerebrovascular events, nor contralateral eye CRAO, were detected during the follow-up period. Other HBOT-related complications included hypoglycaemia in 3 patients (11.5%), 2 of whom were known to have diabetes mellitus before the CRAO; and barotrauma in 4 patients (15.4%). All these patients continued to finish the whole course of 10 sessions of HBOT (Table 2).

DISCUSSION

HBOT is based on the theory that hyperbaric oxygenation of the choroidal circulation helps to perfuse the inner retina while allowing the retinal circulation to be restored by different means. The HORA study is the first territory-wide study in Hong Kong that provided data on the prognostic factors for CRAO patients. There was no loss to follow-up in our patients which minimized bias.

Our study demonstrated a comparable VA gain in CRAO patients treated with HBOT to that in previous series at different countries of approximately 0.53 logMAR[18,19]. However, we did not find a significant correlation between symptom onset to HBOT time and VA outcome, which is considered one of the most critical factors in determining the best visual prognosis[20]. This may be a type II error given that our sample size was small. Previous animal studies have shown that irreversible retinal tissue loss occurs with retinal ischemia for 240 min or more[21]. Most human studies have demonstrated the best visual outcome if HBOT is initiated within 12 h of symptom onset. The Undersea and Hyperbaric Medical Society recommended CRAO patients with symptom onset < 24 h and not responding to normobaric oxygen therapy for a course of HBOT[22].

Table 1 Data on baseline parameters investigated, *n* (%)

	Mean	Inter quartile range	SD	Median
Age (years)	67.5	22	13.3	70.5
Pre-HBOT VA (logMAR)	2.0	0.4	0.3	2.0
Pre-HBOT VA (Snellen acuity)	Hand movement	--	--	Hand movement
Post-HBOT VA (logMAR)	1.5	0.4	0.7	1.7
Post-HBOT VA (Snellen acuity)	20/640	--	--	Finger count
VA changes (logMAR)	-0.48	0.65	0.57	-0.3
VA changes (ETDRS letter score)	9	--	--	3
Onset-to-attendance time (min)	139	157	116	105
Symptom-to-HBOT time (min)	789	511	450	585
1 mm zone of CMT (μm)	334	96	64	332
1-to-3 mm circular rim of CMT (μm)	430	76	51	437
Fundus fluorescein angiography complete retinal perfusion time (s)	221	177	212	111
	Anti-platelet	Anticoagulant	Nil	
Anti-platelet/anticoagulant history	8 (30.8)	2 (7.7)	16 (61.5)	

CMT: Central macular thickness; HBOT: Hyperbaric oxygen therapy; LogMAR: Logarithm of minimal angle of resolution; VA: Visual acuity.

Table 2 Complications after hyperbaric oxygen therapy

	n	Percentage
Cerebrovascular stroke	1	3.8
Hypoglycaemia	3 (2 with diabetes mellitus)	11.5
Barotrauma	4	15.4

Diagnosing CRAO is not always straightforward. It was shown that up to 27% of CRAO patients had a normal-looking fundus upon presentation[23]. Different imaging modalities, such as FFA and OCT, were utilized to aid timely diagnosis of CRAO, and FFA is considered the gold standard for confirmation. Typical findings include a delay in filling of retinal arteries, delayed arteriovenous transit time, and sluggish blood flow in arteries[24]. However, these methods are subjective based on the operator's experience, and comparisons with the assumed normal fellow eye are more appropriate. A study revealed that a delayed arteriovenous phase > 23 s was observed in more than half of the CRAO cases only[23]. In addition, the exact transit time should be interpreted with caution, as the transition of fluorescein dye from the peripheral to the eye circulation may be affected by various systemic conditions, such as heart failure and carotid stenosis. Moreover, the machines used to capture FFA images are not often available under emergency settings. By the time an FFA is performed, there might already be partial reperfusion of the retinal vasculature, which might create ambiguity in the diagnosis. Additionally, FFA provides no information regarding the viability of the affected retinal tissues.

Emerging evidence has suggested OCT as a promising modality for diagnosing CRAO. OCT is sensitive for detecting changes in retinal layers during ischemia, even before fundoscopic changes appear. Yilmaz and Durukan[25] reported that retinal thickness increases in a near-linear progression within the first hour of CRAO[25], which allows an estimate when exactly the retinal insult was initiated. Pathognomonic signs in the acute phase of CRAO include an increase in retinal reflectivity, thickness of the inner retina, and a prominent middle limiting membrane[26]. Our study provided additional insight into the 1 mm and 1-to-3 mm circular rim of CMT findings in CRAO eyes. The central 1 mm zone of the CMT consists of mainly photoreceptors and their nuclei layers, particularly at the foveal pit. Theses layers exhibited a smaller increase in thickness compared with the inner retinal layers in acute CRAO. Therefore, our results demonstrated no correlation between the 1 mm zone of the CMT and VA changes. In contrast, the 1-to-3 mm circular rim of the CMT consists of all layers of the neurosensory retina. The increase in thickness of the 1-to-3 mm circular rim upon CRAO insult was more uniform than that of the 1 mm zone where the foveal pit was located. OCT is a faster investigation than FFA without the need for vascular access, and does not carry the risk of fluorescein dye. This approach may have a role in identifying patients who are more likely to benefit from HBOT.

HBOT is a safe treatment modality with only rarely reported serious adverse effects. The most commonly reported complication is barotrauma to the middle ear. Incisional myringotomies may sometimes be needed during HBOT if the

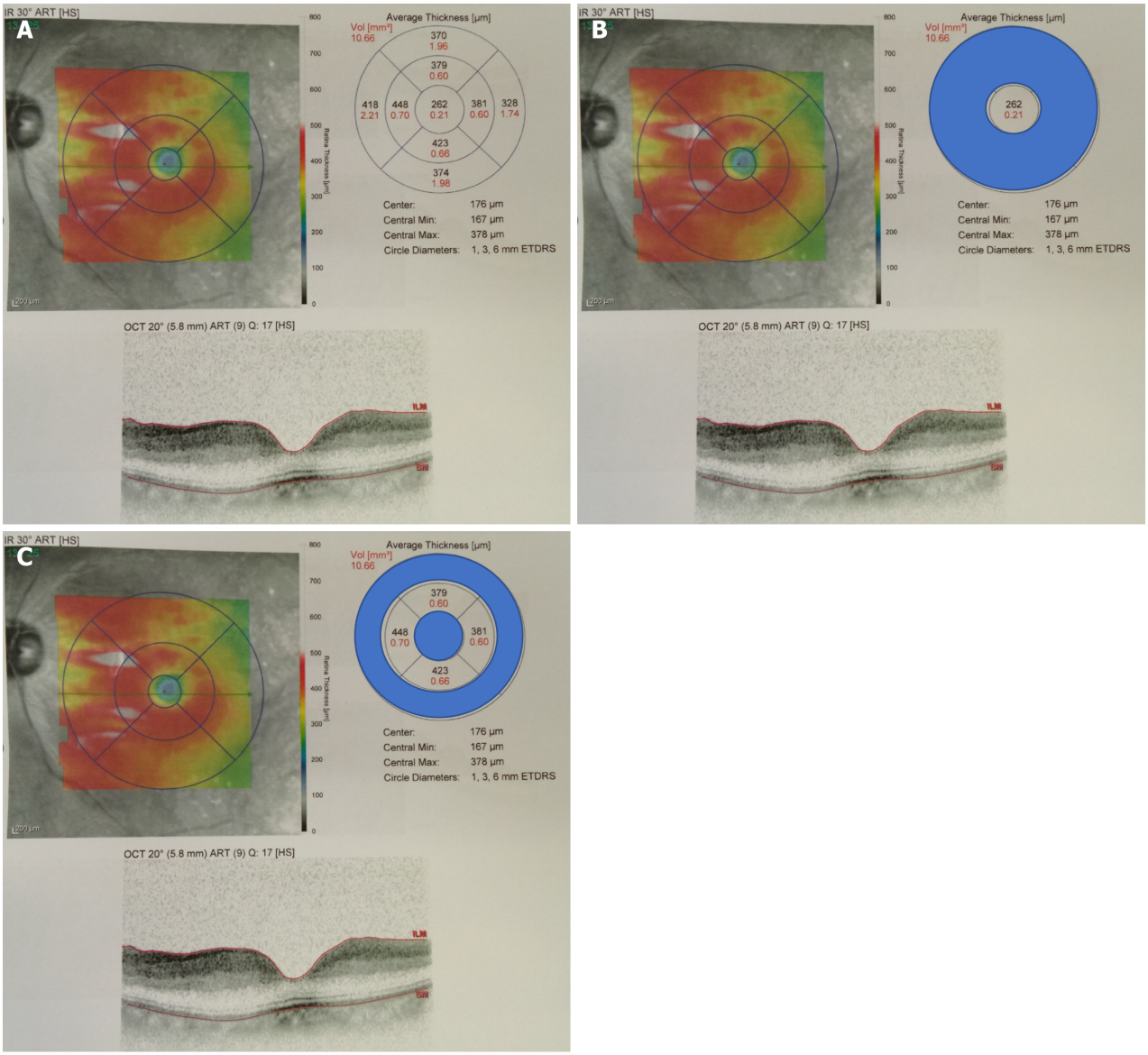

Figure 1 An optical coherence tomography scan report. A: An optical coherence tomography scan report example with machine generated thickness map for a left eye suffering from acute central retinal artery occlusion; B: The encircled central 1 mm zone thickness data was extracted from the printout; C: The highlighted area indicates the central 1-to-3 mm zone on the thickness map.

patient fails to equalize middle ear pressure[27]. Other reported side effects include sinus pain, anxiety, and oxygen toxicity. Interestingly, ocular complications such as reversible myopia and nuclear sclerosis cataract development have also been reported[20]. Hypoglycemia, which was reported in our study, is not a frequent side effect of HBOT. A systemic review demonstrated a reduction in blood glucose levels following a single session of HBOT in patients with type 2 diabetes mellitus, potentially mediated by an increase in insulin sensitivity[28].

Being classified as ocular stroke, CRAO might represent part of the systemic stroke spectrum. It is not surprising that studies have shown CRAO patients to be at risk of stroke at different points in life. In a Canadian cohort, approximately one-third of patients experienced symptomatic stroke before the diagnosis of CRAO, and approximately 5% of the remaining CRAO patients suffered from stroke within 3 years of ocular diagnosis[29]. Magnetic resonance imaging findings corresponding to ischemic stroke were found in nearly 40% of patients in another American cohort at the time of CRAO diagnosis[30]. These findings emphasize the importance of a comprehensive cardiovascular workup and a multi-disciplinary approach with physicians and neurologists in the management of CRAO patients.

The main limitation of the current study lies in its small sample size. This was partially attributed to the 6-h cutoff time for HBOT from symptom onset to diagnosis. Furthermore, bias was inevitable because the study was not randomized or controlled, which also occurred in other researches focusing on rare diseases without known effective alternative treatments. With the ongoing HBOT for CRAO patients in Hong Kong, future studies with larger sample sizes could give more solid evidence.

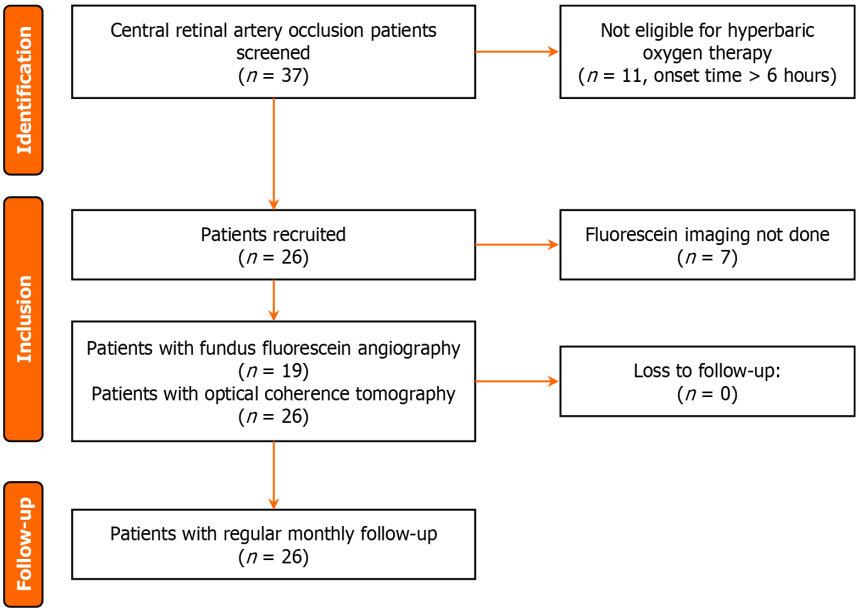

Figure 2 Flowchart of patient recruitment.

CONCLUSION

HBOT is promising for CRAO patients to regain vision for navigation. A thinner 1-to-3 mm circular rim of CMT, but not the central 1 mm zone, is associated with better visual outcome. OCT alone, without FFA, may be used by ophthalmologists for triage of HBOT on CRAO cases. However, further studies with larger sample sizes are necessary to validate these findings and ensure their acceptance.

FOOTNOTES

Author contributions: Au SCL designed the research study, performed the research, and wrote the manuscript; Chong SSY acquired and analyzed the data; all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Hong Kong East Cluster Research Ethics Committee (Approval No. HKECREC-2020-116).

Clinical trial registration statement: This study is registered at https://harec.ha.org.hk/Portal. The registration identification number is HKEC-2020-0130.

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ORIGINAL ARTICLE

Prospective Study

Hemogram-derived ratios as prognostic markers for major adverse cardiovascular events in patients with non-ST-segment elevation myocardial infarction

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Abstract

BACKGROUND

Non-ST segment elevation myocardial infarction (NSTEMI) poses significant challenges in clinical management due to its diverse outcomes. Understanding the prognostic role of hematological parameters and derived ratios in NSTEMI patients could aid in risk stratification and improve patient care.

AIM

To evaluate the predictive value of hemogram-derived ratios for major adverse cardiovascular events (MACE) in NSTEMI patients, potentially improving clinical outcomes.

METHODS

A prospective, observational cohort study was conducted in 2021 at the Internal Medicine Clinic of the University Hospital in Tuzla, Bosnia and Herzegovina. The study included 170 patients with NSTEMI, who were divided into a group with MACE and a control group without MACE. Furthermore, the MACE group was subdivided into lethal and non-lethal groups for prognostic analysis. Alongside hematological parameters, an additional 13 hematological-derived ratios (HDRs) were monitored, and their prognostic role was investigated.

RESULTS

Hematological parameters did not significantly differ between non-ST segment elevation myocardial infarction (NSTEMI) patients with MACE and a control group at T1 and T2. However, significant disparities emerged in HDRs among NSTEMI patients with lethal and non-lethal outcomes post-MACE. Notably, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were elevated in lethal outcomes. Furthermore, C-reactive protein-to-lymphocyte ratio (CRP/Ly) at T1 (> 4.737) demonstrated predictive value [odds ratio (OR): 3.690, P = 0.024]. Both NLR at T1 (> 4.076) and T2 (> 4.667) emerged as significant predictors, with NLR at T2 exhibiting the highest diagnostic performance, as indicated by an area under the curve of 0.811 (95%CI: 0.727-0.859) and OR of 4.915 (95%CI: 1.917-12.602, P = 0.001), emphasizing its important role as a prognostic marker.

CONCLUSION

This study highlights the significant prognostic value of hemogram-derived indexes in predicting MACE among NSTEMI patients. During follow-up, NLR, PLR, and CRP/Ly offer important insights into the inflammatory processes underlying cardiovascular events.

Key Words: Hemogram-derived ratios; Prognostic markers; Neutrophil-to-lymphocyte ratio; Myocardial infarction

Core Tip: This study underscores the significant role of hematological-derived ratios in predicting major adverse cardiovascular events (MACE) among NSTEMI patients. Elevated neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were associated with higher mortality rates post-MACE, with NLR at follow-up showing the highest predictive accuracy (area under the curve of 0.811). These findings suggest that monitoring NLR, PLR, and C-reactive protein-to-lymphocyte ratio (CRP/Ly) can offer valuable insights into the inflammatory mechanisms at play in cardiovascular risk, aiding in early intervention and improving patient outcomes.

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INTRODUCTION

Non-ST-segment elevation myocardial infarction (NSTEMI) is a significant and growing subset of acute coronary syndromes (ACS) characterized by partial coronary artery blockage[1,2]. Recent trends show an increase in NSTEMI cases compared to STEMI, with notable variations across populations and demographics[3]. NSTEMI prevalence within ACS ranges from 14.2%[4] to 30.0%[5]. Despite being less dramatic in its presentation, NSTEMI typically has a worse prognosis than STEMI, with increased rates of severe myocardial infarction, stroke, cardiovascular death, and overall mortality[1].

Managing NSTEMI requires early diagnosis and intervention to mitigate adverse outcomes[6]. The rise in percutaneous coronary intervention underscores evolving strategies to improve clinical outcomes for NSTEMI patients [7]. However, there is a critical need for reliable prognostic markers to refine risk stratification and guide therapeutic

decisions.

Hematologic-derived ratios (HDR) have emerged as promising prognostic tools in NSTEMI[8]. Their importance is also reflected in the assessment of inflammation. Coronary diseases are accompanied by inflammation due to the complex interplay of immune processes. These processes contribute to significant changes in the hematopoietic system, directly reflected in the absolute and relative number of cells. Usually, these are leukocytes such as neutrophils, lymphocytes, and monocytes. This is precisely one of the reasons for the increasing need for detailed research on HDRs in coronary disease to justify their use in daily practice, as they can help clinicians understand the pathophysiologic mechanism of disease. Elevated levels of these indices correlate with worse outcomes, including increased mortality, in-hospital complications, and long-term adverse cardiovascular events[9-12].

Most studies have used traditional HDR such as neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and platelet/lymphocyte ratio (PLR)[13-16]. In addition to hematological parameters, inflammatory parameters such as C-reactive protein (CRP) values have been used to calculate HDR[17]. Determining CRP as an acute phase reactant is important for evaluating patients with an inflammatory response in ACS, monitoring disease progression, and patient stratification. CRP levels have been observed to correlate with higher mortality and myocardial damage[18]. However, caution should be exercised when interpreting the results, as these patients often have an atherosclerotic mass and underlying inflammation. Given the risk of individual variations in CRP levels and certain hematologic parameters in cardiovascular events, several studies have investigated the potential of the new HDR understudied in NSTEMI patients[19]. Evaluating their predictive accuracy for major adverse cardiovascular events (MACE) in NSTEMI patients could significantly enhance clinical decision-making and patient management in resource-limited settings. This study aims to evaluate the predictive value of hemogram-derived ratios for MACE in NSTEMI patients, potentially improving clinical outcomes.

MATERIALS AND METHODS

Study design and patients

A prospective, observational cohort study was conducted in the first half of 2021 at the Internal Medicine Clinic of the University Hospital in Tuzla, Bosnia and Herzegovina. The study included 170 hospitalized patients over 18 years old with newly diagnosed NSTEMI and without previous conventional therapy treatment with clopidogrel. All patients with (1) Prior clopidogrel treatment for any indication; (2) STEMI; (3) Stable coronary artery disease; (4) Previous NSTEMI; (5) Renal dysfunction; and (6) Hematologic diseases were excluded from this study. The study was approved by the Ethical Committee of the University Clinical Centre Tuzla, Bosnia and Herzegovina (No: 02-09/2-97-21). The patients were divided into two groups based on the occurrence of MACE following NSTEMI, and further analysis subdivided the MACE group into those with fatal and non-fatal outcomes.

All NSTEMI patients underwent a follow-up for six months after admission to assess MACEs. MACE included patients who experienced myocardial infarction, cardiovascular death, revascularization such as angioplasty or CABG, and hospitalization due to unstable angina or heart failure. The definitions for clinical outcomes (MACE) were according to the international classification of diseases. Clinical follow-up was performed by telephone or through a patient's examination.

Methods

Venous blood samples were taken from all patients at two-time points: On admission (T1) and after 24 hours (T2). Blood samples for the determination of complete blood count parameters were collected in test tubes containing K2EDTA (dipotassium ethylenediaminetetraacetic acid) as an anticoagulant and analyzed using a Sysmex XN-1000 automated haematology analyzer (Sysmex Corporation, Japan). For white blood cells, optical detection of semiconductor lasers and flow cytometry were used, while for red blood cells and platelet counting, sheath flow direct current detection was used. CRP quantification was performed using the immunoturbidimetric method using a Beckman Coulter DxC 700 AU biochemical analyzer (Beckman Coulter Diagnostic, Switzerland). Both analyzers are equipped with original reagents, controls, and calibrations, and were operated according to the manufacturer's instructions.

We calculated 13 HDR based on laboratory test results, following the methodology in Segalo *et al*[12]. The NLR was calculated as neutrophils divided by lymphocytes. The Derived NLR was computed as neutrophils divided by the difference between total white blood cells and neutrophils. The neutrophil-to-platelet ratio was determined by neutrophils divided by platelets, and the neutrophil-to-lymphocyte platelet ratio (NLPR) by neutrophils divided by the product of lymphocytes and platelets. The PLR was calculated as platelets divided by lymphocytes. The monocyte to neutrophil ratio (MNR) was calculated by dividing monocytes by neutrophils, and the MLR by dividing monocytes by lymphocytes. The lymphocyte to monocyte ratio was calculated as lymphocytes divided by monocytes. The lymphocyte to CRP ratio (LCR) was calculated as lymphocytes divided by CRP, and the CRP to lymphocyte ratio (CRP/Ly) was computed by CRP divided by lymphocytes. The systemic immune inflammation index (SII) was determined by dividing the product of neutrophils and platelets by lymphocytes. The aggregate index of systemic inflammation (AISI) was calculated as the product of neutrophils, monocytes, and platelets divided by lymphocytes, and the systemic inflammation response index as the product of neutrophils and monocytes divided by lymphocytes.

Statistical analysis

SPSS software (version 27.0, IBM Inc., United States) was utilized for the statistical analysis. Continuous variables were presented as the mean and SD. Categorical variables were reported as frequencies (*n*) and percentages (%). The

Kolmogorov-Smirnov test was conducted to assess the normality of distributions. When deviations from normality were identified, non-parametric methods were employed, including Pearson's χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables. An area under the curve (AUC) analysis was performed for variables with statistically significant differences between the observed groups, illustrated using the receiver operating characteristic curve. Additionally, cut-off values were determined, along with their corresponding sensitivity and specificity. Logistic regression analysis was conducted for highly diagnostic-accuracy variables (AUC > 0.7). The level of statistical significance was set at 5% ($P \leq 0.05$).

RESULTS

Out of 170 patients, 86 (50.6%) had MACE, while 84 (49.4%) were in the control group. There were no significant differences in age (MACE: 69.5 years, Control: 66 years), weight (MACE: 86.5 kg, Control: 86 kg), height (MACE: 1.71 meters, Control: 1.70 meters), or body mass index (MACE: 28.75, Control: 30.5). However, hypertension was more prevalent in the MACE group (93% *vs* 82.1%, $P = 0.026$), and tobacco consumption was higher in the control group (57.1% *vs* 43%, $P = 0.050$). Among MACE patients, 40.7% had lethal outcome, while 59.3% had non-lethal events (Table 1).

No differences were observed between the MACE and control groups in leukocytes, erythrocytes, platelets, monocytes, basophils, eosinophils, lymphocytes, or neutrophils at both time points (T1 and T2). However, platelet levels at T1 showed a near difference ($P = 0.056$), with higher median levels in the MACE group (238.5) compared to the control group (220.0). At T2, CRP levels approached significance ($P = 0.051$), with higher median levels in the MACE group (30.5) compared to the control group (13.4) (Table 2). Only the MNR at T2 differed significantly between the MACE and control groups (0.111 *vs* 0.138, $P = 0.022$). MNR at T2 (Table 3) had poor predictive value for MACE with an AUC of 0.602 (95%CI: 0.516-0.687) (Figure 1A).

HDRs showed significant differences between NSTEMI patients with lethal and non-lethal outcomes (Table 4). The NLR was higher in lethal outcomes with medians of 7.432 [interquartile range (IQR): 4.542-12.551] at T1 and 6.934 (IQR: 3.672-12.165) at T2, compared to 3.816 (IQR: 2.423-5.783) and 2.794 (IQR: 2.167-5.580) in non-lethal outcomes ($P < 0.001$). PLR was also higher in lethal outcomes, with medians of 238 (IQR: 150.420-303.448) at T1 and 195.349 (IQR: 149.359-353.846) at T2, *vs* 124.887 (IQR: 92.446-191.566) and 122.619 (IQR: 83.529-169.186) in non-lethal outcomes ($P = 0.007$ and 0.001). Conversely, MNR was higher in non-lethal outcomes, with medians of 0.111 (IQR: 0.072-0.144) at T1 and 0.131 (IQR: 0.099-0.172) at T2, compared to 0.067 (IQR: 0.054-0.107) and 0.074 (IQR: 0.043-0.112) in lethal outcomes ($P = 0.028$ and < 0.001).

The AUC analysis for predicting death in NSTEMI patients shows that NLR at T2 has the highest diagnostic performance, with an AUC of 0.811 (95%CI: 0.727-0.859), a cut-off > 4.667, sensitivity of 74.0%, and specificity of 76.72% ($P < 0.001$), marking it as a strong prognostic marker (Table 5). Other significant indices include CRP/Ly, with AUCs of 0.702 at T1 and 0.718 at T2, AISI with AUCs of 0.675 at T1 and 0.690 at T2, and PLR with AUCs of 0.676 at T1 and 0.719 at T2 (Figure 1B).

CRP/Ly at T1 (> 4.737) has an OR of 3.690 (95%CI: 1.140-11.942, $P = 0.024$), demonstrating strong predictive value. NLR at T1 (> 4.076) and T2 (> 4.667) are also significant predictors, with ORs of 1.300 (95%CI: 1.121-1.743, $P = 0.009$) and 4.915 (95%CI: 1.917-12.602, $P = 0.001$) respectively, indicating that NLR at T2 is the most powerful predictor of lethal MACE (Table 6).

DISCUSSION

This study aimed to investigate the predictive role of HDR for MACE, particularly lethal outcomes, in patients with NSTEMI. Significant predictors identified in our study included NLR, NLPR, PLR, and CRP/Ly, with key findings showing that NLR at T2 had the highest diagnostic performance (AUC of 0.811), and CRP/Ly at T1 and T2, AISI, and PLR were also notable predictors. Our findings highlight the important role of inflammation in the etiology of NSTEMI and subsequent MACE occurrences.

Atherosclerosis is a chronic condition characterized by plaque formation in the inner lining of the blood vessels. Cholesterol build-up and inflammation are the main underlying causes of cardiovascular disease. Inflammation has long been recognized as a key factor in atherosclerosis and its complications. Researchers have conducted laboratory and animal studies to explore targeting the inflammatory cascade associated with atherosclerosis. Elevated biomarkers can help identify patients at risk for MACE and guide the appropriate treatment options. CRP is the most promising and widely used biomarker, with extensive research data available[20]. Hematologic parameters are also considered prognostic, considering their role in inflammation. In the present study, the primary hematological parameters, including total leucocyte count and all of its subtypes (monocytes, basophils, eosinophils, lymphocytes, and neutrophils), as well as erythrocytes and platelets, showed no significant differences comparing NSTEMI patients with MACE to a control group. On the other hand, our data showcases significant differences in HDRs between NSTEMI patients who had fatal and non-fatal outcomes following a MACE. Elevated levels of NLR, NLPR, PLR, and CRP/Ly in patients who experienced lethal outcomes reflect inflammatory involvement and provide important prognostic information[21].

NLR was identified as the most potent predictor of MACE. There is a significant increase in mortality risk among patients with NSTEMI who have elevated NLR as a marker of a severe inflammatory disease. Similarly, a meta-analysis that included 9406 patients with ACS and an elevated pretreatment NLR value was useful in predicting MACE occurrence[22-24]. In our study, elevated NLPR levels were found to have predictive potential for predicting mortality at

Table 1 Sociodemographic data, median, median (25th-75th percentiles)/*n* (%)

Variable		MACE (*n* = 86)	Control (*n* = 84)	*P* value
Age		69.5 (60.0-79.0)	66.0 (60.0-73.0)	0.557
Weight		86.5 (81.0-107.0)	86 (81.0-107.0)	0.287
Height		1.71 (1.64-1.88)	1.70 (1.65-1.84)	0.119
BMI		28.75 (27.2-36.2)	30.5 (27.7-35.8)	0.453
Hypertension	No	6 (7.0)	15 (17.9)	0.026
	Yes	80 (93.0)	69 (82.1)	
Diabetes mellitus	No	53 (61.6)	46 (54.8)	0.276
	Yes	33 (38.4)	38 (45.2)	
Hyperlipoproteinemia	No	25 (29.1)	21 (25.0)	0.859
	Yes	61 (70.9)	63 (75.0)	
Alcohol consumption	No	51 (59.3)	56 (66.7)	0.700
	Yes	35 (40.7)	28 (33.3)	
Tobacco consumption	No	49 (57.0)	36 (42.9)	0.050
	Yes	37 (43.0)	48 (57.1)	
MACE	Lethal	35 (40.7)		
	Non-lethal	51 (59.3)		

BMI: Body mass index; MACE: Major adverse cardiovascular event.

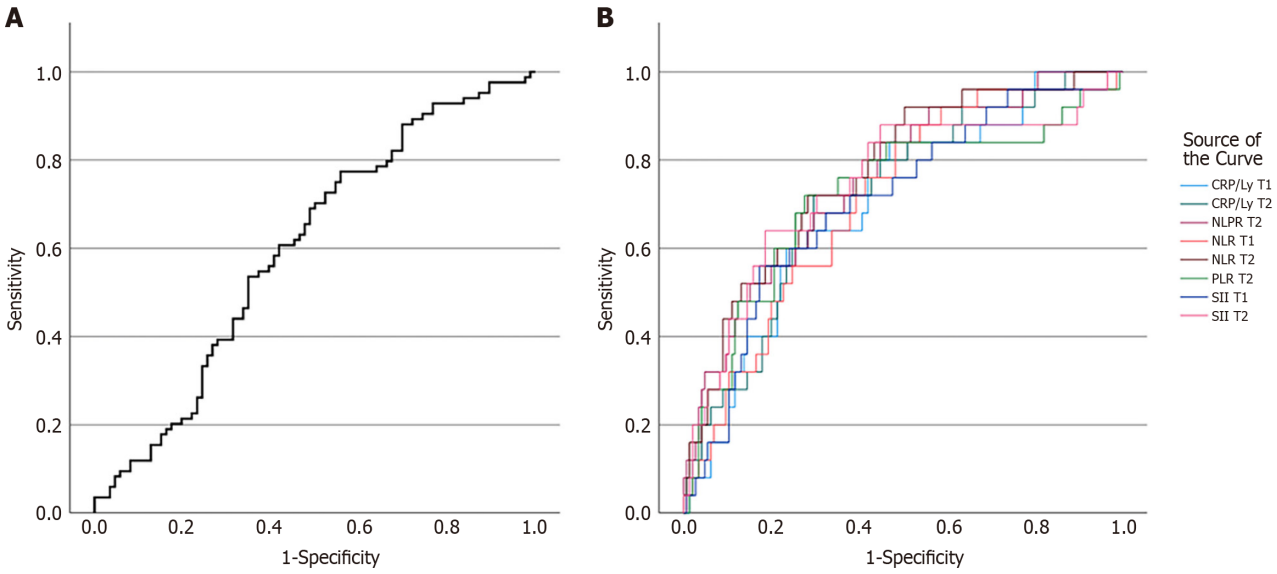

Figure 1 Receiver operating curve analysis for hematological-derived ratios with area under curve > 0.7. A: Monocyte to neutrophil ratio at T2 for major adverse cardiovascular event in non-ST segment elevation myocardial infarction patients; B: Hematological-derived ratios predicting lethal outcomes. CRP/Ly: C-reactive protein-to-lymphocyte ratio; NLPR: Neutrophil-to-lymphocyte and platelet ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune inflammation index.

T2. As it is a relatively new biomarker, few studies have investigated its potential in cardiovascular disease. One of the studies is that of Fan *et al*[25] in which it was observed that an elevated NLPR level is associated with a higher risk of MACE. Their study included NSTEMI patients as well as STEMI patients undergoing percutaneous coronary intervention for the first time. It is interesting to note that the same cut-off value ≥ 0.018 was used in their study, although the sensitivity and specificity was slightly lower at T1 and T2 compared to our study.

In our study, higher values of PLR were seen among patients who suffered MACEs, making it another significant predictor. The median PLR in the fatal outcome group at T1 and T2 was notably higher. Interestingly, elevated PLR is

Table 2 Primary hematological and inflammatory parameters in studied groups, median (25th-75th percentiles)

Parameter	Time	MACE (*n* = 86)	Control (*n* = 84)	*P* value
Leukocytes	T1	9.9 (7.9-11.9)	9.3 (7.4-11.8)	0.322
	T2	9.1 (7.3-11.3)	8.9 (6.7-10.6)	0.264
Erythrocytes	T1	4.5 (4.1-5.0)	4.3 (3.9-4.8)	0.078
	T2	4.5 (4.0-4.9)	4.4 (4.0-4.9)	0.581
Platelets	T1	238.5 (187.0-286.0)	220.0 (176.5-253.5)	0.056
	T2	240.0 (174.0-283.0)	216.5 (180.0-257.0)	0.287
Monocytes	T1	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.344
	T2	0.7 (0.6-1.0)	0.8 (0.6-0.9)	0.882
Basophils	T1	0.0 (0.0-0.0)	0.0 (0.0-0.1)	0.563
	T2	0.0 (0.0-0.0)	0.0 (0.0-0.1)	0.403
Eosinophils	T1	0.0 (0.0-0.1)	0.1 (0.0-0.1)	0.111
	T2	0.0 (0.0-0.1)	0.1 (0.0-0.2)	0.321
Lymphocytes	T1	1.6 (1.1-2.1)	1.5 (1.2-2.0)	0.130
	T2	1.7 (1.2-2.3)	1.8 (1.2-2.3)	0.090
Neutrophils	T1	7.3 (5.6-9.0)	6.4 (4.7-9.8)	0.611
	T2	6.2 (4.9-8.7)	5.8 (4.2-7.5)	0.374
C-reactive protein	T1	7.4 (2.6-30.4)	8.9 (2.2-21.5)	0.215
	T2	30.5 (6.3-67.7)	13.4 (5.0-48.5)	0.051

MACE: Major adverse cardiovascular event.

associated with increased thrombotic and inflammatory activity, suggesting its significance as a relevant prognostic marker in ACS, according to a comprehensive review and meta-analysis literature search conducted by Pruc *et al*[14].

It is well known that CRP is an acute-phase reactant produced by the liver that rises in response to inflammation[26]. Elevated CRP levels reflect systemic inflammation and have been associated with adverse outcomes in cardiovascular diseases[27]. To date, there are not enough studies that have investigated the potential of LCR as a new biomarker for the prediction of MACE in NSTEMI patients. A slightly greater interest has been noted in STEMI patients, as shown in the study by Ye *et al*[17], in which an association with traditional risk factors such as diabetes, hypertension and smoking was observed, which was also found in our study. In their study, LCR showed high sensitivity and specificity as a predictor of long-term MACEs in STEMI patients at admission and 24 hours after percutaneous coronary intervention, which could contribute to improving the quality of life of these patients. In relation to our research, slightly lower sensitivity and specificity in the T2 category has been reported in NSTEMI patients, and more extensive studies are needed to demonstrate the predictive potential of LCR in these patients.

The CRP/Ly ratio combines this marker with the lymphocyte count, offering a more nuanced view of the inflammatory state. In our study, CRP/Ly at T1 and T2 showed significant predictive value. The AUC for CRP/Ly at T2 was 0.718, indicating its predictive efficacy in identifying inflammation and the probability of adverse outcomes[15,16]. These findings are consistent with research by Gupta *et al*[28] that found a correlation between the extent of inflammation and myocardial damage and CRP levels, which makes CRP/Ly a useful predictive tool in cardiovascular risk stratification [28].

Nevertheless, a study by Stefano *et al*[29] suggests a differential inflammatory pattern in NSTEMI patients. The absence of significant correlations between inflammatory indexes and myocardial infarction in NSTEMI supports the hypothesis that a different pattern of inflammation occurs in these patients[29]. These observations indicate that AISI, which combines several inflammatory markers, was also a significant predictor. Although specific median values and ranges were not provided in the summary, the significant *P*-values ($P < 0.001$) for both T1 and T2 indicate that AISI effectively captures systemic inflammation and is predictive of adverse cardiovascular events[30].

Inflammatory markers are not fully considered by conventional risk evaluation scores, including widely used Thrombolysis in Myocardial Infarction and Global Registry of Acute Coronary Events scores; instead, they mainly rely upon clinical and biochemical factors. These models could become more predictive and provide a more complete assessment of patient risk if they incorporate NLR, PLR, and CRP/Ly[31,32]. Emerging data supports this strategy by indicating that multi-marker tactics integrate many risk markers and provide better prognosis accuracy than single-marker approaches[33].

Table 3 Comparative analysis of hematological-derived ratios between major adverse cardiovascular event group and controls, median (25th-75th percentiles)

HDR	Time	MACE	Control	*P* value
NLR	T1	4.394 (2.974-7.432)	4.179 (2.534-7.715)	0.537
	T2	3.804 (2.231-7.092)	3.053 (2.186-4.903)	0.070
dNLR	T1	2.775 (1.803-4.643)	2.258 (1.669-4.204)	0.214
	T2	2.486 (1.481-4.377)	1.915 (1.430-3.088)	0.100
NPR	T1	0.031 (0.024-0.041)	0.029 (0.020-0.047)	0.685
	T2	0.028 (0.020-0.042)	0.024 (0.018-0.039)	0.103
NLPR	T1	0.020 (0.012-0.032)	0.018 (0.012-0.037)	0.762
	T2	0.017 (0.010-0.034)	0.013 (0.009-0.024)	0.086
PLR	T1	152.678 (95.053-238.760)	138.596 (100.865-187.930)	0.597
	T2	147.935 (92.642-219.337)	120.218 (93.713-169.146)	0.259
MNR	T1	0.095 (0.060-0.141)	0.119 (0.081-0.145)	0.088
	T2	0.111 (0.076-0.158)	0.138 (0.105-0.168)	0.022
MLR	T1	0.432 (0.279-0.639)	0.453 (0.304-0.664)	0.407
	T2	0.441 (0.285-0.628)	0.389 (0.308-0.628)	0.692
LMR	T1	2.315 (1.564-3.586)	2.207 (1.507-3.286)	0.407
	T2	2.270 (1.593-3.504)	2.572 (1.592-3.243)	0.692
LCR	T1	0.180 (0.041-0.642)	0.180 (0.046-0.800)	0.551
	T2	0.103 (0.021-0.356)	0.139 (0.031-0.391)	0.194
CRP/Ly	T1	5.539 (1.418-24.320)	5.347 (1.233-20.531)	0.556
	T2	9.664 (2.813-47.006)	7.172 (2.559-32.454)	0.194
SII	T1	1044.079 (588.656-1812.658)	933.499 (553.663-1471.157)	0.355
	T2	935.137 (467.116-1778.563)	636.296 (458.472-1214.234)	0.071
AISI	T1	730.143 (392.295-1399.338)	619.153 (367.070-1231.876)	0.663
	T2	645.503 (306.489-1525.542)	509.665 (265.857-831.593)	0.121
SIRI	T1	2.795 (1.767-4.904)	2.955 (1.585-5.844)	0.968
	T2	2.576 (1.511-6.067)	2.124 (1.359-4.433)	0.144

HDR: Hematological-derived ratios; NLR: Neutrophil-to-lymphocyte ratio; dNLR: Derived neutrophil-to-lymphocyte ratio; NPR: Neutrophil-to-platelet ratio; NLPR: Neutrophil-to-lymphocyte and platelet ratio; PLR: Platelet-to-lymphocyte ratio; MNR: Monocyte to neutrophil ratio; MLR: Monocyte/lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; LCR: Lymphocyte to C-reactive protein ratio; CRP/Ly: C-reactive protein-to-lymphocyte ratio; SII: Systemic immune inflammation index; AISI: Aggregate index of systemic inflammation; SIRI: Systemic inflammation response index; T1: Analysis at admission; T2: Analysis after 24 hours.

It is crucial to use more aggressive therapy options and maintain ongoing, close monitoring if a patient has been identified as having a high risk of MACE and a fatal outcome to achieve a more successful clinical outcome[34]. These inflammatory indicators derived from hematological analysis could be useful in detecting high-risk patients suffering from NSTEMI myocardial infarction early. These indicators are easily collected from routine blood tests; they are widely available, affordable, and simple; hence, they are valuable tools for risk stratification, but their importance needs to be considered and addressed[35].

Despite the valuable insights gained from our study, several limitations must be acknowledged. First, the single-center design may limit the generalizability of our findings, as institutional practices and resources could have influenced the results. Additionally, the relatively small sample size underscores the need for future studies to validate our findings in larger, multi-center cohorts. We also did not fully explore the impact of potential confounding factors, such as concomitant infections or inflammatory diseases, which could affect the interpretation of these markers. Further research should investigate the molecular mechanisms linking inflammation and cardiovascular events to enhance our understanding of the pathophysiological pathways involved[36,37]. Moreover, integrating these markers into existing risk models warrants further exploration, particularly regarding their potential influence on clinical decision-making and

Table 4 Comparative analysis of hematological-derived indices among non-ST segment elevation myocardial infarction patients with major adverse cardiovascular event with lethal and non-lethal outcome, median (25th-75th percentiles)

HDR	Time	Lethal outcome (*n* = 35)	Non-lethal outcome (*n* = 51)	*P* value
NLR	T1	7.432 (4.542-12.551)	3.816 (2.423-5.783)	< 0.001
	T2	6.934 (3.672-12.165)	2.794 (2.167-5.580)	< 0.001
dNLR	T1	3.955 (2.721-6.764)	2.618 (1.667-3.675)	0.009
	T2	3.142 (2.056-5.686)	2.124 (1.436-3.295)	0.027
NPR	T1	0.032 (0.028-0.045)	0.030 (0.023-0.038)	0.090
	T2	0.031 (0.026-0.053)	0.026 (0.018-0.038)	0.047
NLPR	T1	0.029 (0.021-0.043)	0.016 (0.011-0.030)	0.005
	T2	0.035 (0.017-0.056)	0.013 (0.009-0.028)	< 0.001
PLR	T1	238.000 (150.420-303.448)	124.887 (92.446-191.566)	0.007
	T2	195.349 (149.359-353.846)	122.619 (83.529-169.186)	0.001
MNR	T1	0.067 (0.054-0.107)	0.111 (0.072-0.144)	0.028
	T2	0.074 (0.043-0.112)	0.131 (0.099-0.172)	0.000
MLR	T1	0.609 (0.424-0.892)	0.365 (0.272-0.509)	0.008
	T2	0.559 (0.428-0.756)	0.417 (0.282-0.553)	0.028
LMR	T1	1.641 (1.121-2.358)	2.742 (1.966-3.681)	0.008
	T2	1.788 (1.324-2.337)	2.400 (1.808-3.549)	0.028
LCR	T1	0.047 (0.015-0.163)	0.371 (0.084-0.748)	0.001
	T2	0.027 (0.008-0.102)	0.151 (0.027-0.424)	0.002
CRP/Ly	T1	21.145 (6.137-66.303)	2.321 (1.327-10.517)	0.001
	T2	37.403 (9.790-121.186)	6.630 (2.361-37.340)	0.002
SII	T1	1812.658 (950.655-3283.542)	919.518 (561.464-1277.483)	0.001
	T2	1778.563 (852.908-2800.333)	673.179 (413.184-1362.656)	0.001
AISI	T1	1399.338 (695.922-2265.644)	536.824 (370.566-910.278)	0.003
	T2	1353.896 (625.428-1836.498)	473.738 (293.227-1110.313)	0.011
SIRI	T1	4.511 (2.677-9.560)	2.473 (1.565-3.845)	0.003
	T2	4.653 (2.639-9.270)	2.244 (1.482-4.164)	0.009

HDR: Hematological-derived ratios; NLR: Neutrophil-to-lymphocyte ratio; dNLR: Derived neutrophil-to-lymphocyte ratio; NPR: Neutrophil-to-platelet ratio; NLPR: Neutrophil to lymphocyte and platelet ratio; PLR: Platelet-to-lymphocyte ratio; MNR: Monocyte to neutrophil ratio; MLR: Monocyte/lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; LCR: Lymphocyte to C-reactive protein ratio; CRP/Ly: C-reactive protein-to-lymphocyte ratio; SII: Systemic immune inflammation index; AISI: Aggregate index of systemic inflammation; SIRI: Systemic inflammation response index; T1: Analysis at admission; T2: Analysis after 24 hours.

patient outcomes. Nonetheless, a notable strength of our study is its prospective nature, enabling systematic data collection and detailed analysis.

CONCLUSION

This study highlights the significant prognostic value of HDIs in predicting MACE among NSTEMI patients. In particular, during follow-up, NLR, PLR, and CRP/Ly offer important insights into the inflammatory processes that underlie cardiovascular events. Enhancing risk categorization and improving patient outcomes may be possible by incorporating these markers into current risk models and therapeutic practices. Validating these results and investigating the molecular pathways connecting inflammation to harmful cardiovascular events should be the main goals of future research.

Table 5 Area under the curve analysis for observed hematological-derived ratios regarding death

Variable	Time	AUC/ROC analysis				
		AUC (95%CI)	Cut-off	Se	Sp	*P* value
AISI	T1	0.675 (0.599-0.745)	> 1113.861	64.0	76.6	0.004
	T2	0.690 (0.615-0.759)	> 911.4	68.0	75.9	0.004
CRP/Ly	T1	0.702 (0.448-0.603)	> 4.737	84.0	53.1	< 0.001
	T2	0.718 (0.643-0.784)	> 22.3	72.00	70.34	< 0.001
dNLRT	T1	0.681 (0.606-0.751)	> 2.46	84.0	51.0	0.002
	T2	0.671 (0.595-0.741)	> 4.81	44.0	89.0	0.007
LCR	T1	0.698 (0.623-0.766)	≤ 0.202	84.00	52.45	< 0.001
	T2	0.699 (0.637-0.774)	≤ 0.041	71.00	69.34	< 0.001
LMRT	T1	0.634 (0.557-0.707)	≤ 1.926	64.00	66.90	0.038
	T2	0.638 (0.561-0.710)	≤ 1.952	64.00	69.66	0.033
MLR	T1	0.634 (0.557-0.707)	> 0.509	64.00	66.90	0.039
	T2	0.637 (0.560-0.710)	> 0.509	64.00	69.66	0.033
MNR	T1	0.673 (0.597-0.743)	≤ 0.08	64.00	71.03	0.004
	T2	0.681 (0.649-0.724)	≤ 0.079	60.00	74.28	< 0.001
NLPR	T1	0.664 (0.588-0.735)	> 0.018	80.00	55.17	0.004
	T2	0.757 (0.686-0.819)	> 0.021	68.00	70.34	< 0.001
NLR	T1	0.707 (0.632-0.774)	> 4.076	84.00	51.72	< 0.001
	T2	0.811 (0.727-0.859)	> 4.667	74.00	76.72	< 0.001
NPR	T1	0.598 (0.520-0.672)	> 0.028	72.00	48.97	0.072
	T2	0.657 (0.580-0.728)	> 0.025	76.00	52.41	0.005
PLR	T1	0.676 (0.600-0.745)	> 230.232	52.00	84.14	0.005
	T2	0.719 (0.645-0.785)	> 159.74	72.00	72.41	< 0.001
SII	T1	0.706 (0.631-0.773)	> 1745.18	56.00	82.76	< 0.001
	T2	0.744 (0.671-0.808)	> 1400.466	64.00	81.38	< 0.001
SIRI	T1	0.661 (0.584-0.731)	> 3.907	68.00	66.90	< 0.001
	T2	0.684 (0.608-0.753)	> 4.164	64.00	74.48	0.003

HDR: Hematological-derived ratios; NLR: Neutrophil-to-lymphocyte ratio; dNLR: Derived neutrophil-to-lymphocyte ratio; NPR: Neutrophil-to-platelet ratio; NLPR: neutrophil to lymphocyte and platelet ratio; PLR: Platelet-to-lymphocyte ratio; MNR: Monocyte to neutrophil ratio; MLR: Monocyte/lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; LCR: Lymphocyte to C-reactive protein ratio; CRP/Ly: C-reactive protein-to-lymphocyte ratio; SII: Systemic immune inflammation index; AISI: Aggregate index of systemic inflammation; SIRI: Systemic inflammation response index; T1: Analysis at admission; T2: Analysis after 24 hours; AUC: Area under the curve; ROC: Receiver operating characteristic.

Table 6 Logistic regression predictive analysis regarding major adverse cardiovascular events-lethal outcome among patients with non-ST segment elevation myocardial infarction

Variable	OR	95%CI		*P* value
		Lower	Upper	
CRP/Ly (T1) > 4.737	3.690	1.140	11.942	0.024
CRP/Ly (T2) > 22.3	2.839	0.835	9.650	0.095
NLPR (T2) > 0.021	2.780	0.751	10.285	0.126
NLR (T1) > 4.076	1.300	1.121	1.743	0.009

NLR (T2) > 4.667	4.915	1.917	12.602	0.001
PLR (T2) > 159.74	3.262	0.958	11.102	0.059
SII (T1) > 1745.18	2.642	0.650	10.743	0.175
SII (T2) > 1400.466	1.352	0.295	6.205	0.698

NLR: Neutrophil-to-lymphocyte ratio; NLPR: Neutrophil-to-lymphocyte and platelet ratio; PLR: Platelet-to-lymphocyte ratio; CRP/Ly: C-reactive protein-to-lymphocyte ratio; SII: Systemic immune inflammation index; T1: Analysis at admission; T2: Analysis after 24 hours; OR: Odds ratio.

FOOTNOTES

Author contributions: Bećirović E and Bećirović M designed the research study; Bećirovic A, Hadžić S, and Ljuca K performed the research; Šegalo S and Papić E supervised the research; Ferhatbegović L, Ejubović M and Ejubović AJ wrote the manuscript; Kovčić A, Šljivo A and Begagić E analyzed the data. All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Basic Study

Anticonvulsant potential of rosuvastatin in combination with carbamazepine and valproate in animal models of epilepsy

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Abstract

BACKGROUND

Epilepsy impacts millions of people, with many not responding to existing treatments. Some evidence links neuroinflammatory processes to epilepsy. Statins exhibit anti-inflammatory and neuroprotective properties, potentially offering antiepileptic effects.

AIM

To evaluate the anticonvulsant effects of rosuvastatin in animal models of epilepsy.

METHODS

Ninety-six albino mice were divided into 16 groups. In the maximal electroshock seizure (MES) model, eight groups received intraperitoneal vehicle, carbamazepine, rosuvastatin, or a combination. Outcomes measured included seizure protection [tonic hind limb extension (THLE)], duration of THLE, seizure duration, and mortality. In the pentylenetetrazol (PTZ) model, eight groups were pretreated with vehicle, valproate, rosuvastatin, or a combination, with outcomes measured as seizure latency, seizure duration, and mortality.

RESULTS

In the MES model, rosuvastatin exhibited protection against THLE in a small percentage of mice. Rosuvastatin shortens the duration of THLE in a dose-dependent manner. However, none of these were statistically significant compared to the control group. The combination of rosuvastatin 10 mg/kg with

carbamazepine 4 mg/kg resulted in a significant reduction in seizure duration compared to the control group, better than carbamazepine alone at 4 mg/kg and 6 mg/kg. In the PTZ model, rosuvastatin alone showed no significant effects on latency, duration of seizure, or mortality. However, rosuvastatin 10 mg/kg combined with valproate 100 mg/kg significantly delayed the onset of seizures, seizure duration and mortality percentage, better than valproate alone at 100 mg/kg.

CONCLUSION
Rosuvastatin enhanced the anticonvulsant effects of carbamazepine and valproate. Further studies are required to explore the antiepileptic potential of rosuvastatin at various doses, durations, dosage forms, routes and models.

Key Words: Antiepileptic; Anticonvulsant; Statins; Rosuvastatin; Maximal electroshock seizure; Pentylenetetrazol

Core Tip: Many patients do not benefit from the available antiepileptics. Statins are known for their pleiotropic effects, which include neuroprotective properties. We investigated whether rosuvastatin, a potent statin, has anticonvulsant properties on its own or if it potentiates the effects of standard anticonvulsants. The study used maximal electroshock and pentylenetetrazol seizure models in albino mouse We observed that rosuvastatin potentiated some of the anticonvulsant effects of the standard antiepileptics carbamazepine and valproate.

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INTRODUCTION

Epilepsy, a prevalent neurological disorder affecting more than 50 million individuals globally, is characterized by abnormal brain activity leading to seizures and various neurological manifestations[1]. Despite the availability of numerous antiepileptic drugs, a considerable proportion of patients remain unresponsive to standard treatment and even add-on therapies[2]. The ongoing pursuit of innovative anticonvulsant strategies underscores the intricate nature of epilepsy and the imperative need for novel therapeutic interventions.

Recent evidence has linked neuroinflammatory processes to epilepsy, emphasizing the role of inflammation in determining the seizure threshold and recurrence. Clinical observations support the notion that inflammation contributes to epilepsy, as evidenced by the prevalence of seizures in patients with autoimmune disorders, increased proinflammatory cytokines in febrile seizures, and the anticonvulsant efficacy of steroids in infantile spasms. Experimental studies conducted in rodent models have provided additional support for the notion that brain inflammation facilitates seizures and neuronal hyper-excitability[3,4]. This insight has sparked interest in pharmacological strategies targeting neuroinflammation for potential antiepileptic effects.

Statins, inhibitors of the 3-hydroxy-3-methylglutaryl Coenzyme A reductase enzyme, exhibit pleiotropic effects, including antithrombotic, anti-inflammatory, and antioxidative effects, in addition to their primary role in reducing cholesterol levels. A substantial body of evidence supports the neuroprotective effects of statins in various neuropathological conditions, including stroke, traumatic brain injury, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and epilepsy[5]. Statins have been shown to suppress the expression of pro-inflammatory genes, as well as the release of pro-inflammatory cytokines, chemokines, adhesion molecules, and matrix metalloproteinases. Furthermore, preliminary research suggests that statins' net effect on neurosteroids may contribute to their antiepileptic properties[6,7].

Research on the antiepileptic effects of statins has focused predominantly on atorvastatin, revealing its protective role in chemically induced convulsions and audiogenic seizures[8,9]. Rosuvastatin, a potent statin, has been shown to reduce neuroinflammation, improve blood-brain barrier (BBB) integrity, and increase endothelial nitric oxide synthase mRNA expression[10]. A recent study showed that rosuvastatin has protective effect against pentylenetetrazol (PTZ)-induced seizures, increasing current electroshock-induced seizures, and PTZ-induced status epilepticus[11]. Hence, this study was undertaken to explore the protective effects of rosuvastatin against PTZ seizures and maximal electroshock induced seizures and examine its interaction with commonly prescribed antiepileptic drugs.

MATERIALS AND METHODS

The study was conducted on albino mice at the Central Animal Facility and Department of Pharmacology, Maulana Azad Medical College (MAMC), New Delhi. Approval for the study was obtained from the Institutional Animal Ethics

Committee MAMC, New Delhi.

Animals

A total of 96 mice were used for this study. Albino mice aged 2-3 months and weighing 20-30 g were procured from the CSIR Institute of Genomics and Integrative Biology. The mice were housed in polypropylene cages under controlled environmental conditions, with a 12-hour light-dark cycle and free access to food and water. Animals were acclimatized to laboratory conditions before the experiments.

Drugs and reagents

Drugs (rosuvastatin, carbamazepine, and valproate) were procured from MedChemExpress Pvt. Ltd. PTZ and polypropylene glycol were provided by Sun Pharmaceutical Industries Ltd.

Drug treatment

The 96 mice were randomly divided into 16 groups. Randomization was performed using computer-generated random number tables. For the maximal electroshock seizure (MES) model, various treatments were administered intraperitoneally to eight groups of six mice each. The control group received vehicle (polypropylene glycol) at a dose of 10 mg/kg. The three groups received carbamazepine at doses of 4 mg/kg, 6 mg/kg, and 8 mg/kg, respectively. Another three groups received rosuvastatin at doses of 10 mg/kg, 20 mg/kg, and 30 mg/kg. The final group received a combination of carbamazepine and rosuvastatin at doses of 4 mg/kg and 10 mg/kg, respectively. In the PTZ seizure model study, eight groups of six mice each were similarly treated by intraperitoneal injection. The control group received vehicle (polypropylene glycol) at a dose of 10 mg/kg. Three groups received valproate at doses of 100 mg/kg, 200 mg/kg, and 400 mg/kg, respectively. Another three groups received rosuvastatin at doses of 10 mg/kg, 20 mg/kg, and 30 mg/kg. The final group received a combination of valproate and rosuvastatin at doses of 100 mg/kg and 10 mg/kg, respectively.

Experimental models and assessment parameters

Two experimental seizure models were used: (1) The MES model (8 groups); and (2) The PTZ model (8 groups).

MES was induced *via* an electroconvulsiometer with transauricular electrodes after 40 minutes of intraperitoneal administration of the vehicle or test drugs. A current of 30 milliamperes was applied at a frequency of 50 Hz for a period of 0.2 seconds. The outcomes measured were seizure protection [presence or absence of tonic hind limb extension (THLE)], mean duration of THLE, mean duration of seizure activity, and percentage mortality.

PTZ (dose 30 mg/kg) was administered intraperitoneally to the mice to induce seizures after 40 minutes of intraperitoneal administration of vehicle or test drugs. The outcomes measured were seizure onset latency (the time to whole-body clonus event, determined after the intraperitoneal administration of PTZ), the mean duration of tonic-clonic convulsions, and percentage mortality.

Statistical analysis

The sample size of 6 mice per group was determined on the basis of a power of 80%, with the type 1 error rate set at 5%, the duration of PTZ-induced seizure standard deviation of 18.05, and an effect size of 30[12]. The data were compiled and analyzed using MS Excel Office 365 and Statistical Package for the Social Sciences version 25. Fisher's exact test was used to compare proportions. Continuous variables were analyzed *via* the Kruskal-Wallis test for multigroup analysis. Post hoc analysis for intergroup comparisons was performed *via* Dunn's post hoc test. A P value of ≤ 0.05 was considered significant.

RESULTS

Effect of pretreatment on the MES model

Seizure protection from MES: All the mice in the control group exhibited maximal electroshock induced seizures characterized by THLE. All the mice in groups given carbamazepine at various doses and in combination with rosuvastatin showed 100% protection against THLE. THLE was absent in 1 of the 6 mice given rosuvastatin alone at a dose of 10 mg/kg, whereas it was absent in 2 of the 6 mice in the rosuvastatin 20 mg/kg and 30 mg/kg groups. However, this protection was not statistically significant compared with that of control group (Table 1).

Duration of THLE: The mean duration of THLE in the control group was 6.73 seconds ± 0.51 seconds. THLE was not observed in groups administered carbamazepine either alone or in combination with rosuvastatin. We observed a shorter mean duration of THLE in the groups of mice pretreated with rosuvastatin, *i.e.*, 5.8 seconds ± 1.18 seconds in the rosuvastatin 10 mg/kg group, 4.47 seconds ± 1.41 seconds in the rosuvastatin 20 mg/kg group and 4.93 seconds ± 1.58 seconds in the rosuvastatin 30 mg/kg group. However, these reductions were not statistically significant compared with those in the control group (Table 2).

Duration of seizure activity: The mean duration of seizure activity in the control group of mice was 22.01 seconds ± 1.09 seconds. A dose-dependent decrease in the duration of seizure activity was observed with carbamazepine. The mean duration of seizure activity was 14.37 seconds ± 0.68 seconds, 11.63 seconds ± 0.39 seconds and 10.33 seconds ± 0.58 seconds in mice pretreated with carbamazepine at 4 mg/kg, 6 mg/kg, and 8 mg/kg, respectively. Compared with that in the control group, the duration of seizure activity in the 8 mg/kg carbamazepine group was significantly shorter.

Table 1 Tonic hind limb extension in maximal electroshock induced seizures in mice (*n* = 6)

Treatment groups	THLE present	% with THLE present
Vehicle (control group)	6	100.00%
Carbamazepine 4 mg/kg	0	0.00%[a]
Carbamazepine 6 mg/kg	0	0.00%[a]
Carbamazepine 8 mg/kg	0	0.00%[a]
Rosuvastatin 10 mg/kg	5	83.33%
Rosuvastatin 20 mg/kg	4	66.67%
Rosuvastatin 30 mg/kg	4	66.67%
Rosuvastatin 10 mg/kg + carbamazepine 4 mg/kg	0	0.00%[a]

[a]*P* value < 0.05 in comparison with control group (Fischer exact test).
THLE: Tonic hind limb extension.

Table 2 Mean duration of tonic hind limb extension in maximal electroshock induced seizures in mice (*n* = 6)

Treatment groups	Mean duration of tonic hind limb extension (seconds)	SEM
Vehicle (control group)	6.73	0.51
Carbamazepine 4 mg/kg	0[a]	0
Carbamazepine 6 mg/kg	0[a]	0
Carbamazepine 8 mg/kg	0[a]	0
Rosuvastatin 10 mg/kg	5.80	1.18
Rosuvastatin 20 mg/kg	4.47	1.41
Rosuvastatin 30 mg/kg	4.93	1.58
Rosuvastatin 10 mg/kg + carbamazepine 4 mg/kg	0[a]	0

[a]*P* value < 0.05 in comparison with control group (Dunn Post hoc analysis).

In mice administered rosuvastatin 10 mg/kg, 20 mg/kg, and 30 mg/kg, the mean duration of seizure activity was similar to that of the control group. The combined administration of rosuvastatin 10 mg/kg and carbamazepine 4 mg/kg resulted in a significant reduction in the mean seizure duration (10.20 seconds ± 0.60 seconds), whereas the reduction in seizure duration in the mice treated with carbamazepine (4 mg/kg) alone was not statistically significant compared with that in the control group (Table 3).

Mortality in the MES model: No mortality was observed in the mice subjected to MES in any of the groups, including the control group.

Effect of pretreatment on PTZ seizure model

Latency period: The mean latency to seizure onset observed in the control group was 8.80 seconds ± 0.53 seconds (Figure 1A). In mice pretreated with 200 mg/kg or 400 mg/kg valproate, the mean latency was significantly greater (34-38 seconds). We also observed a longer mean latency in mice pretreated with 10 mg/kg, 20 mg/kg, and 30 mg/kg rosuvastatin (10.43 seconds ± 0.60 seconds, 10.50 seconds ± 0.59 seconds, and 10.23 seconds ± 0.43 seconds, respectively). Although slightly longer latency was observed in the rosuvastatin groups than in the control group, this difference was not statistically significant. In mice pretreated with rosuvastatin 10 mg/kg + valproate 100 mg/kg, the mean latency time was 33.70 seconds ± 0.87 seconds and was significantly longer compared to the control group. Moreover, the latency period in the valproate 100 mg/kg group was not statistically different from that in the control group (Figure 1A).

Duration of tonic-clonic convulsions: The tonic-clonic convulsions lasted an average of 149.33 seconds ± 3.58 seconds in the control group (Figure 1B). In the mice pretreated with 100 mg/kg, 200 mg/kg, and 400 mg/kg valproate, the mean durations of tonic-clonic convulsions were 54.47 seconds ± 1.41 seconds, 50.93 seconds ± 2.15 seconds, and 50.47 seconds ± 0.97 seconds, respectively. The shorter seizure duration observed at doses of 200 mg/kg and 400 mg/kg valproate was statistically significant compared with that of the control group.

Table 3 Duration of seizure activity in maximal electroshock induced seizures in mice (*n* = 6)

Treatment groups	Mean duration of seizure (seconds)	SEM
Vehicle (control group)	22.00	1.09
Carbamazepine 4 mg/kg	14.37	0.68
Carbamazepine 6 mg/kg	11.63	0.39
Carbamazepine 8 mg/kg	10.33[a]	0.58
Rosuvastatin 10 mg/kg	23.80	1.14
Rosuvastatin 20 mg/kg	21.13	0.74
Rosuvastatin 30 mg/kg	22.53	0.61
Rosuvastatin 10 mg/kg + carbamazepine 4 mg/kg	10.20[a]	0.60

[a]*P* value < 0.05 in comparison with control group (Dunn Post hoc analysis).

We observed that in the mice pretreated with 10 mg/kg, 20 mg/kg, and 30 mg/kg rosuvastatin, the mean durations of tonic-clonic convulsions were 140.13 seconds ± 2.91 seconds, 141.20 seconds ± 2.40 seconds, and 142.00 seconds ± 1.05 seconds, respectively. Although a slightly shorter duration of tonic-clonic convulsions was observed in the rosuvastatin groups than in the control group, the differences were not statistically significant. In mice pretreated with 10 mg/kg rosuvastatin + 100 mg/kg valproate, the mean duration of tonic-clonic convulsions was 48.17 seconds ± 1.19 seconds, which was significantly shorter than that in the control group. We also noted a slightly shorter duration of tonic-clonic convulsions in the rosuvastatin 10 mg/kg + valproate 100 mg/kg combination group than in the valproate (100 mg/kg) alone group. However, this difference was not statistically significant (Figure 1B).

Mortality in PTZ model: We recorded 100% mortality in the control group and in the groups administered rosuvastatin at dosages of 10 mg/kg, 20 mg/kg, and 30 mg/kg (Figure 1C). In the 100 mg/kg and 200 mg/kg valproate groups, four out of six mice (66.7%) died, whereas the 400 mg/kg valproate group exhibited a mortality rate of 50%. We also observed a mortality of 50% in the group receiving a combination of rosuvastatin (10 mg/kg) and valproate (100 mg/kg). When mortality was compared with that of the control group, only valproate 400 mg/kg and rosuvastatin (10 mg/kg) + valproate (100 mg/kg) provided statistically significant protection (Figure 1C).

DISCUSSION

The aim of the present study was to evaluate and compare the anticonvulsant potential of rosuvastatin alone and in combination with standard antiepileptic drugs in albino mice. Two different seizure models were used for evaluation, namely the MES model for inducing generalized tonic-clonic seizures (GTCS) and the PTZ model for inducing absence seizures. Carbamazepine, indicated in the GTCS was used as the comparison standard for the MES model, whereas sodium valproate was used as the comparison standard for the PTZ model. The results of the present study revealed a dose-dependent decrease in seizure activity with both carbamazepine and valproate in the MES and PTZ seizure models, respectively. These observations are consistent with previous studies that have demonstrated the effectiveness of carbamazepine and valproate in reducing seizure activity in various animal models of seizures[13].

In the MES model, only a small proportion of mice treated with rosuvastatin at different doses exhibited protection against THLE. We also found that increasing rosuvastatin doses resulted in a shorter duration of THLE than did the control. However, these findings were not statistically significant compared with that in control mice. We were unable to ascertain whether rosuvastatin has a synergistic effect because both mice treated with carbamazepine alone and mice treated with the combination of carbamazepine-rosuvastatin showed 100% protection against THLE. This finding is in line with earlier studies using atorvastatin, which, when given as a single acute dose in MES animal models, did not demonstrate any protective effect[14-16]. However, in a study administration of acute dose of fluvastatin (80 mg/kg) enhanced the anticonvulsant potential of carbamazepine and valproate by decreasing their half effective dose values[14]. The interaction of fluvastatin with carbamazepine was found to be pharmacokinetic in nature as it resulted in a 61% significant increase in total brain concentration of carbamazepine. Similarly, in another study, acute lovastatin dose (10 mg/kg) was observed to significantly enhance the anticonvulsant effect of valproate in MES model, which was accompanied with a 34% significant increase in total brain concentration of valproate[17]. Their findings also revealed that chronic administration of lovastatin (10 mg/kg, once daily for 7 consecutive days) potentiated the antiseizure properties of phenytoin in the MES test in mice but this was without any impact on total brain level of phenytoin in mice [17].

In our study, the mean seizure duration was not shorter in the rosuvastatin alone group than in the control group at any of the tested doses. However, the combination of rosuvastatin 10 mg/kg with carbamazepine 4 mg/kg resulted in a significant reduction in seizure duration compared with that to the control group. It should be noted that seizure duration was not significantly shortened when carbamazepine 4 mg/kg was administered alone. Previous studies did not

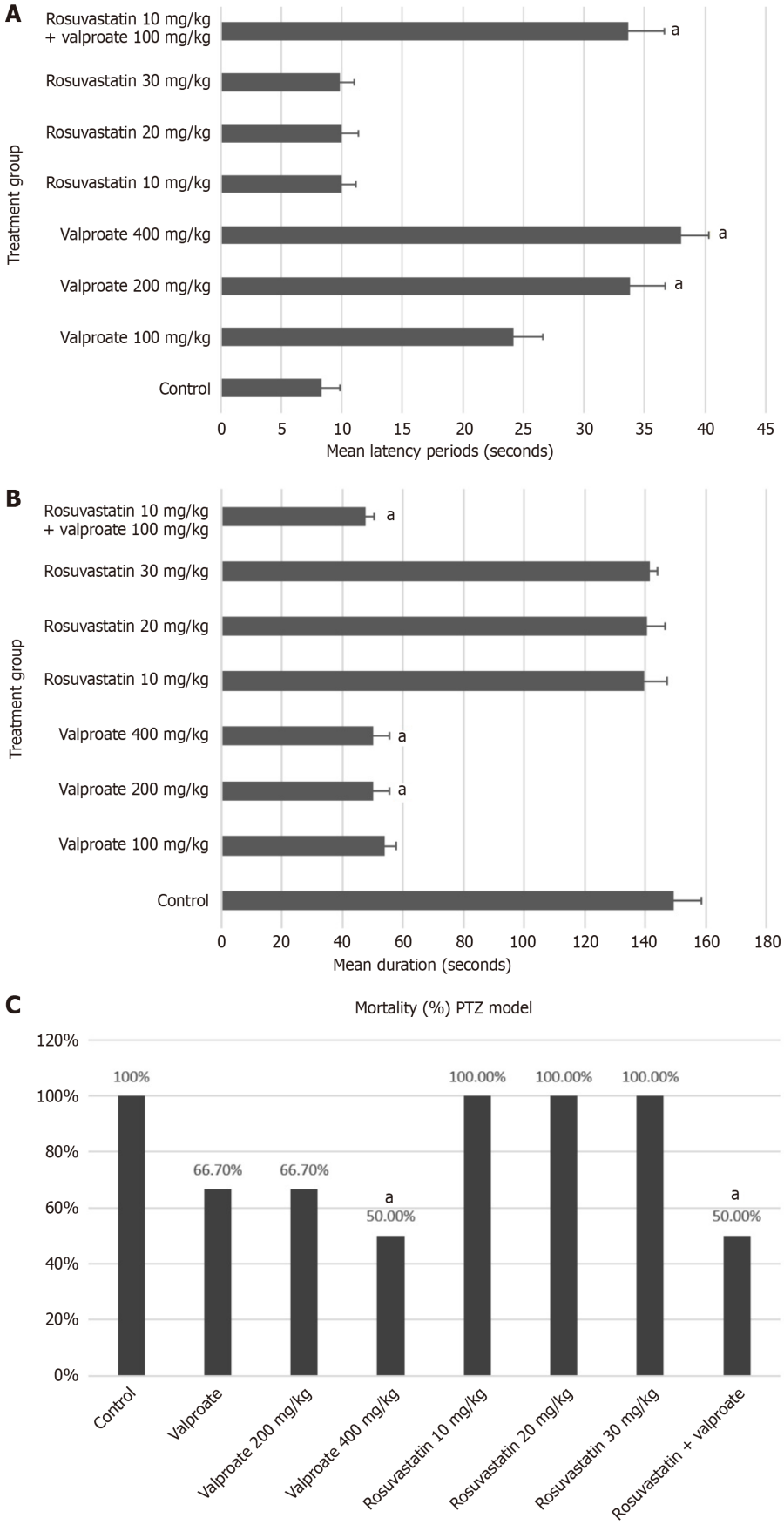

Figure 1 Effect of pretreatment on pentylenetetrazol seizure model. A: Latency period for onset of seizures in pentylenetetrazol (PTZ) administered mice (n = 6) (Dunn Post hoc analysis); B: Duration of tonic-clonic convulsions in PTZ induced seizures in mice (n = 6) (Dunn Post hoc analysis); C: Mortality in PTZ induced seizures in mice (n = 6) (Fischer exact test). [a]*P* value < 0.05 in comparison with control group.

mention the total duration of seizure activity in MES models[17].

Based on the above findings, we assume that rosuvastatin has the potential to potentiate the antiepileptic effects of carbamazepine through either pharmacokinetic or pharmacodynamic interactions. We could not ascertain from the existing literature the precise mechanism through which rosuvastatin may have enhanced carbamazepine, which thus needs to be explored in further studies.

In the PTZ model, rosuvastatin 10 mg/kg in combination with valproate 100 mg/kg significantly delayed seizure onset in mice. Compared with that in the control group and the 100 mg/kg valproate group, the mean latency period was significantly longer in the group pretreated with the rosuvastatin-valproate combination. However, in mice pretreated with rosuvastatin 10 mg/kg, 20 mg/kg, or 30 mg/kg, the latency period was similar to that in the control group. In a previous study which investigated the protective role of intranasal rosuvastatin liquid crystal nanoparticles against PTZ-induced seizures, it was observed that intranasal rosuvastatin had significantly longer latency and was more effective than oral and intraperitoneal rosuvastatin groups[11]. The study was based on the fact that rosuvastatin is more hydrophilic and the BBB permeability is comparatively poor compared to atorvastatin, simvastatin, *etc*. The same limitation of rosuvastatin may have undermined the antiepileptic potential of rosuvastatin, as shown in our study[9]. Likewise, no effect on the mean duration of PTZ-induced tonic-clonic convulsions was observed after administration of rosuvastatin at any dose.

In one study, a single oral dose of atorvastatin (10 mg/kg) did not alter the latency of PTZ-induced seizures, whereas chronic treatment (over 7 days) delayed PTZ-induced generalized seizures[9]. In another study, a single oral dose of atorvastatin in rats significantly prolonged the time to seizure onset[15]. However, in the PTZ model, simvastatin was found to be ineffective, although it had an anticonvulsant effect on kainic acid-induced, picrotoxin-induced, and audiogenic seizure models[17]. In another study, lovastatin at higher doses administered intraperitoneally four days before testing significantly increased the threshold for PTZ-induced convulsions in mice[18].

We observed a 50% significant reduction in mortality in mice pretreated with the combination of 10 mg/kg rosuvastatin and 100 mg/kg valproate. Similar protection was found in mice administered a higher dose of valproate (400 mg/kg). We assume that rosuvastatin might have enhanced the protective anticonvulsant effect of valproate here. Even in the mice given rosuvastatin alone, 33% of mice were protected, but this difference was not statistically significant. In a previous study, intraperitoneal rosuvastatin prevented mortality in PTZ-induced status epilepticus by only 17%, while intranasal rosuvastatin protected 66% of the mice from mortality[11]. In a previously published study with atorvastatin, mortality protection from PTZ-induced seizures was only up to 33%[19].

Some inconsistencies between the present study results and those of previous studies with different statins may be attributed to several factors, such as differences in animal species, dose, duration, dosage form/route of administration, and seizure models. The hydrophilic nature of rosuvastatin and poor BBB permeability may be a major limiting factor for its potential antiepileptic effect[20].

CONCLUSION

The present results showed that acute single-dose treatment with rosuvastatin, when administered alone, had no anticonvulsant effect in either the maximal electroshock-induced seizure model or the pentylene-tetrazole-induced seizure model. However, a combination of rosuvastatin and standard anticonvulsants provided protection in the MES and PTZ models; therefore, rosuvastatin may have the potential to enhance the antiepileptic effects of carbamazepine and valproate. Therefore, further studies are needed to explore the potential of rosuvastatin with longer durations, different dosage forms, and routes of administration in different seizure models and to further clarify the anticonvulsant potential of rosuvastatin in epilepsy.

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FOOTNOTES

Author contributions: Tayal V, Mandal A and Haque MI interpreted the data and wrote the manuscript; Tayal V, Mandal A, and Mishra A designed, performed the experiments, acquired and analyzed the data; Kalra BS and Roy V were involved in the conceptualization of the study, literature review, and revising the manuscript for intellectual content; all authors read and approved the final version of the manuscript.

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SYSTEMATIC REVIEWS

Strategic insights of telehealth platforms and strengths, weaknesses, opportunities, and threats analysis of Amazon's clinical endeavors

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Abstract

BACKGROUND

The adoption of telehealth services surged after the coronavirus disease 2019 pandemic, revolutionizing traditional healthcare delivery models. Amazon

Clinic's recent nationwide launch marks a significant milestone in this trend. This study aims to offer a strengths, weaknesses, opportunities, and threats (SWOT) analysis of Amazon Clinic and compare its features with leading virtual healthcare platforms.

AIM

To evaluate Amazon Clinic's telehealth services through a SWOT analysis and compare its features with other leading virtual healthcare platforms.

METHODS

The initial search terms included were, amazon clinic odds ratio (OR) amwell OR Teladoc OR Walmart virtual health service OR CVS minute clinic OR CirrusMD OR brightside health, from 2000 to 2023. This search yielded 111 articles, from which duplicates were removed, and unrelated titles were filtered out. Eight articles were retained for a final review, including comparative studies, usability research, retrospective analyses, observational studies, and review articles. The data was organized and analyzed using Rayyan software and summarized in a table and PRISMA flowcharts.

RESULTS

The review included eight articles focusing on various aspects of telehealth. Comparative studies highlighted differences between Teladoc and traditional physician offices, noting lower diagnostic imaging orders and antibiotic prescriptions for Teladoc. User demographics for Teladoc showed younger, less engaged patients. Usability studies emphasized the importance of website design for telemedicine adoption. Tele-mental health platforms like Brightside showed superior outcomes in treating depression compared to traditional methods. Telemedicine for specialized fields like skin reconstruction demonstrated cost efficiency and reduced waiting times. The SWOT analysis identified Amazon Clinic's strengths, such as its vast consumer base and transparent pricing, and weaknesses like the lack of pediatric care. Opportunities included potential partnerships and service expansions, while threats involved competition and regulatory challenges.

CONCLUSION

Amazon Clinic's entry into the telehealth sector represents a significant development with various strengths and opportunities. However, it faces challenges from established healthcare providers and regulatory landscapes. The future success of Amazon Clinic will depend on strategic collaborations, addressing service gaps, and navigating competition and regulations. Telemedicine's impact will hinge on its ability to effectively leverage these opportunities and overcome inherent challenges in the ever-evolving healthcare landscape.

Key Words: Tele-health; Amazon; COVID-19; Primary Care; Outpatient clinic; SWOT; Telemedicine

Core Tip: Telemedicine has been in the armamentarium for patient care for a while. It surged during and after the coronavirus disease 2019 pandemic. To address the shortage of healthcare providers and the accessibility of care, business industries and venture capitalists have invested resources in providing 24/7 virtual healthcare. This review discusses telemedicine, its implications, and the role of major organizations such as Amazon in providing telehealth. It also assesses strengths, weaknesses, opportunities, and threats.

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INTRODUCTION

During and after the coronavirus disease 2019 (COVID-19) pandemic witnessed a surge in the demand for virtual healthcare[1]. Telemedicine-delivering healthcare services *via* digital platforms and media devices has successfully navigated numerous hurdles associated with conventional doctor-patient encounters by adding convenience and efficiency[2]. The recent nationwide launch of Amazon Clinic[3], a fully virtual healthcare service by Amazon Inc., demonstrates this move towards increasing healthcare accessibility using technology. The ability of Telemedicine to expand patient outreach underscores its immense potential in fostering efficient and equitable healthcare.

MATERIALS AND METHODS

Methods

The initial search terms included were, amazon clinic odds ratio (OR) amwell OR Teladoc OR Walmart virtual health service OR Consumer Vale Stores Minute clinic OR CirrusMD OR brightside health, from 2000 to 2023. This PubMed search yielded a total of 111 articles. A filter for yielding only (Title/Abstract) was used. One duplicate article was removed. All articles with titles not related to the topic were eliminated. After reviewing the abstracts, 8 articles were retained for a final review. Studies were exported from PubMed to Rayyan software. Afterwards, the authors assessed the full texts of the articles to determine final eligibility. Table 1 summarizes the parameters evaluated in the analyzed articles. Figure 1 demonstrates the PRISMA 2009 flowchart diagram depicting the process of selecting studies for the review.

This manuscript has been submitted as a preprint to the QEIOS server[4].

RESULTS

The final review included 8 articles, including one comparative research study, two usability research studies, two retrospective analyses, one observational study, and one review article.

In one of the comparison studies by Uscher-Pines *et al*[5] between a telehealth platform, Teladoc, and traditional physician offices revealed some disparities. Teladoc providers were less likely to order diagnostic imaging and performed poorly in prescribing antibiotics for bronchitis. For the bronchitis measure and not ordering antibiotics, Teladoc performed worse than physician offices (16.7 *vs* 27.9%, $P < 0.01$)[5]. In adjusted models, Teladoc users were not likelier to be located within a healthcare professional shortage area (OR = 1.12, $P = 0.10$) or rural location (OR = 1.0, $P = 0.10$)[5]. This finding points to the need for targeted marketing strategies to educate and increase the user base among the underserved population.

In another study, Uscher-Pines and Mehrotra[6] found that adult Teladoc users were generally younger and less engaged with the traditional healthcare system, with 75% of patients aged 18 to 50. These users predominantly sought care for acute respiratory infections, urinary tract infections, and skin problems, highlighting the challenge of ensuring follow-up visits in telemedicine[6]. Six percent of Teladoc visits resulted in a follow-up visit for a similar condition, in contrast to 13 percent of office visits and 20 percent of Emergency Department visits, underscoring a critical challenge concerning the reduced probability of subsequent follow-up visits[6]. Teladoc is demonstrating a significant role in broadening healthcare access to patient populations that are otherwise not engaged with traditional healthcare providers.

Telehealth's benefits extend to both physicians and patients. Physicians can diagnose and prescribe for routine non-emergency conditions *via* telephone, a practice that expands their role and enhances patient access to care, supporting the 'medical home' model as demonstrated in a study by Gorton *et al*[7].

The design and interaction of telemedicine websites also play a critical role in their acceptance and widespread use, as shown in a study by Campbell and Monkman[8], which focused on the usability of the Teladoc website before and after a redesign. The study revealed that the pre-redesign website had higher usability compared to the post-redesign version, with participants struggling more to complete critical tasks such as locating essential information and understanding how to initiate a virtual consultation. This indicates that despite the redesigning efforts, Teladoc's website usability did not improve, suggesting the need for more effective user testing in future redesigns to ensure enhanced patient interaction and satisfaction with telemedicine platforms. The study emphasizes the importance of context-specific usability testing for the effective adoption of health information technology[8].

Telemedicine's impact extends beyond general healthcare to specialized fields like psychiatry. Chokshi *et al*'s study on the tele-mental health platform Brightside demonstrated its effectiveness in treating depression, offering superior outcomes compared to traditional treatment approaches, with 80% of telemental health platform patients experiencing a reduction of 5 or more points from their baseline Patient Health Questionnaire-9 (PHQ-9) as compared to 52% of patients receiving traditional treatment ($P \leq 0.001$)[9].

Differential access to mental health care based on income levels was explored by Belanger *et al*[10], who found significant improvements in depression symptoms across various income groups using telehealth. The study demonstrates a significant decrease in depression severity over time for both income groups undergoing telepsychiatry treatment, as indicated by declining PHQ-9 scores ($F = 696.88$, $P < 0.001$, $\eta 2 = 0.480$)[10]. By week 10, both groups' PHQ-9 scores reduced to below 10, signaling an overall improvement in depression severity. This emphasizes the importance of making tele-mental health services more accessible to all income brackets[10].

The scope of telemedicine in specialized areas such as skin reconstruction was explored by Du *et al*[11]. They compared face-to-face consultations with store-and-forward techniques and live video chats. While face-to-face interactions were preferred for skin cancer reconstruction, there was a noticeable shift towards virtual care, driven by factors like cost efficiency and reduced waiting times. This shift highlights the growing potential of telemedicine in providing equitable healthcare solutions, especially for those facing socioeconomic barriers to traditional healthcare access. Live video consultations offer an additional dimension to telemedicine, providing real-time interactions. This method has proven effective in maintaining continuity of care during events such as the COVID-19 pandemic, where in-person visits were prohibited. Studies have shown that live video consultations can be as effective as in-person visits for many conditions, including chronic disease management and follow-up care[12]. The Centers for Medicare & Medicaid Services (CMS) also highlights the growing acceptance and integration of telehealth services in the healthcare system, with improvements in patient access and satisfaction with virtual care options. The CMS toolkit provides guidelines for implementing telehealth

Table 1 Summary of the parameters evaluated in the analyzed articles

Ref.	Parameters evaluated	Key findings	Methodology
Access and quality of care in direct-to-consumer telemedicine, Uscher-Pines *et al* [5]	Antibiotic Prescribing for Acute Respiratory Infections in telemedicine visits *vs* traditional office visits	Antibiotic prescribing practices differed significantly between telemedicine and traditional settings	Retrospective analysis of telemedicine session records to evaluate prescribing patterns
Analysis of teladoc use seems to indicate expanded access to care for patients without prior connection to a provider, Uscher-Pines and Mehrotra[6]	Utilization patterns of Teladoc services	Teladoc appears to expand access to care for patients without prior connection to a provider	Analysis of claims data for 3701 Teladoc visits, comparing usage patterns and follow-up rates
Welcome to the world of telehealth: Physicians reaping significant benefits, Gorton[7]	Evaluating benefits to physicians from telemedicine	Physicians can diagnose and prescribe for routine conditions *via* telephone, expanding their role, enhancing patient access to care, supporting the 'medical home' model	Narrative review
The application of a novel, context specific, remote, usability assessment tool to conduct a pre-redesign and post redesign usability comparison of a telemedicine website, Campbell *et al*[8]	Usability of Teladoc website pre- and post-redesign	The Teladoc website had better usability prior to the redesign	Remote usability testing using a novel data collection tool with 50 participants before and after the website redesign
A comparative evaluation of measurement-based psychiatric care delivered *via* specialized tele-mental health platform versus treatment as usual: A retrospective analysis: Chokshi *et al*[8]	Efficacy of tele-mental health among different incomes	Lower and higher income groups both improved in depression symptoms, with higher income groups showing more improvement	Retrospective analysis of clinical data from telepsychiatry sessions, comparing outcomes by income level
Exploring social determinants of health: Comparing lower and higher income individuals participating in telepsychiatric care for depression; Belanger *et al*[8]	Comparison between lower income (below $30000 annually) and higher income (above $60000 annually) groups. And depression severity using PHQ-9 over several time points (baseline, 6, 8, 10, 12, 14, and 16 weeks)	Both income groups showed significant improvement in depression symptoms over the course of treatment. Lower income individuals, although showing significant improvement, had slightly worse outcomes compared to higher income individuals, particularly at later stages of measurement	Retrospective analysis of data from 5426 patients undergoing telepsychiatric treatment for depression, sourced from Brightside Health Inc. Propensity matching and repeated measures ANOVA were employed to compare depression severity changes between lower and higher income groups using PHQ-9 scores over time
Factors shifting preference toward telemedicine in the delivery of skin cancer reconstruction care; Du *et al*[11]	Preferences for telemedicine in oncology care	Majority of patients preferred in-person visits over telemedicine options, however noted shift towards tele-medicine, influenced by costs and wait times	Cross-sectional survey using a custom scenario-based survey, distributed both online and in-person
Implementation and outcomes of virtual care across a tertiary cancer center during COVID-19; Berlin *et al*[14]	Care delivery volumes, quality of care, patient and practitioner experiences, cost savings to patients	Virtual care effectively maintained outpatient caseloads, ensured care quality, and achieved high satisfaction rates among patients and practitioners	Implemented a virtual care management system across a tertiary cancer center, assessed through a cohort study involving care delivery data, quality measures, and satisfaction surveys from March 23 to May 22, 2020

COVID-19: Coronavirus disease 2019; PHQ-9: Patient Health Questionnaire-9.

effectively, emphasizing the need for secure, high-quality video calling software and robust internet connections to ensure optimal patient care[13].

Amazon Clinic's entry into the telemedicine sector marks a significant milestone amid these developments. This evolution can be traced back to the COVID-19 pandemic when virtual care platforms were implemented to maintain outpatient caseloads. The success of these platforms, noted for their quality of care, patient retention, and high satisfaction rates among patients and providers, was underscored in a study from Berlin[14]. They demonstrated significant adoption with 440 practitioners (76%) and 22085 virtual clinics (VC) visits, achieving the goal of over 50% ambulatory visits *via* VC. Patient satisfaction was high for VC, with 68% recommending this care model, and the implementation led to substantial cost savings[14].

Leveraging its vast consumer network and technological acumen, Amazon is uniquely poised to make a breakthrough in mass healthcare delivery. Prior to launching Amazon Clinic, the e-commerce behemoth had already ventured into this domain by introducing a digital pharmacy. This initiative's success has allowed them to expand their efforts with the introduction of the Amazon Clinic. The telehealth landscape has seen prior endeavors by tech titans such as Google and IBM, albeit with limited success. In 2015, Google's foray into this realm materialized as Google Helpouts, a platform facilitating digital interactions between doctors and patients. The venture did not gain traction primarily due to stringent healthcare regulations and the challenge of navigating an industry outside of Google's primary expertise. Similarly, IBM's

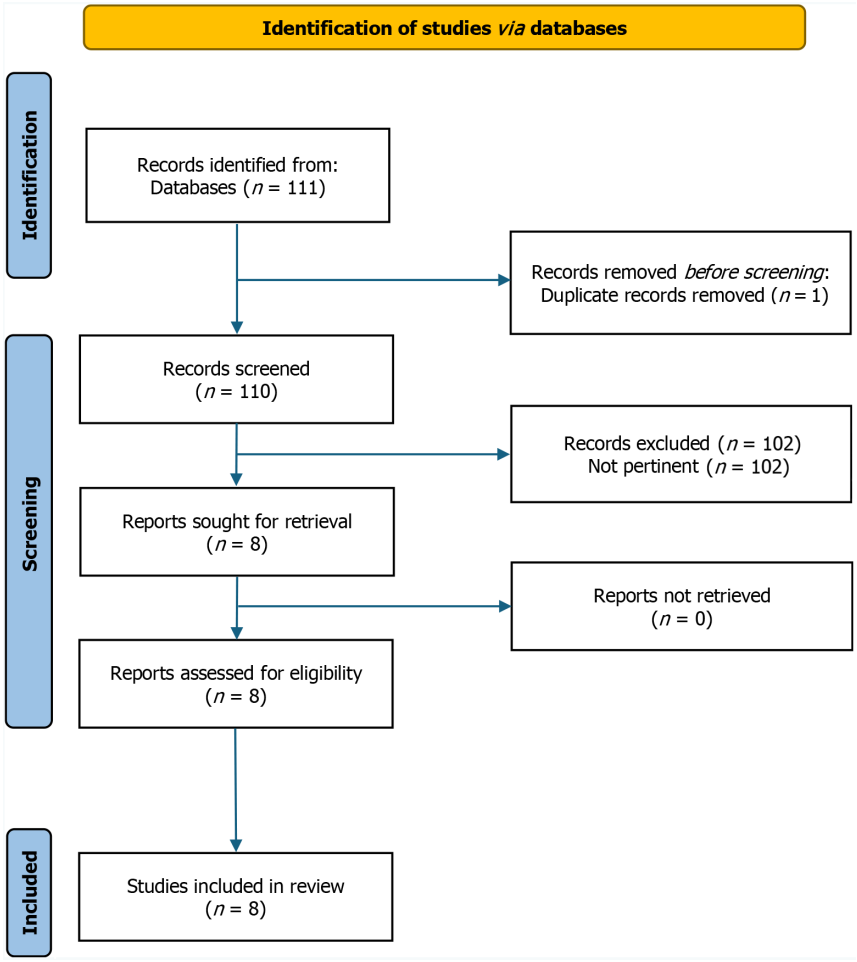

Figure 1 PRISMA 2009 flowchart for selecting studies for telehealth literature search.

Watson Health Unit encountered difficulties integrating healthcare with Artificial Intelligence and was unable to deal with scaling issues essential for nationwide expansion[15].

Based on the scoping review above, we have also conducted a SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis to outline the potential trajectory and implications of the newest entrant, Amazon Clinics, and compare it with the leading, concurrent virtual healthcare platforms.

DISCUSSION

SWOT analysis

A SWOT analysis is a strategic planning tool that helps projects identify their Strengths, Weaknesses, Opportunities, and Threats. This methodological framework provides a comprehensive view of the current landscape, enabling effective decision-making and strategy development[16].

Strengths

Amazon, a global e-commerce giant, is making a foray into virtual healthcare[3]. Given its global brand recognition, vast consumer base, and implicit trust, the company is best placed to make this venture successful. The factors outlined below will aid its swift user adoption:

Existing data: Since Amazon already has vital customer details, like credit card information and home addresses, the initial setup process for users is just a few clicks away[17].

Nationwide access: The service's nationwide availability ensures that users can access it anywhere within the country, even when traveling[18].

On-demand model: This approach mirrors Amazon's strength in other sectors. It offers 24/7 healthcare on the go, suiting modern consumers' desire for prompt services[19].

Transparent pricing with flexible payment options: Amazon's virtual healthcare service eliminates cost ambiguities with clear fee structures such as $75 for video appointments and $35 for text-based consultations[9]. Patients are consistently informed of the costs of their care, ensuring no surprise charges. Moreover, accepting FSA (Flexible Spending Account) and HSA (Health Savings Account) cards adds another layer of payment flexibility, catering to various financial

preferences and needs[20].

Insurance: The competitive pricing structure democratizes telehealth access, potentially enhancing overall health outcomes for a broader population segment, many of whom may be without insurance coverage[20].

Partnerships: By collaborating with prominent online telehealth platforms like Curai Health, Hello Alpha, SteadyMD, and Wheel, Amazon Clinic allows users to choose their preferred interface[10]. Moreover, slight price variations among these platforms afford patients additional cost choices[20].

Certified and Local Physicians: A key assurance for patients is that all physicians in Amazon's virtual healthcare service are board-certified, licensed, and located within the U.S. This establishes a standard of care and professionalism that patients expect from licensed providers. This standardization ensures that patients consult with professionals trained in high-quality care[19]. Consultations with a licensed physician remove the ethical considerations that may have been associated with direct-to-consumer healthcare products[21].

Artificial intelligence-powered patient intake: Amazon has integrated artificial intelligence (AI) capabilities to streamline the patient registration process[20]. This innovative addition ensures a smooth and efficient onboarding experience, reducing potential hurdles and waiting times typically associated with healthcare registrations. By utilizing AI, patients can expect a more intuitive and user-friendly intake, which enhances their overall experience from the first interaction[22].

Diverse health condition coverage: Amazon's virtual healthcare service offers treatment for a broad spectrum of health conditions, from common skin issues like acne and eczema to prescribing birth control pills. This wide-ranging scope ensures that a diverse patient population can find the care they need, thus making the service versatile and comprehensive[19].

Weaknesses

The Amazon telehealth program, while innovative, also has certain limitations. One primary concern is that it does not cover the pediatric population[20], which excludes a significant portion of the population from receiving virtual healthcare for basic health needs. Moreover, denying insurance plans could deter patients who are unwilling to pay directly and those who do not have any copay for their visits when using insurance[23].

While online messaging and video consultations offer quick healthcare access, they fail to deliver a personalized experience[24]. There needs to be consistent patient-doctor relationship building, which is crucial for establishing trust. Each consultation might pair a patient with a different doctor, disrupting continuity of care. The platform might be adequate for treating common conditions, but it struggles with more complicated healthcare needs. Especially with the aging United States population having multiple health issues[25], managing numerous previous records and devising detailed treatment plans is challenging in such an on-demand setup. Obtaining patients' prior health records for continuity of care will be difficult unless Amazon has a secure portal for patients to upload their data. Additionally, there is no coverage provided for behavioral health conditions or therapies, although these problems make up for a significant disease burden[26].

Furthermore, continuity with a consistent care team is vital for advising patients on lifestyle changes, and this model's fragmented approach could hinder the uptake of such guidance. Understandably, surgical procedures and other hands-on treatments are beyond their reach. Additionally, if the consulting physician isn't locally based, they might need to be made aware of the best diagnostic and imaging facilities available or their reliability. This geographical disconnect also negates the possibility of a physical examination, a fundamental diagnostic tool. Common parts of physical examination, like blood pressure checks, must rely on the functionality of the patient's equipment, its appropriate condition, and the patient's ability to use it properly. Relying solely on video calls compromises diagnostic accuracy[27], increasing the risk of medical errors of omission and commission.

Opportunities

Numerous opportunities can render this venture successful for Amazon and contribute to the broader objective of enhancing healthcare access for the United States population. The younger demographic, particularly college students, has increasingly sought healthcare opinions from unreliable digital platforms such as YouTube and TikTok[28]. Amazon's clinic can bridge this gap by appealing to college students through strategies like issuing student discounts.

Amazon can collaborate with existing traditional healthcare systems. They can augment patient care by leveraging their hospitals, field expertise, and local market presence, offering a more personalized experience to patients. Amazon's potential expansion of its services beyond mere consultations to include integration with laboratories, specialists, and other healthcare services is a viable prospect. With its pricing model, Amazon could cater specifically to the uninsured segment of the population.

Another possibility is introducing a subscription system for patients. Such a system would allow them to have multiple consultations within a specified period without incurring individual charges. This approach could enhance coverage and lead to more universal healthcare access. Successful government-run programs offering universal healthcare coverage, as seen in Canada, the United Kingdom, and recently in India[29], can be referenced as models for this endeavor.

Additionally, there is an option to monitor and analyze the data from many wearable devices which track health data such as the Fitbit Sense, Samsung Galaxy Watch, Garmin watch, and Apple Watch, potentially expanding outreach and providing actionable information to the patients from this data[30].

Amazon can also utilize Amazon Web Services and Internet of Things to telemonitor certain health conditions and physiological parameters[31]. Amazon can also collaborate with services, which can provide physiological data about a patient's sleep, crucial to overall health. Targeted marketing approaches can further enhance outreach.

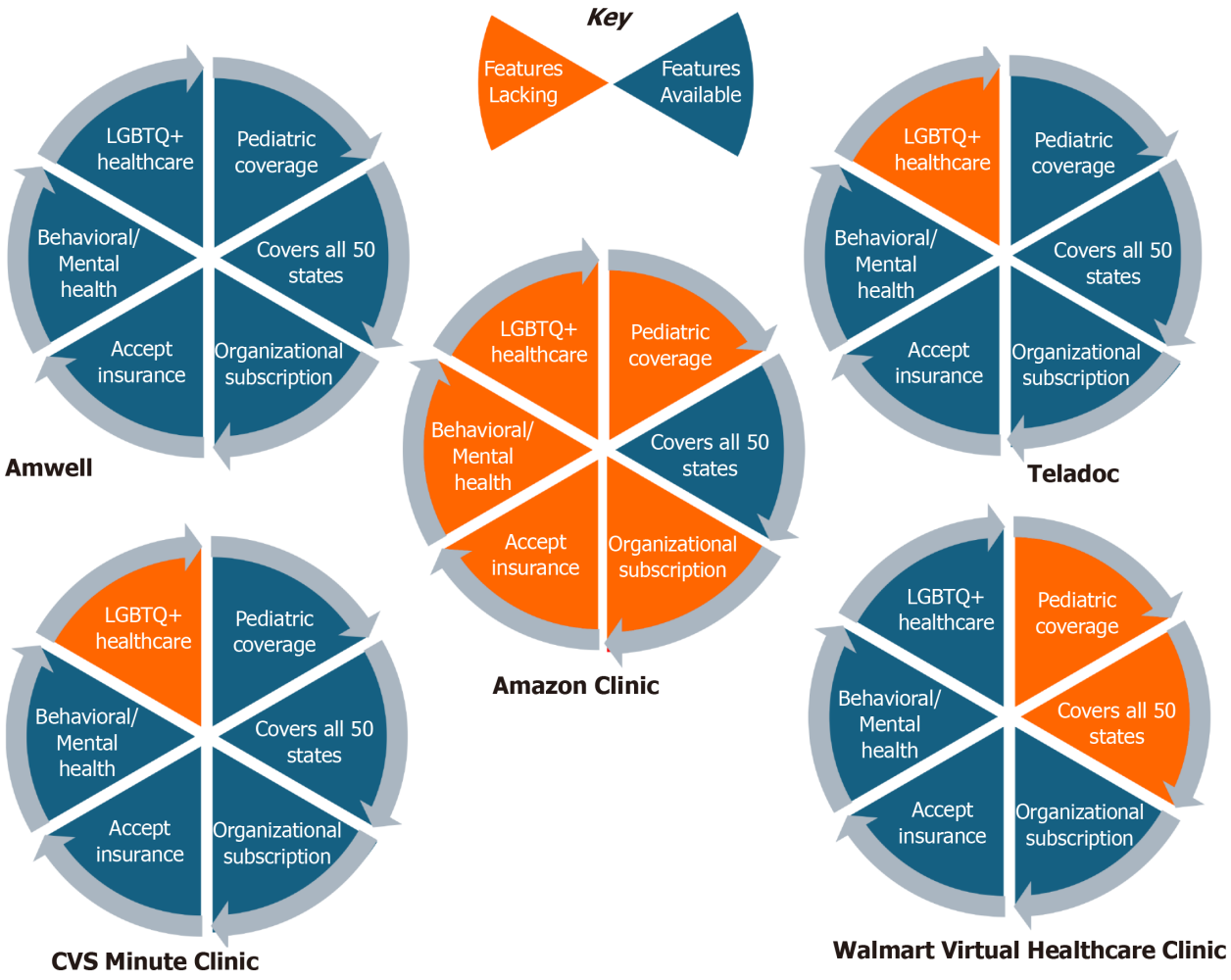

Figure 2 Comparative analysis between amazon clinic and the concurrent leading virtual healthcare providers.

Lastly, Amazon could intertwine its telehealth services with other offerings, like pharmacy services, to create a comprehensive end-to-end healthcare solution. This integration would increase the accessibility of reliable healthcare, strengthening Amazon's position in the healthcare industry.

Threats

Established healthcare systems present constant challenges to new entrants like Amazon Clinic. These traditional providers serve a large population and offer a mix of in-person and virtual visits. Amazon Clinic doesn't offer in-person visits, which puts it at a disadvantage compared to these established players. Additionally, traditional healthcare systems are working hard to enhance their online services, but they have the advantage of existing doctor-patient relationships.

Other competitors in this space, such as CVS Minute Clinic, Amwell[32], Teladoc[33], and Walmart Health Virtual Clinic[34], each have their unique strengths and weaknesses, making the field highly competitive. For example, CVS Minute Clinic accepts insurance[35], and Walmart Health Virtual Clinic provides therapy for teens, services that Amazon Clinic doesn't currently offer[34]. Multiple competitors provide access to pediatric virtual healthcare and organizational/enterprise subscription plans which remain a significant threat for wider outreach of Amazon Clinic. Also, the lack of care targeted towards the LGBTQ + community[36] is conspicuously absent, which is provided by competitors like Amwell. Amazon Clinic currently needs to catch up in a few areas, as summarized in Figure 2.

Legal aspect

The ever-changing regulatory environment in healthcare poses a risk, as new regulations disrupt the on-demand healthcare business model. Violation of the Stark law[37] in certain situations due to conflict of interest also remains a potential challenge. Lastly, there could be public concerns over Amazon treating healthcare more as a business than a service, potentially leading to conflicts of interest or issues with public perception.

CONCLUSION

In summary, the telemedicine landscape is rapidly evolving, marked by innovations and challenges alike. Studies across

various aspects of telehealth reveal its potential to transform healthcare delivery, making it more accessible, efficient, and patient-centric. Amazon Clinic's entry into the telehealth space is marked by several strengths, including its vast consumer network, transparent pricing, and AI-powered patient intake. However, challenges include the need for more pediatric care, the absence of insurance acceptance, and the potential for fragmented patient-doctor relationships. Opportunities exist for Amazon to bridge healthcare gaps, especially among younger demographics and the uninsured, through strategic collaborations and service expansions. Yet, threats from established healthcare providers, other competitors and evolving regulatory landscapes could hinder its growth. Overall, telemedicine's impact will depend on how effectively it navigates the inherent challenges and leverages opportunities in this ever-changing field.

FOOTNOTES

Author contributions: Grewal H and Kashyap R conceptualized the study and coordinated the research activities; Dhillon G and Budhavarapu V contributed to data analysis, literature review; Verma R, Munjal R, and Sharma P contributed to data collection, methodology section; Sidhu G performed manuscript editing and proofreading; Surani S reviewed and supervised the manuscript.

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META-ANALYSIS

Comparative efficacy of hyperbaric bupivacaine *vs* hyperbaric ropivacaine in spinal anesthesia for cesarean section: A meta-analysis

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Abstract

BACKGROUND

Intrathecal bupivacaine is the traditional anesthetic drug used in spinal anesthesia for caesarean sections (CSs), but ropivacaine has emerged as a potential alternative. This meta-analysis compares the efficacy and safety of intrathecal hyperbaric bupivacaine *vs* hyperbaric ropivacaine for cesarean sections.

AIM

To systematically evaluate and compare the efficacy and safety of intrathecal hyperbaric bupivacaine and hyperbaric ropivacaine for spinal anesthesia in CSs.

METHODS

A thorough search of electronic databases was carried out to find pertinent randomized controlled trials (RCTs) comparing intrathecal hyperbaric ropivacaine and hyperbaric bupivacaine during CSs. PubMed, Cochrane database, Google Scholar, and Scopus were searched, and papers from January 2000 to January 2024 were deemed eligible and filtered using predetermined inclusion and exclusion criteria. Studies were assessed for methodological quality, and data were extracted for time to adequate anesthesia (sensory and motor blockade), duration of sensory and motor block, hemodynamic changes and side effect profile. The standardized mean difference with 95%CI was used for continuous data. Dichotomous variables were assessed using the Mantel-Haenszel test and the random effect model to compute the odds ratio.

RESULTS

Total 8 RCTs were selected from a pool of 119 search results for meta-analysis. The meta-analysis evaluated pooled effect sizes and assessed heterogeneity

among the studies. The primary objective was to compare key outcomes to identify any significant variances in efficacy and safety profiles between two local anesthetics. The analysis revealed that the difference in the onset of sensory blockade between the two local anesthetics was statistically insignificant ($P = 0.1586$). However, the onset of motor blockade appeared to be faster with bupivacaine ($P = 0.03589$). Additionally, the regression of sensory and motor blockade occurred earlier in the ropivacaine group. Furthermore, the duration of the first analgesic effect was shorter with a significance level of $P < 0.05$. Regarding side effects profile, including hypotension, nausea, and shivering, the study did not observe any significant differences between the two groups.

CONCLUSION

This meta-analysis offers insights into the effectiveness and safety of hyperbaric bupivacaine *vs* ropivacaine for cesarean sections. Hyperbaric ropivacaine had a comparable safety profile and faster regression of sensory and motor blockade than hyperbaric bupivacaine, perhaps aiding early mobilization of parturient and facilitating mother-child bonding. Choosing ropivacaine may offer benefits beyond efficacy for cesarean section patients and short surgical procedures.

Key Words: Ropivacaine; Bupivacaine; Anesthesia; Spinal; Cesarean section; Meta-analysis

Core Tip: Hyperbaric bupivacaine had been the standard local anesthetic drug for spinal anesthesia in caesarean sections. Its drawbacks include high incidences of adverse events (hypotension, nausea) and delayed ambulation. Ropivacaine, a newer local anesthetic agent, offers potential advantages such as improved safety and shorter motor blockade duration. Recent marketing of heavy ropivacaine has reignited interest in this. This meta-analysis compares the hyperbaric preparation of ropivacaine and bupivacaine in the context of spinal anesthesia for cesarean sections. This analysis aims to shed light on the comparative benefits of these agents, paving the way for informed decision-making in obstetric anesthesia practices.

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INTRODUCTION

The latest data over the last 2 decades, encompassing 94.5% of global live births reveals significant increases in caesarean section (CS) rates worldwide. Approximately 21.1% of women underwent cesarean deliveries, with rates varying from 5% in sub-Saharan Africa to 42.8% in Latin America and the Caribbean. Notably, CS rates have been escalating in all regions since 1990, and projections indicate a further increase, with an estimated 28.5% of women globally expected to give birth *via* CS by 2030[1]. The CS contributes to a significant perioperative workload at many healthcare centers, underscoring the critical importance of their anesthetic management.

The choice between general anesthesia (GA) and neuraxial anesthesia (NA) for CS depends on various factors such as maternal co-morbidities, the urgency of the procedure, and the availability of equipment and expertise. NA, notably spinal anesthesia, is favored and widely adopted due to its ease of administration, rapid onset, high success rates, and documented improvements in maternal and fetal outcomes compared to GA[2]. Spinal anesthesia is widely acknowledged as a safe and efficient NA method for CS, providing benefits such as fewer neonatal complications, fewer block failures, and lower chances of aspiration pneumonia in compared to other NA techniques and GA respectively[3,4]. Bupivacaine and ropivacaine as amino amide local anesthetic agents have been widely used for spinal anesthesia. They are now available commercially as hyperbaric and isobaric preparations. Bupivacaine was discovered in 1957 and became available commercially in 1965. Its closely related compound, ropivacaine, underwent clinical trials starting in 1990 and was introduced clinically in 1996[5].

The ideal drug for spinal anesthesia should have minimal hemodynamic effects, provide appropriate anesthesia duration, ensure prompt return of sensation and movement, and have a favorable side effect profile[4]. For decades, bupivacaine, either hyperbaric or isobaric, had been the preferred choice for spinal anesthesia, backed by its extensive clinical history[6]. The baricity of local anesthetics is crucial in determining their distribution in the intrathecal space, influencing the anesthetic block level. Achieving a consistent sensory blockade with an isobaric solution may be unpredictable during pregnancy, which alters local anesthetic requirements and increases variability in sensory block extension. The hyperbaric solution was preferrable due to more predictable sensory blockade in spinal anesthesia[7]. However, significant hypotension occurs during its administration. It is manageable with fluids and vasopressors, but it can lead to nausea and vomiting, negatively impacting the patient experience during the perioperative period[8]. However, intrathecal bupivacaine associated with prolonged sensory blockade and delayed motor function recovery extends post-delivery stay in the post-anesthesia care unit. It may delay bonding with the neonate after childbirth[9].

Reducing the local anesthetic dose, incorporating adjuvants, and considering alternatives such as ropivacaine and levobupivacaine can help diminish side effects without compromising anesthesia efficacy[10].

Ropivacaine, an S-enantiomer amide local anesthetic like bupivacaine, has been studied for spinal anesthesia in obstetric patients undergoing cesarean deliveries[4,11,12]. Ropivacaine has shown comparable efficacy with minimal impact on hemodynamics and shorter duration of sensory and motor blocks, enhancing recovery and patient safety[13]. With the introduction of hyperbaric ropivacaine for commercial use, its application among anesthesiologists should rise. Notably, no prior meta-analysis has directly compared hyperbaric ropivacaine with hyperbaric bupivacaine without additional adjuvants in obstetrical setting, making this meta-analysis an important effort to fill this knowledge gap. This meta-analysis attempts to evaluate the comparative effectiveness of intrathecal bupivacaine *vs* intrathecal ropivacaine, focusing on hyperbaric preparations without adjuvants, in CS.

MATERIALS AND METHODS

This meta-analysis adhered to the preferred reporting items for systematic reviews and meta-analyses guidelines. It focused on women scheduled for elective CSs under spinal anesthesia receiving either intrathecal hyperbaric bupivacaine or hyperbaric ropivacaine without any adjuvant.

Objective

To compare the efficacy and safety of hyperbaric intrathecal bupivacaine and hyperbaric intrathecal ropivacaine for spinal anesthesia in cesarean section by assessing: (1) Onset and duration of sensory and motor blockade; (2) Duration of analgesia; (3) Incidence of hypotension; and (4) Frequency of adverse effects (nausea and shivering).

Research question for meta-analysis

What is the comparative efficacy and safety of hyperbaric intrathecal bupivacaine *vs* hyperbaric intrathecal ropivacaine in terms of onset, duration, and regression of sensory and motor blockade, duration of analgesia, incidence of hypotension, nausea and shivering in women undergoing cesarean section?

Inclusion criteria

The study selection criteria comprised randomized controlled trials (RCTs) comparing hyperbaric intrathecal bupivacaine with hyperbaric intrathecal ropivacaine in patients undergoing cesarean sections.

Studies: RCTs.

Population: Adult women (age > 18 years) American Society of Anesthesiologists I-II, undergoing elective or semi-elective cesarean section.

Interventions: Hyperbaric intrathecal ropivacaine.

Comparison: Hyperbaric intrathecal bupivacaine.

Outcomes: Studies must report data on duration of the sensory blockade, motor blockade, duration of analgesia, incidence of hypotension, and frequency of side effects (*e.g.*, nausea, vomiting, and shivering).

Exclusion criteria

Studies not employing randomized controlled trial design. Studies including emergency cesarean sections. Studies with unavailable data on the specified outcomes. Studies with significant methodological flaws. Studies using additional medications alongside local anesthetics which could affect the outcomes.

Search strategy

A comprehensive search approach was undertaken, including a variety of search phrases across significant databases such as MEDLINE (*via* PubMed), Scopus, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from January 2000 to January 2024. The search terms covered aspects related to the population (including key words "Cesarean section", "cesarean delivery", "parturient", and "obstetrical"), interventions (such as "hyperbaric bupivacaine", "hyperbaric ropivacaine", "intrathecal bupivacaine", "intrathecal bupivacaine", and "spinal anesthesia"), outcomes (key words "sensory block", "motor block", "analgesia", "hypotension", and "side effects"), and randomized controlled trial requirements. The search procedure was deliberately refined using "Boolean operators" (AND, OR, NOT). Only English language studies were considered, and other language articles were excluded. Trial registers were also searched for trials at the completion stage.

Statistical analysis

Two reviewers conducted data extraction independently, with any discrepancies resolved through discussion or consultation with a third reviewer if needed. The extracted data encompassed study characteristics, participant demographics, intervention specifics, and outcomes systematically.

A random-effects model was employed to compute summary effect estimates for continuous outcomes (*e.g.*, duration of sensory and motor block) and risk ratios for dichotomous outcomes (*e.g.*, incidence of hypotension). Heterogeneity was assessed using the I^2 statistic, while a qualitative evaluation of studies investigated potential sources of heterogeneity. Funnel plots and Egger's test assessed publication bias.

For data collection Microsoft Excel 365[14] was used. Subsequently, data analysis was performed using the online web tool[15] [based on the Meta and Metafor packages, R programming environment (R version 4.2.2)] and results verified with Jamovi statistical software package [Version 2.5.6][16].

RESULTS

Two reviewers conducted a literature search between April 1, 2024, and May 31, 2024. They initially identified 115 records through database searching across platforms such as PubMed, Scopus, Cochrane, and Google Scholar. They found 4 more records through clinical trial registries. For a total of 119 records subjected to initial screening (Figure 1). After removing duplicates, the total number of records was reduced to 89. Among these records, 1 was excluded due to being in a non-English language, while 4 were excluded for being incomplete trials. Following the initial screening, 84 full-text articles were assessed for eligibility, out of which 76 articles were excluded as they did not meet the inclusion criteria. Finally, 8 studies were included in the quantitative synthesis, forming the basis for the meta-analysis findings (Table 1)[18-25]. All studies were assessed for risk of bias using the revised Cochrane risk of bias tool for randomized trials RoB 2.0[17] with assessment based on journal article content (Figure 2).

In the analysis of 8 studies[18-25] involving a total of 288 subjects in the ropivacaine cohort and 293 subjects in the Bupivacaine cohort, a comparison was made using a random effects model with the Inverse variance method (summarized standardized mean difference) for continuous variables (Table 2, Figure 3).

A comparison was made between the ropivacaine and bupivacaine cohorts, using the Mantel-Haenszel method to determine the risk ratio (Table 3, Figure 4). The results showed no significant difference between the two cohorts. Ropivacaine had a lower incidence of hypotension, nausea and shivering as suggested by risk ratio analysis, but the results lack statistical significance. No heterogeneity was indicated by I^2 values, which indicated consistency in results among studies.

Result summary

Onset of blockade: Intrathecal ropivacaine and bupivacaine exhibited a similar onset of sensory blockade, but ropivacaine showed delayed onset of complete motor blockade.

Duration of block: Ropivacaine demonstrated a significantly shorter time to achieve sensory regression, complete motor blockade recovery, and analgesia duration compared to bupivacaine.

Side effects: The frequency of side effects such as hypotension, nausea, and shivering appeared lower with ropivacaine, although statistical significance was not established in this analysis.

Publication bias analysis

Multiple parameters were subjected to funnel chart tests and Eggers tests. The analysis suggests publication bias in the onset and regression of sensory blockade and regression of motor blockade. However, funnel charts of the onset of motor blockade, analgesia duration and incidence of hypotension suggest lack of bias (Figure 5). Egger's test results supported the findings (Table 4).

DISCUSSION

This meta-analysis, which included 8 research studies with 288 participants in the ropivacaine group and 293 participants in the Bupivacaine group, examined the effects of spinal anesthesia on parameters during cesarean sections using hyperbaric solutions. All findings were subjected to appropriate statistical analysis.

Block characteristics

This meta-analysis aimed to compare the onset and duration of sensory and motor blockade, duration of analgesia and side effect profile, between hyperbaric solutions of ropivacaine and bupivacaine in the clinical context of spinal anesthesia for cesarean section. Our findings indicate that while ropivacaine exhibited a faster onset of sensory blockade, this difference did not reach statistical significance. However, there was a significantly longer onset time for complete motor blockade with ropivacaine compared to bupivacaine. Conversely, ropivacaine demonstrated a quicker and more significant regression of both blockade and motor blockade. The post-spinal duration of analgesia was lower with statistical significance in the case of ropivacaine.

The quicker onset of motor blockade observed with bupivacaine is consistent with prior research and is probably due to its higher lipid solubility when compared to ropivacaine. While the disparity in onset times for sensory and motor blockade may not be clinically significant during elective surgical procedures due to minor variations, the faster regression time could promote early mobility and shorten recovery. In obstetric anesthesia, this faster regression time might aid in early bonding between mother and child and facilitate breastfeeding, potentially leading to higher

Table 1 Study characteristics

Ref.	Type	Blinding	Randomisation	Sample size		Hyperbaric drug concentration		Dose (mg)	
				R	B	R	B	R	B
Kiran *et al*[18], 2023	RCT	Double	Unclear	30	30	0.75	0.5	15	10
Kasza *et al*[19],2006	RCT	Single	Random allocation	36	39	0.75	0.5	15	10
Lunia *et al*[20], 2023	RCT	Double	Unclear	43	43	0.75	0.5	15	10
Shah *et al*[21], 2023	RCT	Double	Unclear	40	40	0.75	0.5	15	10
Chung *et al*[22], 2001	RCT	Double	Random number table	30	30	0.5	0.5	18	12
Subba *et al*[23], 2019	RCT	Single	Random number table	30	30	0.5	0.5	15	12.5
Modi *et al*[24], 2017	RCT	Single	Random number table	40	40	0.5	0.5	15	10
Srivastava *et al*[25], 2012	RCT	Double	Sealed envelop	39	41	0.5	0.5	15	11

B: Bupivacaine; RCT: Randomized control trial; R: Ropivacaine.

Table 2 Results for continuous variable

Parameter	Standardized mean difference	95%CI	*P* value	I^2	Interpretation
Onset of sensory blockade	1.07	-0.73 to 2.87	0.2	0.95	Statistically insignificant. High heterogeneity. Ropivacaine group is comparable to bupivacaine
Onset of complete motor block	0.91	0.07-1.74	< 0.05	0.92	Significant difference. High heterogeneity. Bupivacaine is faster in onset than ropivacaine
Sensory blockade regression	-0.92	-1.81 to -0.03	< 0.05	0.93	Significant difference. High heterogeneity. Regression is faster with ropivacaine
Motor blockade recovery	-1.24	-2.15 to -0.32	< 0.05	0.94	Significant difference. High heterogeneity. Recovery is faster with ropivacaine
Duration of analgesia	-0.68	-1.18 to -0.19	< 0.05	0.79	Significant difference. High heterogeneity. Duration of analgesia is longer with bupivacaine

Table 3 Side effects profile evaluation

Parameter	Risk ratio	95%CI	*P* value	Heterogeneity (I^2)	Interpretation
Hypotension	0.86	0.72-1.03	0.58	0	No significant difference was observed in hypotension risk
Nausea and Vomiting	0.85	0.58-1.23	0.86	0	No significant difference was observed in nausea and vomiting risk
Shivering	0.81	0.45-1.45	0.58	0	No significant difference was observed in shivering risk

Table 4 Eggers test results

Parameter	Publication bias	Publication bias (Egger's test)
Onset of sensory blockade	Yes	Yes (t = 4.914, P = 0.003)
Onset of complete motor block	No	No (t = 2.02, P = 0.099)
Sensory blockade regression	Yes	Yes (t = -3.199, P = 0.019)
Motor blockade recovery	Yes	Yes (t = -2.754, P = 0.033)
Duration of analgesia	No	No (t = -0.345, P = 0.744)

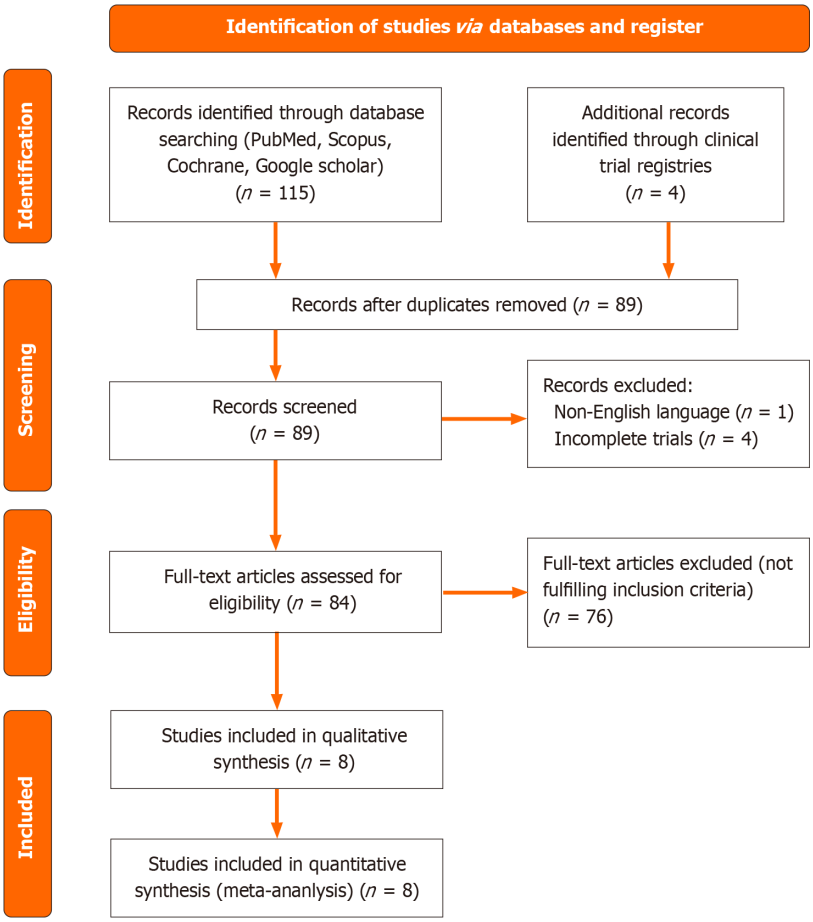


Figure 1 Flow diagram as per Preferred Items for Systematic Reviews and Meta-Analysis guidelines.

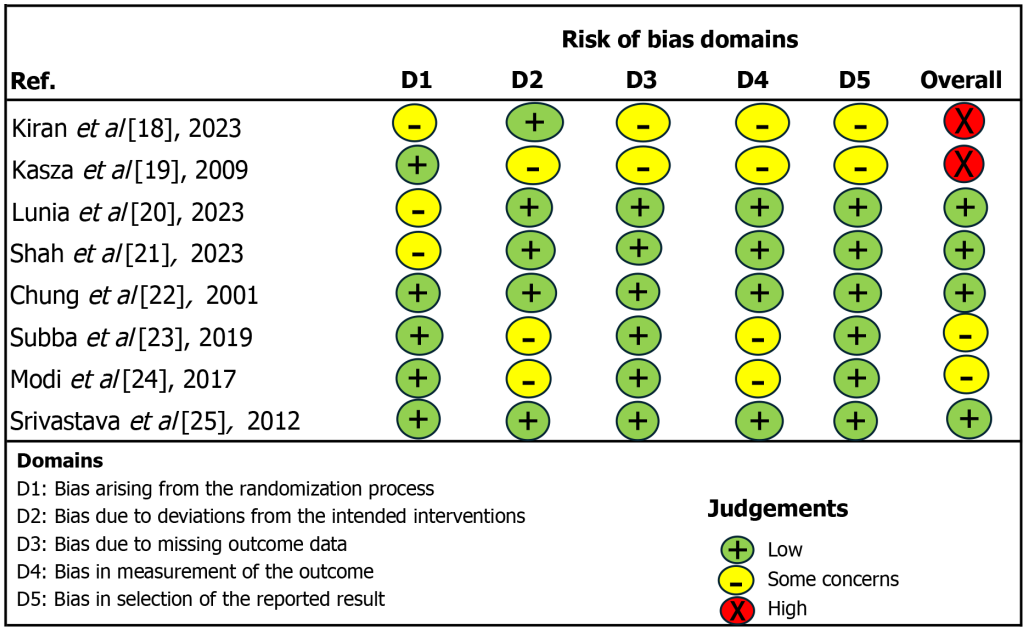


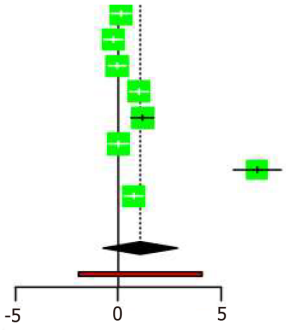
Figure 2 Risk of bias assessment using RoB 2.0.

satisfaction levels. Conversely, the shorter duration of analgesia provided by ropivacaine could lead to an earlier need for analgesic medication. For short-duration procedures, ropivacaine can be used with equivalent efficacy to bupivacaine in terms of block characteristics. However, cases of prolonged surgery may require higher conversion rates to GA. Anesthesiologists may prefer either drug depending on their clinical needs, as local anesthetics have advantages and downsides.

A

Ref.	Ropivacaine			Bupivacaine				SMD, 95%CI
	Mean	SD	Total	Mean	SD	Total	Weight	
Kiran *et al* [18], 2023	2.39	0.49	30	2.31	0.58	30	12.70%	0.15 (-0.36 to 0.65)
Kasza *et al* [19], 2009	6.10	1.10	36	6.40	1.40	39	12.80%	-0.23 (-0.69 to 0.22)
Lunia *et al* [20], 2023	4.27	1.64	43	4.35	1.51	43	12.90%	-0.05 (-0.47 to 0.37)
Shah *et al* [21], 2023	4.13	0.79	40	3.40	0.63	40	12.80%	1.01 (0.55 - 1.48)
Chung *et al* [22], 2001	10.60	2.20	30	8.10	2.00	30	12.60%	1.17 (0.62 - 1.72)
Subba *et al* [23], 2019	4.87	1.72	30	4.87	1.46	30	12.70%	0.00 (-0.51 to 0.51)
Modi *et al* [24], 2017	11.45	0.46	40	8.03	0.54	40	10.60%	6.75 (5.59 - 7.91)
Srivastava *et al* [25], 2012	9.70	2.24	39	7.66	3.00	41	12.80%	0.76 (0.31 - 1.22)
Total			**288**			**293**	**100.00%**	**1.07 (-0.73 to 2.87)**
Prediction interval								(-1.93 to 4.07)
Heterogeneity:	τ^2=1.3254 ; χ^2 = 145.77, df = 7 (P < 0.01) , I^2 = 95%							
Test for overall effect:	t_7 = 1.41 (P = 0.20)							

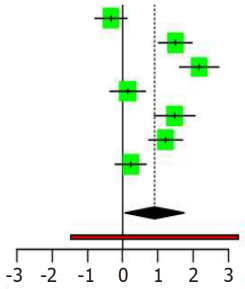
Forest chart



B

Ref.	Ropivacaine			Bupivacaine				SMD, 95%CI
	Mean	SD	Total	Mean	SD	Total	Weight	
Kiran *et al* [18], 2023	10.40	2.20	36	11.20	2.60	39	14.50%	-0.33 (-0.78 to 0.13)
Lunia *et al* [20], 2023	11.95	3.78	43	6.83	2.97	43	14.40%	1.49 (1.01 - 1.97)
Shah *et al* [21], 2023	7.10	0.84	40	5.28	0.82	40	14.00%	2.17(1.61 - 2.73)
Chung *et al* [22], 2001	6.30	2.20	30	6.00	1.90	30	14.30%	0.14 (-0.36 to 0.65)
Subba *et al* [23], 2019	14.33	6.19	30	7.53	1.72	30	13.90%	1.48 (0.90 - 2.05)
Modi *et al* [24], 2017	8.45	1.06	40	6.90	1.43	40	14.40%	1.22 (0.74 - 1.70)
Srivastava *et al* [25], 2012	6.97	2.36	39	6.40	2.58	41	14.60%	0.23(-0.21 to 0.67)
Total			**258**			**263**	**100.00%**	**0.91 (0.07 - 1.74)**
Prediction interval								(-1.47 to 3.28)
Heterogeneity:	τ^2 = 0.7410; χ^2 = 75.90, df = 6 (P < 0.01); I^2 = 92							
Test for overall effect:	%t_6 = 2.65 (P = 0.04)							

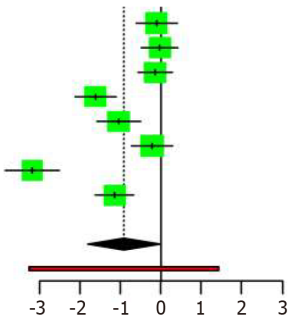
Forest chart



C

Ref.	Ropivacaine			Bupivacaine				SMD, 95%CI
	Mean	SD	Total	Mean	SD	Total	Weight	
Kiran *et al* [18], 2023	72.67	12.37	30	73.83	9.44	30	12.50%	-0.10 (-0.61 to 0.40)
Kasza *et al* [19], 2009	129.00	29.00	36	130.00	24.00	39	12.70%	0.04 (-0.49 to 0.42)
Lunia *et al* [20], 2023	121.80	37.18	43	127.50	41.03	43	12.80%	-0.14 (-0.57 to 0.28)
Shah *et al* [21], 2023	70.50	10.85	40	87.75	10.25	40	12.50%	-1.62 (-2.13 to -1.11)
Chung *et al* [22], 2001	162.50	20.20	30	188.50	28.20	30	12.40%	-1.05 (-1.59 to -0.50)
Subba *et al* [23], 2019	131.50	38.71	30	140.50	41.03	30	12.50%	-0.22 (-0.73 to 0.29)
Modi *et al* [24], 2017	107.60	6.33	40	128.00	6.34	40	11.90%	-3.19 (-3.86 to -2.52)
Srivastava *et al* [25], 2012	110.60	12.00	39	135.00	26.80	41	12.60%	-1.15 (-1.63 to 068)
Total			**288**			**293**	**100.00%**	**-0.92 (-1.81 to -0.03)**
Prediction interval								(-3.27 to 1.43)
Heterogeneity:	τ^2 = 0.8098; χ^2 = 93.90, df = 7 (P < 0.01); I^2 = 93%							
Test for overall effect:	t_7 = -2.43 (P = 0.05)							

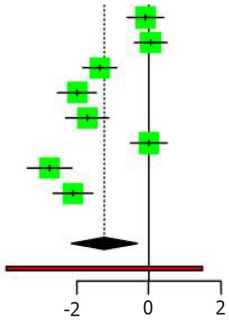
Forest chart



D

Ref.	Ropivacaine			Bupivacaine				SMD, 95%CI
	Mean	SD	Total	Mean	SD	Total	Weight	
Kiran *et al* [18], 2023	140.00	27.23	30	142.17	16.17	30	12.60%	-0.10 (-0.60 to 0.41)
Kasza *et al* [19], 2009	79.20	12.50	36	78.40	16.60	39	12.70%	0.05 (-0.40 to 0.51)
Lunia *et al* [20], 2023	105.80	43.37	43	163.13	39.98	43	12.70%	-1.36 (-1.83 to -0.89)
Shah *et al* [21], 2023	140.50	11.18	40	164.50	12.60	40	12.50%	-2.00(-2.54 to -1.45)
Chung *et al* [22], 2001	113.70	18.60	30	158.00	31.00	30	12.30%	-1.71 (-2.31 to -1.11)
Subba *et al* [23], 2019	98.50	34.47	30	98.50	34.47	30	12.60%	0.00 (-0.51 to 0.51)
Modi *et al* [24], 2017	102.75	12.03	40	146.00	18.40	40	12.20%	-2.76 (-3.37 to -2.14)
Srivastava *et al* [25], 2012	127.00	20.42	39	182.90	30.83	41	12.40%	-2.11 (-2.66 to -1.56)
Total			**288**			**293**	**100.00%**	**-1.24 (-2.15 to -0.32)**
Prediction interval								(-3.96 to 1.49)
Heterogeneity:	τ^2 = 1.0942; χ^2 = 114.17, df = 7 (P < 0.01); I^2 = 94%							
Test for overall effect:	t_7 = -3.20 (P = 0.02)							

Forest chart



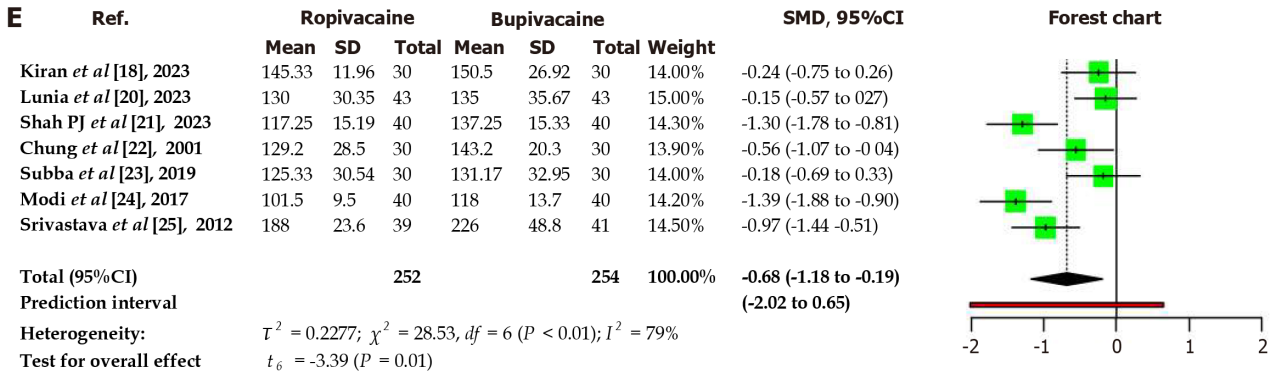


Figure 3 Forest chart and continuous variables. A: Forest chart, onset of sensory blockade to maximal level; B: Forest chart, time to complete motor blockade; C: Forest chart, time for sensory blockade regression; D: Forest chart, time to recover from motor blockade; E: Forest chart, duration of analgesia.

Ropivacaine, an S-enantiomer amide local anesthetic, exhibits a distinct nerve block profile by causing less motor nerve blockade compared to bupivacaine, possibly due to its lower potency, reduced lipid solubility, and selective blockade of sodium channels specific to pain-sensing neurons[26]. Reduced duration of a motor blockade could offer postoperative benefits such as a decreased immobilization period and a more favorable recovery profile. Another meta-analysis by Malhotra *et al*[12] compared ropivacaine with bupivacaine irrespective of the nature of the solution (hyperbaric/isobaric) and adjuvants. They also interpreted that intrathecal ropivacaine results in a shorter duration of motor block (P value < 0.0001) than intrathecal bupivacaine and this reduction in motor block duration is consistent regardless of the doses of ropivacaine and bupivacaine used. Their subgroup analysis further suggested that patients receiving intrathecal ropivacaine in CS experienced motor block resolution approximately 35.7 minutes earlier than those receiving intrathecal bupivacaine.

Khalil *et al*[27] conducted a meta-analysis comparing intrathecal ropivacaine with bupivacaine in non-obstetrical surgeries, yielding comparable results. Their study indicated that sensory and motor blockade duration was notably shorter in the ropivacaine group. Additionally, they observed a reduced hypotension and a decreased need for vasopressors. While our results align with theirs, the limited number of studies in our analysis hindered the attainment of statistical significance regarding the incidences of hypotension, nausea and shivering.

Heterogeneity

There was significant heterogeneity across studies for all outcomes except for the hypotension, nausea, and shivering. Heterogeneity suggests that other factors beyond the local anesthetic type might influence the results. It underscores the variability in study methodologies, patient populations, and drug concentrations, highlighting the need for caution when interpreting the findings. Studies were conducted with different ethnic populations, with single blinding in 3 studies[19,23,24] and double blinding in others. Four studies[22-25] in our metanalysis used 0.5 % ropivacaine whereas the rest used 0.75% ropivacaine heavy. In these studies, ropivacaine heavy was prepared by using dextrose instead of commercial preparation, except by Kiran *et al*[18] and Shah *et al*[21]. The dose varied among studies. These factors may influence block characteristics and may have contributed to heterogeneity. Further research is needed with due consideration for potential sources of this variation, such as differences in study populations, dosage regimens, or assessment techniques.

Publication bias

Evidence of publication bias was detected for the onset and regression of sensory blockade but not with the onset of motor blockade and categorical data. This may suggest variation in the assessment and reporting of sensory and motor blockade by authors as these are subjective, and variation may occur due to differences in assessment, time interval for observation, patient knowledge, and cooperation. Despite the wide time selection, only 8 studies fulfilled the inclusion criteria. It may have introduced time lag-bias, too. As 3 out of 8 studies were single-blinded, researcher bias and publication practice bias cannot be ruled out. Only English language paper selection is another source of potential bias. The presence of publication bias could potentially overestimate the observed effects. Although suggestive of publication bias, funnel plot asymmetry, should be interpreted with caution due to its limitations.

Side effects

There were no significant differences between ropivacaine and bupivacaine regarding the incidence of hypotension, nausea, vomiting, or shivering. However, incidences appear to be lower with ropivacaine. This meta-analysis suggests that both drugs have a comparable safety profile regarding these common adverse effects. Further studies with larger sample sizes will help in definitive interpretation regarding the incidence of adverse effects.

The meta-analysis highlights several key findings regarding hyperbaric ropivacaine as a drug in spinal anesthesia. Ropivacaine has shown a slower onset of motor blockade, which can enhance maternal comfort and safety during surgery by allowing for careful monitoring and time to manage adverse events. However, in obstetrical emergencies small difference in duration may affect neonatal outcome. It also features a faster regression of sensory blockade, enabling quicker recovery and early engagement with newborns, which is vital for bonding. Additionally, its faster motor

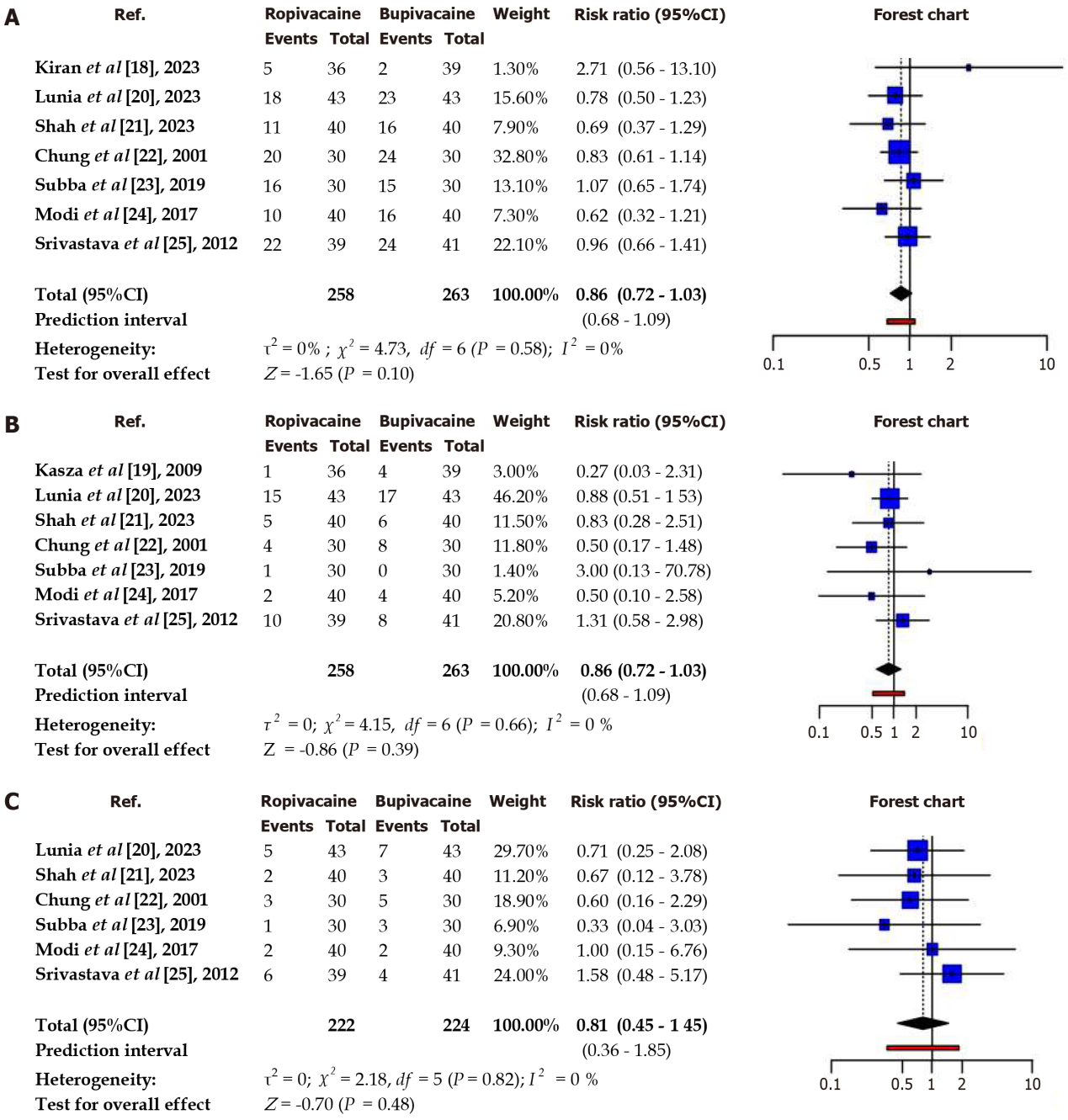


Figure 4 Forest chart and dichotomous variables. A: Forest chart incidence of hypotension; B: Forest chart incidence of nausea and vomiting; C: Forest chart incidence of shivering.

blockade recovery helps mothers regain mobility sooner, facilitating skin-to-skin contact. Although ropivacaine offers a shorter duration of analgesia compared to bupivacaine, this can be managed with supplemental analgesics, promoting quicker postoperative activity. Favorable risk ratios for side effects suggest that ropivacaine may lead to fewer adverse effects, such as hypotension, nausea, and shivering. This is crucial for enhancing maternal satisfaction and ensuring a positive experience during the perioperative period.

These findings emphasize the importance of individualized patient care, tailoring anesthetic choices based on individual needs and preferences. Anesthesiologists can make an informed decision after considering the benefits and trade-offs associated with each agent. Using ropivacaine as an alternative to bupivacaine in obstetrical anesthetic management may improve maternal experiences by providing effective anesthesia experience while minimizing adverse effects, supporting quicker recovery times and promoting early bonding between mother and neonate.

Future research should focus on research areas to enhance the understanding of hyperbaric ropivacaine and its effects in obstetric anaesthesia. First, comparative studies on dosage variations are needed to investigate how different dosages of hyperbaric ropivacaine and bupivacaine impact maternal and neonatal outcomes, with an emphasis on finding optimal dosing strategies that maximize analgesic efficacy while minimizing side effects such as hypotension and nausea. Additionally, longitudinal studies assessing maternal satisfaction over time post-cesarean delivery with various anaesthetic agents could provide insights into how anaesthetic choices influence long-term maternal well-being, bonding

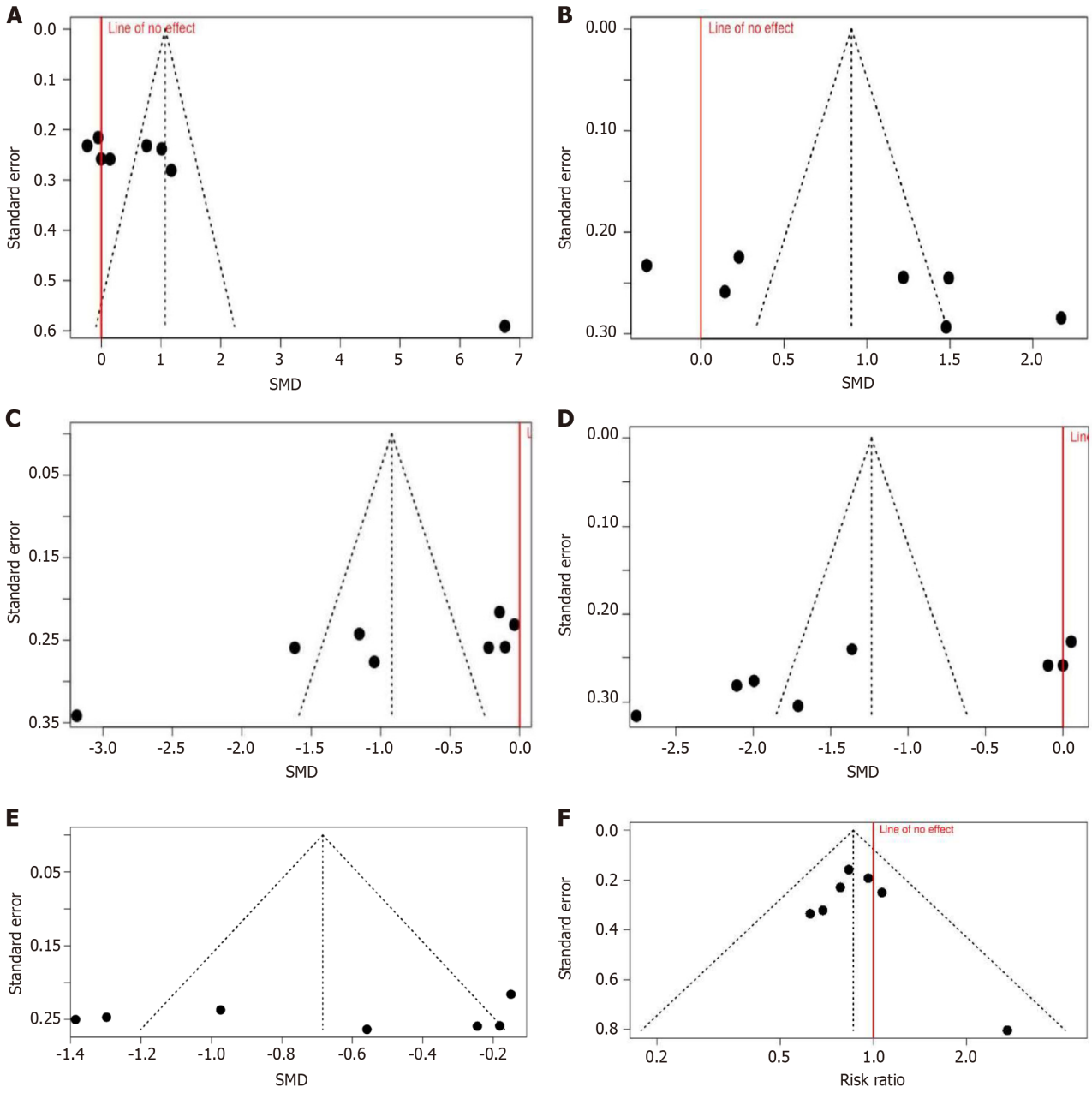


Figure 5 Funnel chart. A: Onset of sensory blockade; B: Onset of motor blockade; C: Sensory regression duration; D: Motor regression duration; E: Duration of analgesia; F: Incidence of hypotension. SMD: Standardized mean difference.

experiences, and psychological outcomes.

Moreover, research should focus on special populations, including patients with preeclampsia or comorbidities that complicate anesthesia management, to better understand their responses to different anesthetics. Finally, exploring patient-centred outcomes beyond satisfaction-such as quality of life measures, recovery times, and psychological impacts-will help inform more effective and individualized anaesthetic strategies in clinical practice.

Limitations

Heterogeneity: The included studies displayed significant heterogeneity, potentially impacting the outcomes of the meta-analysis.

Publication bias: There is a possibility of publication bias, particularly concerning sensory blockade results, which could have led to overestimating the observed effects.

Language restriction: Only English language papers were considered for inclusion, possibly limiting the diversity of data sources.

Incomplete trials: Registered ongoing trials utilizing commercially available preparations were incomplete, reducing the available sample size for analysis.

Future research: Further investigations with larger sample sizes and standardized methodologies must validate these findings and explore potential patient subgroups that may respond differently to ropivacaine or bupivacaine.

Unassessed parameters: The meta-analysis did not specifically evaluate postoperative pain scores, severity of hypotension, other side effects, and patient satisfaction, indicating areas for future research and analysis.

Absence of subgroup and sensitivity analyses: Outcome may differ due to variation in dose and concentration. However, we could not conduct subgroup analyses due to the limited number of studies and smaller subgroup sizes. Smaller subgroups may result in underpowered analysis with possibility of the false positive results leading to incorrect interpretation.

CONCLUSION

In conclusion, our meta-analysis suggests that ropivacaine has a comparable onset of sensory blockade, but a significantly longer onset time for complete motor blockade and a quicker regression of both sensory and motor blockade. Both drugs demonstrated a comparable safety profile regarding hypotension, nausea and vomiting, and shivering. The presence of heterogeneity and potential publication bias underscores the need for a cautious interpretation of the results and further research to clarify the clinical implications of these findings. However, based on this meta-analysis ropivacaine appears to be an acceptable alternative to bupivacaine heavy, particularly for short-duration surgeries where early ambulation may be beneficial.

FOOTNOTES

Author contributions: Anand R, Nag DS designed the overall concept and outline of the manuscript; Patel R, Sharma P, Uppalapati VK, Singh UK contributed to the discussion and design of the manuscript; Anand R, Nag DS, Patel R, Sharma P, Uppalapati VK, Singh UK contributed to this paper, the writing, and editing the manuscript and review of literature; all of the authors read and approved the final version of the manuscript to be published.

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SCIENTOMETRICS

Global trend of review articles focused on cardiopulmonary bypass: Perspectives from bibliometrics

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Peer-review report's classification

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Abstract

BACKGROUND

Cardiopulmonary bypass (CPB) is a life-support technology widely used in surgery. Review articles reflect research advances in a certain topic or field within a certain period of time.

AIM

To perform a bibliometric analysis of the review articles that focused on CPB for cardiovascular surgery.

METHODS

This study was based on a bibliometric analysis. Data were acquired from the Web of Science and basic bibliometric parameters were analyzed and visualized using VOSviewer and Excel.

RESULTS

We identified 141 review articles on CPB. Generally, the number of publications increased, and most of them were published in the 2010s (n = 57, 40.4%) and the 2020s (n = 45, 31.9%). There were 113 (80.1%) narrative review articles, 21 (14.9%) meta-analysis studies and 7 (5.0%) systematic review papers. The United States (n = 25, 17.7%) and China (n = 21, 14.9%) were the leading countries in terms of publication number. The articles were published in 98 different journals. The *Journal of Cardiothoracic and Vascular Anesthesia* (n = 14, 10.0%) and *Perfusion-United Kingdom* (n = 11, 7.8%) were preferred by the authors. The high-frequency keywords included inflammatory response, children, acute kidney injury, meta-

analysis and off-pump, except for CPB and cardiac surgery. Inflammatory response had the closest relationship with CPB during cardiac surgery. The complications of CPB, including inflammatory response, kidney injury and ischemia, caught lots of concern.

CONCLUSION
The rapid increase of review papers shows that the research on CPB in cardiac surgery is increasingly being emphasized by scholars and clinical staff worldwide. Meta-analysis has been widely conducted to analyze clinical controversies and further guide clinical practice. Strategies to improving the outcomes of patients undergoing cardiac surgery with CPB are the hot spots in this field.

Key Words: Cardiopulmonary bypass; Review article; Bibliometric analysis; Cardiac surgery; Hot spots

Core Tip: The present study analyzed the characteristics of review articles on cardiopulmonary bypass. The primary findings include: (1) The 141 review articles in Web of Science were identified, of which 113 (80.1%), 21 (14.9%) and 7 (5.0%) were narrative review, meta-analysis and systematic review, respectively; (2) The United States and China published most articles; and (3) Keywords analysis showed that inflammatory response, kidney injury and ischemia were highly focused in this field.

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INTRODUCTION

Cardiopulmonary bypass (CPB), also called extracorporeal circulation, is a life support technology that uses a series of special artificial devices to drain the returning venous blood outside the body, exchange gas, regulate temperature, filter it manually, and then transfuse it back into the arterial system of the body[1]. In the process of extracorporeal circulation, the artificial device replaces the human body function; therefore, an extracorporeal circulation machine is also called an artificial heart-lung machine. The purpose of CPB is to maintain the blood supply to tissues and organs throughout the body during open-heart surgery[1]. Merendino was the first surgeon who successfully conducted a series of cardiac surgery by CPB in the United States[1,2]. With the development of clinical medicine, the use of extracorporeal circulation continues to expand. It is not only applied in heart, liver, kidney, lung and other large vascular surgery, but has also made remarkable achievements in tumor treatment and life support for patients with cardiopulmonary failure, and has become an important technology in clinical medicine[3-7].

Although there have been many advances in CPB and cardiac anesthesia, such as hemodilution, mechanical components, heparin management, potential of hydrogen (pH) management, application of transesophageal echocardiography, and protection of major organs, high-level evidence of how we conduct CPB remains lacking[8]. More randomized controlled trials and large-sample cohort studies are still needed. Therefore, it is crucial to have a thorough knowledge of CPB research progress.

Review articles reflect research advances in a certain topic and field within a certain period of time. The primary aim of this study was to perform a bibliometric analysis of review articles that focused on CPB for cardiovascular surgery.

MATERIALS AND METHODS

Data acquirement and analysis

The Web of Science (WoS) database was used as the data source. To include as many related articles as possible, all databases in WoS, such as MEDLINE, WoS Core Collection (WoSCC), SciELO Citation Index and Chinese Science Citation Database, were used for literature retrieval. Reviews focusing on both CPB and cardiovascular surgery were eligible for inclusion. The following formula was applied: [TI = (CPB) OR TI = (extracorporeal circulation) OR TI = (heart-lung machine) OR TI = (cardiopulmonary support)] AND [TI = (cardiac surgery) OR TI = (heart surgery) OR TI = (cardiovascular surgery)]. The option "Review Article" of the filter "Document Type" was selected. No other restrictions were imposed. The literature retrieval was conducted on 6 March 2024.

Two investigators independently screened the records and removed articles with unmatched document types or research topics. Eligible records were consequently extracted into an excel file. Information such as journal impact factor (IF) and Journal Citation Report (JCR) location were manually extracted from WoS, except journals that were not enrolled

in JCR or did not have an IF. For journals belonging to more than one category, the highest JCR location was displayed in our study. Through an artificial review of the articles, we determined the study population (adults, pediatric patients and uncertain patients) and document type (systematic review, meta-analysis and narrative review). Other parameters, such as publication number, were analyzed using WoS or Excel. Descriptive statistical methods were employed to analyze the distribution of publication year, publication number, and number of citations. Owing to the peculiarity of the VOSviewr software and the items in different databases, records from WoSCC were used to analyze keywords using VOSviewer. The synonyms for the keywords were merged.

RESULTS

In total, 148 records focused on CPB during cardiovascular surgery. Among them, 3 records discussed non-cardiac surgery and 4 were not review articles. Thus, 141 review articles were included in the analysis.

Distribution of study population, study type, language and database

The study population and type were determined based on the titles and abstracts of the articles. Nineteen articles focused on adult patients, 28 on pediatric patients, and 94 did not stress adults or children (Figure 1A). There were 7 pure systematic reviews, 21 meta-analysis papers and 113 narrative reviews (Figure 1B). As shown in Figure 1C, the number of articles written in English, Chinese, German, French, Russian, Polish, Hungarian, Italian, Portuguese, Hebrew and Spanish were 105, 10, 7, 4, 4, 3, 2, 2, 2, 1 and 1, respectively. Most of the articles were collected by WoSCC (n = 97), followed by MEDLINE (n = 33), the Chinese Science Citation Database (n = 10) and the SciELO Citation Index (n = 1) (Figure 1D).

Analyses of publications and citations by time

The first review in this area was published in 1969 and the latest was published in 2024. Considering the long timeline, we divided the time periods according to our definition. Most of the articles were published after the 2010s; that is, 57 were published in the 2010s and 45 were published in the 2020s (Figure 2). In addition, the number of publications from 1969 to 1999 was comparable to that of the 2000s (18 and 21, respectively) (Figure 2). The total number of citations of the articles in each period is shown in Figure 2. Articles in the 2010s had the most citations, followed by those in the 2000s, 1969–1999, and the 2020s. However, the trends in the mean number of citations were different. The descending order was the 2000s, the 2010s, 1969-1999, and the 2020s.

Contributions of the authors and countries/regions

The first review of this field was published by German in 1969. The information of the top-10 authors in terms of publication number is presented in Table 1. There were 4 authors with 4 publications, and 7 authors with 3 publications. The authors came from 5 hospitals of 5 countries (Greece, Turkey, Italy, Singapore and England). Six of them specialized in cardiothoracic surgery, 4 majored in pediatric critical care medicine, and 1 was an anesthesiologist.

Table 2 shows the top-10 countries in terms of publication number. With 25 review papers, the United States was the number one in this field, closely followed by China (n = 21). Regarding the cited times of the articles, countries in North America and Europe took the leading position, including the United States, Canada, Germany, Italy, the Netherlands, Greece and England. We further analyzed the number of publications in different time of the top-10 countries. Five countries, namely, China, the Netherlands, Italy, Greece and England, started to publish review articles focused on CPB in the 2010s (Table 3). Besides, Germany, France, Canada and the United States started to summary the advances in CPB in the early stages (Table 3).

Journal analysis

A total of 98 journals recorded the 141 review articles. *Der Anaesthesist*, a German journal, published the first review on CPB. The *Journal of Cardiothoracic and Vascular Anesthesia* published 14 papers, closely followed by Perfusion-United Kingdom (n = 11). The 2 journals were far ahead of the other journals (Table 4). Considering the decentralized distribution of the articles, we only exhibited the top-5 journals in terms of publication number and the publication timeline in Table 4.

Keywords analysis

Co-occurrence analysis of the keywords (provided by the authors and WoS) is shown in Figure 3. The high-frequency keywords included inflammatory response, children, acute kidney injury, meta-analysis and off-pump, except for CPB and cardiac surgery. Inflammatory response had the closest relationship with CPB during cardiac surgery. This map provides several additional clues. For instance, some technological factors of CPB, such as heparin and hemodilution, have received considerable attention. The complications of CPB, including inflammatory response, kidney injury and ischemia, caught lots of concern.

DISCUSSION

As the first bibliometric analysis of review articles on CPB, the present study recognizes the development and the

Table 1 Information of the top-10 authors on publication number

Authors	Documents	Cited times	H-index	Affiliations	Countries	Departments
Anastasiadis K	4	208	3	Ahepa University Hospital	Greece	Department of Cardiothorac
Antonitsis P	4	208	3	Ahepa University Hospital	Greece	Department of Cardiothorac
Argiriadou H	4	208	3	Ahepa University Hospital	Greece	Department of Cardiothorac
Deliopoulos A	4	208	3	Ahepa University Hospital	Greece	Department of Cardiothorac
Gunaydin S	3	126	3	Ankara City Hospital	Turkey	Department of Cardiovasc Surg
Ranucci M	3	182	3	IRCCS Policlin San Donato	Italy	Department of Cardiovasc Anesthesia and Intens Care Unit
Hwang NC	3	28	3	Singapore Gen Hospital	Singapore	Department of Anaesthesiol
Murdoch IA	3	31	3	PICU Evelina London Childrens Hospital	England	Department of Women and Childrens Health
Hunt BJ	3	31	3	PICU Evelina London Childrens Hospital	England	Department of Women and Childrens Health
Siemens K	3	31	3	PICU Evelina London Childrens Hospital	England	Department of Women and Childrens Health
Tibby SM	3	31	3	PICU Evelina London Childrens Hospital	England	Department of Women and Childrens Health

Table 2 The top-10 countries in term of publication number

Countries	Documents	Cited times	H-index
United States	25	623	11
China	21	123	6
Germany	13	335	7
Canada	10	219	5
Netherlands	9	280	5
England	7	224	5
France	7	154	4
Italy	7	296	5
Brazil	6	23	3
Greece	6	238	4

worldwide contributions within this surgical topic. Most of the reviews were published in this century (123 publications, 87%), and the publication speed has increased significantly.

The first review paper, entitled *Postoperative monitoring following surgery with use of the heart-lung machine*, was published in 1969 in Germany[9]. Within 20 years of the successful application of CPB, medical staff have summarized the postoperative monitoring for cardiac patients, which is of great importance to increase the survival rate. Pharmacological and non-pharmacological strategies to optimize CPB have been proposed and verified, including hemodilution, mechanical components, heparin management and pH management[10-13].

With 213 citations, this article Postoperative pulmonary dysfunction in adults after cardiac surgery with cardiopulmonary bypass: Clinical significance and implications for practice was the most influential review in this field[14]. Published in 2004, this review focuses on the significance and implications of postoperative pulmonary dysfunction in nursing practice. Influenced by this review, improvements of nursing have been investigated to help with fast recovery [15,16].

One interesting thing is that the latest several publications are mainly meta-analysis articles. One of them systematically evaluated the role of electroacupuncture in improving myocardial function and postoperative rehabilitation for CPB-based cardiac patients[17]. The authors declare that electroacupuncture is a promising treatment for alleviating myocardial ischemia-reperfusion injury and enhancing patient recovery. However, considering the low or moderate quality of most evidence, these findings need to be further verified by more high-quality randomized controlled trials.

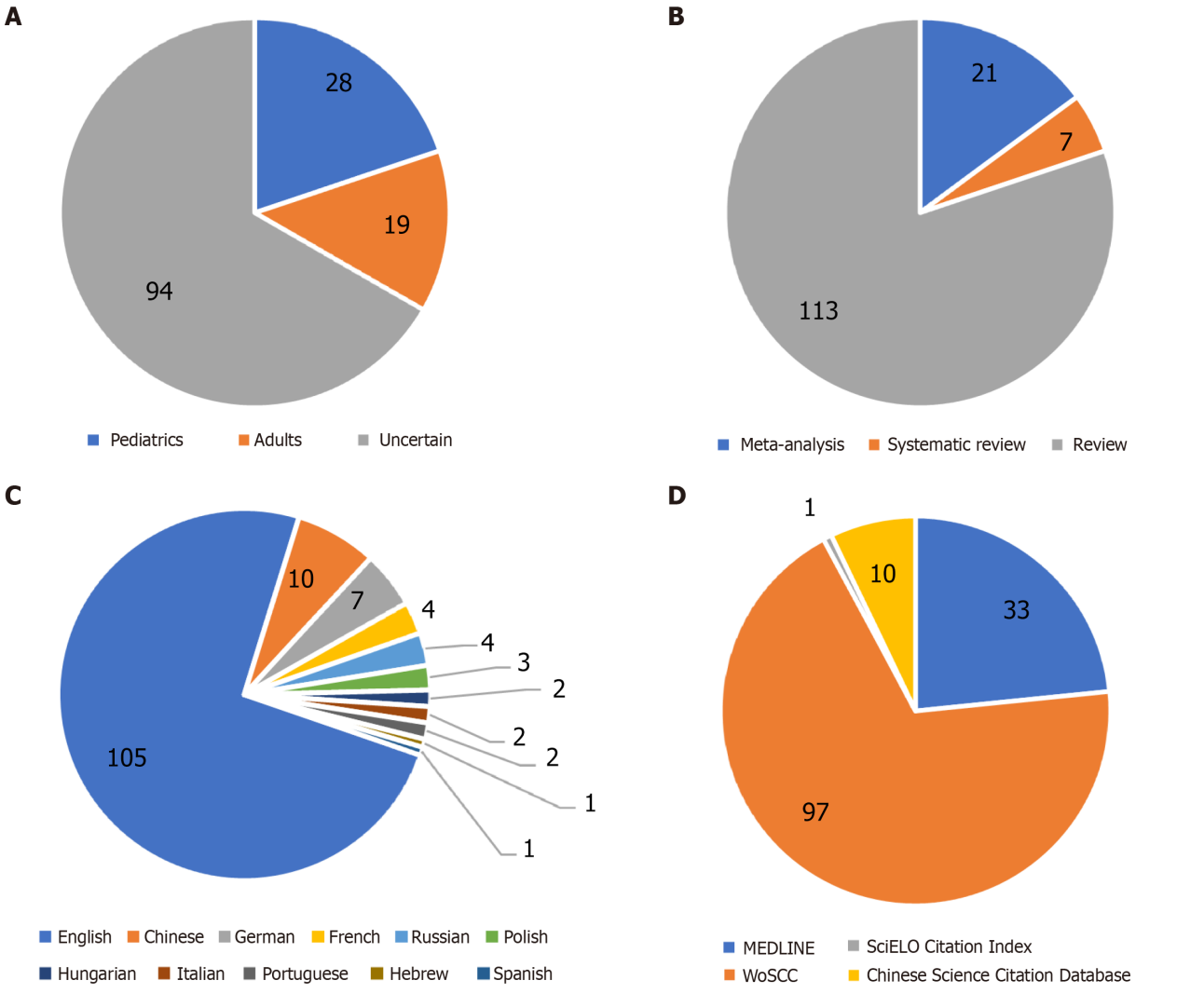

Figure 1 Distribution of study population, study type, language and database. A: Distribution of study population; B: Study type; C: Language; D: Database. WoSCC: Web of Science Core Collection.

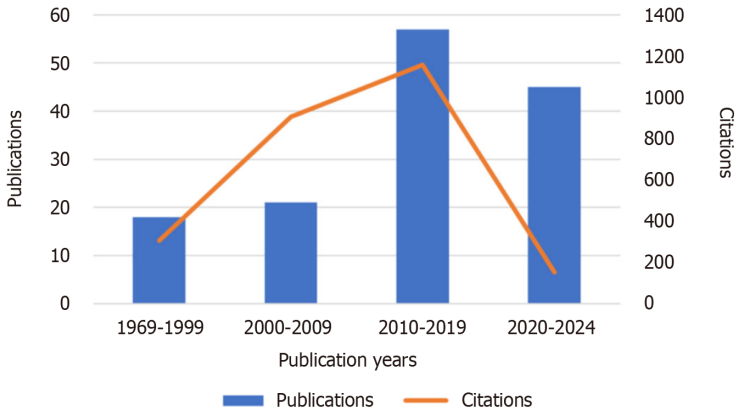

Figure 2 Number of publication and citation in the time intervals.

Another protective strategy involves the use of dexmedetomidine. There are 3 meta-analysis articles to determine the role of dexmedetomidine in cardiac surgery with CPB. The first study was published in 2021 by Zhang *et al*[18]. This study focused on the influence of dexmedetomidine on myocardial ischemia/reperfusion injury, and the results indicated that markers of myocardial injury and length of intensive care unit stay were significantly reduced by dexmedetomidine. The second study was published in 2022 by Chen *et al*[19]. In this study, the myocardial protective and anti-inflammatory effects of dexmedetomidine were investigated by analyzing 9 randomized controlled trials involving 418 participants.

Table 3 Number of publications in different time of the top-10 countries

Countries	T1	T2	T3	T4	Time span
United States	4	1	10	10	1994-2023
China	0	0	8	13	2014-2024
Germany	2	3	4	4	1969-2023
Canada	1	0	6	3	1994-2023
Netherlands	0	0	4	5	2011-2023
England	0	0	3	4	2016-2023
France	1	1	4	1	1980-2023
Italy	0	0	4	3	2010-2023
Brazil	0	1	4	1	2004-2023
Greece	0	0	4	2	2012-2023

T1: 1969-1999; T2: 2000-2009; T3: 2010-2019; T4: 2020-2024.

Table 4 Top-5 journals on publication number and the number of publications in different time

Source title	Documents	If of 2022	IF of 5-year	Journal Citation Report quartile	Time span	T1	T2	T3	T4
Journal of Cardiothoracic and Vascular Anesthesia	14	2.8	2.5	Q3	1999-2022	1	0	10	3
Perfusion- United Kingdom	11	1.2	1.4	Q4	1997-2023	1	1	2	7
Cochrane Database of Systematic Reviews	4	8.4	10.9	Q1	2018-2022	0	0	2	2
The Journal of Extra-Corporeal Technology	4	-	-	-	2003-2010	0	3	1	0
Journal of Cardiac Surgery	3	1.6	1.6	Q3	1994-2022	1	0	0	2

IF: Impact factor. T1: 1969-1999; T2: 2000-2009; T3: 2010-2019; T4: 2020-2024.

These results indicate that dexmedetomidine administration during CPB reduces myocardial injury by inhibiting inflammatory responses. Additionally, the last but the latest one was a study protocol for a meta-analysis which intended to provide support for the role of dexmedetomidine in reducing myocardial ischemia/reperfusion injury in patients undergoing CPB-based cardiac surgery[20].

The primary theme identified in keywords analysis is the inflammatory response, a physiopathologic process that related to self-protection and injury[21]. An overactivated inflammatory response can lead to severe impacts on major organs, such as acute kidney injury and lung injury[22,23]. Major organ dysfunction is strongly associated with adverse prognosis in surgical patients. The high- frequency of outcome-related keywords in this study is in accordance with the truth.

Limitations of the present study must be pointed out. Firstly, we only reviewed papers in the WoS database, which undoubtedly misses some studies and limits our findings. A common concern for bibliometric analysis is that because citations are affected by time, newly published articles are likely to be more influential. We also did not take the self-citations into consideration, or whether the articles are positively or negatively cited. Hence, we cannot determine the evaluation from the academic community to the cited articles.

CONCLUSION

CPB is a vital technique used in cardiac surgery. The rapid increase of review papers shows that the research on CPB in cardiac surgery is being increasingly emphasized by scholars and clinical staff worldwide. The leading countries mainly distribute in North America, Europe, except for China. Meta-analysis has been widely conducted to analyze clinical controversies and further guide clinical practice. Strategies to improve the outcomes of patients undergoing cardiac surgery with CPB are the hot spots in the field.

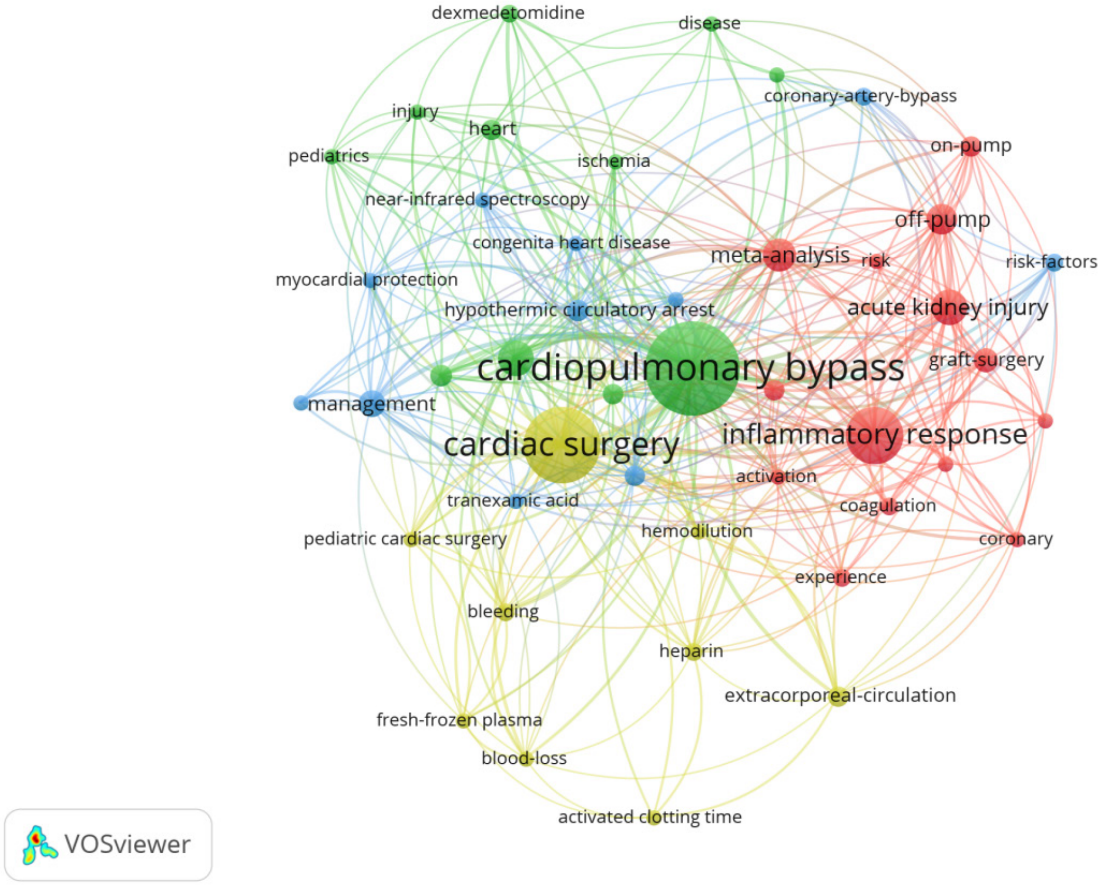

Figure 3 Co-occurrence analysis of the keywords.

FOOTNOTES

Author contributions: Deng L and Zhou R contributed to data analysis and interpretation, participated in data processing and statistical analysis; Deng L, Peng YH and Zhou R conceived and designed the study; Deng L, Peng YH, Zhou R, Zhang XJ drafted the manuscript; Zhang XJ supervised the review of the study; all of the authors read and approved the final version of the manuscript to be published.

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LETTER TO THE EDITOR

Evaluating Wharton's jelly-derived stem cell therapy in autism: Insights from a case study

Muzamil Akhtar, Abdulqadir J Nashwan

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Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder affecting over 2% of the global population, marked by social communication deficits and repetitive behaviors. Kabatas *et al* explored the efficacy and safety of Wharton's jelly-derived mesenchymal stem cell (WJ-MSC) therapy in a 4-year-old child with ASD. Using the childhood autism rating scale and Denver II developmental screening test, significant improvements were seen after six WJ-MSC sessions, with no adverse events over 2 years. Despite promising results, the study's single-case design limits generalizability. Larger, multi-center trials are needed to validate the findings and assess long-term effects of WJ-MSC therapy in ASD.

Key Words: Autism spectrum disorder; Stem cell therapy; Neuroinflammation; Neurodevelopmental disorders; Wharton jelly derived mesenchymal stem cell

Core Tip: This letter highlights the groundbreaking study by Kabatas *et al*, which demonstrates the efficacy and safety of Wharton's jelly-derived mesenchymal stem cell (WJ-MSC) therapy in improving developmental outcomes for a child with autism spectrum disorder. Despite limitations such as the single-case design and lack of a control group, the study suggests WJ-MSC therapy as a promising treatment option, emphasizing the need for larger, controlled trials to validate these findings and develop standardized treatment protocols.

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TO THE EDITOR

Neurodevelopmental disorders impact over 2% of the global population, with autism spectrum disorder (ASD) representing a prominent and heterogeneous condition characterized by challenges in social communication and interaction, as well as restricted and repetitive behaviors that typically manifest in early childhood[1,2]. Despite substantial research, the precise etiology of ASD remains elusive, with onset varying across individuals. Proposed mechanisms include advanced parental age, pregnancy-related complications, drug use during pregnancy, toxin exposure, epigenetic factors, oxidative stress, hypoxic damage, neurotransmitter anomalies, and neuroinflammation[3]. Recent literature has emphasized neuroinflammation and altered cytokine levels within the central nervous system as key contributors to the neurobiological changes observed in ASD, suggesting potential therapeutic targets[4]. Given the variability of ASD, assessment and treatment require a multidisciplinary approach. Early interventions are critical in mitigating symptoms and improving the quality of life for young children with ASD. Traditionally, behavioral and psychosocial therapies have been the mainstay of treatment; however, stem cell therapy has recently emerged as a promising alternative[5]. Notably, stem cell therapy has shown significant improvements in social skills and reductions in autistic symptoms, with a meta-analysis indicating no serious adverse effects[6]. A recent study by Kabatas *et al*[7] further investigates the efficacy and safety of Wharton's jelly-derived mesenchymal stem cell (WJ-MSC) transplantation in ASD patients.

MSC TRANSPLANTATION IN ASD

The study by Kabatas *et al*[7] is a detailed single-case assessment of WJ-MSC therapy in ASD. The study involved a 4-year-old child diagnosed with ASD, who presented with impaired eye contact, frequent crying spells, and severe social interaction difficulties. Initial assessments included a childhood autism rating scale (CARS) score of 37 and Denver II developmental screening test results indicating developmental delays. The child underwent six sessions of intravenous and intrathecal WJ-MSC transplantation under sedation. Post-treatment assessments demonstrated improvements in both CARS score and Denver II developmental screening test results, with no adverse events reported during a 2-year follow-up. These findings provide promising evidence for the potential benefits of WJ-MSC therapy in treating ASD symptoms and enhancing developmental outcomes while highlighting its safety profile.

The comprehensive evaluation using both the CARS score and Denver II developmental screening test ensures a robust assessment of developmental progress. Additionally, the use of WJ-MSCs, known for safety and low risk of immune rejection, lends credibility to the findings. Nonetheless, the study has notable limitations. As a single-patient case report, the generalizability of the findings is limited. While the 2-year follow-up is commendable, longer-term studies are necessary to fully assess the enduring effects and safety of WJ-MSC therapy. The study also did not evaluate specific neurobiological markers or mechanisms, which could offer deeper insights into treatment efficacy. Furthermore, the reliance on subjective measures, such as parental reports, may introduce variability in developmental assessments.

Despite its limitations, the study offers significant clinical implications for ASD management. The promising results of WJ-MSC therapy suggest it could be a viable treatment option to improve developmental outcomes in children with ASD. Improvements in social skills and developmental milestones underscore the potential of WJ-MSC therapy to address core ASD symptoms, such as impaired social interaction and communication difficulties. These findings advocate for the development of standardized protocols for WJ-MSC application, including optimal dosing, administration routes, and patient selection criteria. Moreover, interdisciplinary collaboration among neurologists, pediatricians, and stem cell researchers is essential to integrate this emerging therapy into comprehensive ASD management plans. Future research should focus on larger, multi-center trials to confirm these preliminary results and refine treatment approaches.

CONCLUSION

The study by Kabatas *et al*[7] provides valuable initial evidence supporting the use of WJ-MSCs in treating ASD. The observed improvements in developmental assessments and the absence of severe adverse effects during the 2-year follow-up period highlight the potential of WJ-MSC therapy to address core ASD symptoms. Although the study's single-case design limits its generalizability, it paves the way for future research. The promising outcomes emphasize the need for larger, controlled, and longitudinal studies to validate these findings and explore the long-term effects of WJ-MSC therapy. This research contributes to the growing body of evidence on stem cell therapies for neurodevelopmental disorders, and underscores the importance of continued innovation and interdisciplinary collaboration in advancing ASD treatment.

FOOTNOTES

Author contributions: Akhtar M and Nashwan AJ contributed to writing the draft and critically reviewing the literature.

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LETTER TO THE EDITOR

Telemedicine and public health–pearls and pitfalls

Ranjeet Kumar Sinha, Sony Sinha, Prateek Nishant, Arvind Kumar Morya, Arshi Singh

Specialty type: Medical laboratory technology

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Abstract

We hereby comment on the interesting systematic review by Grewal *et al* where they have provided an overall picture of the current status of available tele-health programs in the United States with emphasis on the Amazon Clinic. Their analysis is an appreciable effort in discovering the features available and features lacking in these tele-health programs. The concept of tele-health originated to curtail the need for physical attendance of patients at health clinics, and has been beneficial during the coronavirus disease 2019 pandemic. We implore that the pearls and pitfalls of these programs have to be understood by policymakers prior to forming a consensus regarding the availability, accessibility and affordability of these programs as methods of healthcare delivery. Unrestricted proliferation of tele-health programs in their current form may pose threats to patient and provider safety and medicolegal liability. However, patients and providers must work together to improve them to meet their expectations and enable them to provide the best care for the ailing public.

Key Words: Telemedicine; Remote Access; Availability; Accessibility; Affordability; Ethics; Privacy; Medicolegal liability

Core Tip: The systematic review by Grewal *et al* has provided an overall picture of the current status of available tele-health programs in the United States with emphasis on the Amazon Clinic. We present the pearls and pitfalls of these programs in a critical analysis to conclude with a warning that unrestricted proliferation of tele-health programs in their current form may pose threats to patient and provider safety and medicolegal liability. However, patients and providers must work together to improve them to meet their expectations and enable them to provide the best care for the ailing public.

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TO THE EDITOR

We read with great interest the article entitled 'Strategic insights of telehealth platforms and strengths, weaknesses, opportunities, and threats analysis of Amazon's clinical endeavors' by Grewal *et al*[1] recently published in the *World Journal of Methodology*. They have provided an overall picture of the current status of available tele-health programs which have been launched in the United States of America for the purpose of doctor-patient interaction, teleconsultation, and remote prescription. Their analysis is an appreciable effort in discovering the features available and lacking in these tele-health programs, and allows for an overview of the options available to patients who wish to benefit from these initiatives.

The concept of tele-health originated from observations that some parts of the doctor-patient interaction did not require the physical presence of the patient in front of the healthcare provider (HCP), and could be accounted for by bidirectional high-fidelity audio and/or video interaction. Serious attention to this aspect of tele-health was drawn during the coronavirus disease 2019 (COVID-19) pandemic wherein physical movement of persons was restricted through an international lockdown enforced by governments across the world[2]. Efforts of governments to allay the apprehensions of HCP provided impetus to this approach. However, the pearls and pitfalls of these programs have to be understood prior to forming a consensus regarding the availability, accessibility and affordability of these programs.

The aforesaid systematic review has presented key features of these initiatives. According to the summary presented by the authors, Amwell appears to be the most feature-rich program with accessibility in all 50 states, inclusion of pediatric and LGBTQ+ patients, acceptance of insurance and organizational subscribers, and coverage of behavioral and mental health. One or more of these facilities is not provided by other such tele-health programs–for example, LGBTQ+ patients are not likely to benefit from Teladoc and CVS Minute Clinic. Amazon Clinic does not provide any of these facilities but is accessible in all 50 states. The authors have also provided an analysis of strengths, weaknesses, opportunities and threats for the Amazon Clinic[1]. We would like to add to the authors' evaluation by critically analyzing the basic concept of tele-health programs, in an effort to provide readers the insights regarding the advantages and disadvantages of these programs.

The authors have endeavored to impress that tele-health is beneficial for the underserved population. The exact definition of the population yet underserved despite adequate access to health facilities is a matter of continuous monitoring by local healthcare bodies, which should be supplemented by a system of national reporting which can then engage HCPs from areas of surplus to the areas which need them. For example, the latter may include mountainous terrain or islands that are difficult to reach and have limited healthcare facilities for larger areas, wherein access to immediate consultation is limited by distances. Inequalities in healthcare accessibility also stem from disparities in insurance coverage, availability of preventive services and household income[3].

The authors have rightly pointed out about the difficulties faced by lay public in locating essential information from treatment cards and reports, as also the understanding as to how to initiate a virtual consultation[1]. The concept of doctor-patient relationship has been challenged by concerns that teleconsultation affects the accuracy of the patient's understanding of the treatment and their compliance, leading to an inadequate assessment of the impact of the treatment on the part of the HCP[4]. While there may be complacency on the part of patients who believe they have already come under medical care leading to aggravation of their conditions, identifying the need for surgery may get delayed due to the HCP possessing inadequate information about the exact physical condition of the patient. Thus, not interfacing the patient, and not performing a physical examination by hand can be dangerous. This practice has not been preferred beyond the COVID-19 pandemic, and even made illegal in some countries.[5] In addition, the medicolegal liability of doctors who are not actually examining the patients needs to be determined. How much of an overall responsibility can be fixed on clinicians who have not performed a detailed examination needs to be defined in terms and conditions of liability[6].

The authors reported that 6% of Teladoc consultations resulted in a follow-up visit for similar conditions and that the tele-mental health platform Brightside provided superior outcomes[1]. It is known that tele-health may improve follow-up and have a positive impact on outcome. However, these interim endpoints cannot be utilized to define the success or failure of the tele-health initiative. For instance, explanation is required on the proportion of follow-ups on the teleconsultation portal and physically, the number of new disorders diagnosed on these follow-ups and the quality of life improvements achieved through them, which are difficult to quantify but essential to compare it with similar initiatives[4,7].

We agree that teleconsultation can be effective for elective procedures like post-cancer surgery skin reconstruction and follow-up care. This is also possible for diagnosed ophthalmic conditions like cataract, the surgery for which is elective for most types. How much can this be effective in other disciplines or other conditions is a question yet unanswered[8]. Similarly, the advantages of the Amazon clinic have been enumerated to be the quality of care, patient retention, high satisfaction rates and overall cost saving. The quantitative cutoff for these interim endpoints is yet to be found. While the use of existing customer base data, wide access anywhere in the United States, 24/7 service, video or text facility and payment flexibility can be advantageous for patients, other initiatives such as the Behemoth digital pharmacy, Google helpouts and IBM Watson health unit also had the same opportunities but could not be successful, implying that these are not the only considerations that patients may have[1,4,7,8].

Ethical considerations are an added problem. A tele-health provider is often viewed akin to taxi or hotel aggregators, performing dichotomy of fees against the utilization of their user interface. With growing usage, it must be predetermined how exploitation of registered HCPs would be prevented before the HCPs consider enrolling in these programs. Data privacy and patient autonomy also have the potential to be compromised[4-7]. There is also a need to improve the documentation of user and system quality aspects of these platforms, which are responsible for poor acceptability of such programs[9].

In conclusion, while tele-health as a method of healthcare delivery does have several advantages and disadvantages, policymakers must consider the aspects of patient and provider safety, ethics and medicolegal liability. Unrestricted proliferation of these programs must be effectively regulated, and patients and providers must work together to improve them to meet their expectations and enable them to provide the best care for the ailing public.

FOOTNOTES

Author contributions: Sinha RK and Morya AK conceptualized the study and coordinated the research activities; Nishant P contributed to data analysis, literature review; Sinha S, Sinha RK and Nishant P contributed to data collection; Sinha S and Singh A performed manuscript editing and proofreading; Morya AK reviewed and supervised the manuscript. All authors reviewed the version submitted and agree to be accountable for all aspects of the work presented.

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