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Peer Reviewer of *World Journal of Methodology*, Xingjiang Xiong, MD, PhD, Professor, Department of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, No. 5 Beixian Ge, Xicheng District, Beijing, 100053, China. xiongxingjiangtcm@163.com

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EDITORIAL

Mental health in the virtual world: Are we ready for the metaverse era?

Tuffy Mamede, Patrícia Lordêlo

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Tuffy Mamede, Post Graduation in Medicine and Human Health, Bahiana School of Medicine and Public Health, Salvador 40290-000, Brazil

Patrícia Lordêlo, Pelvic Floor Care Center and Postgraduate, Patricia Lordelo Institute, Bahiana School of Medicine and Public Health, Salvador 40290-000, Brazil

Corresponding author: Patrícia Lordêlo, Doctor, PhD, Adjunct Associate Professor, Physiotherapist, Postdoc, Pelvic Floor Care Center and Postgraduate, Patricia Lordelo Institute, Bahiana School of Medicine and Public Health, Av Dom João VI, 256, Brotas, Salvador 40290-000, Brazil. pvslordelo@hotmail.com

Abstract

The advent of the metaverse, including virtual reality, augmented reality, and artificial intelligence, is an undeniable issue that health care scientists need to update. It influences all fields of knowledge, interpersonal relationships, and health. Regarding mental health since the post-coronavirus disease 2019 pandemic, it is necessary to consider and understand the potential, possibilities, weaknesses, and consequences arising from and provided by this new scenario. Due to the increasing need for mental health monitoring and care, mental health treatments require in-depth training and preparation to achieve the maximum use of the metaverse advantages and possibilities. Currently, very little is known about the effectiveness of remote mental health treatment, but it is certainly suggested that accessibility and the characteristics associated with the use of metaverse technologies may represent new horizons for accessibility and approach tools, as long as more studies are carried out and more evidence is collected to develop accurate guidelines, safe training, solve ethical concerns, and overcome limitations.

Key Words: Mental health; Metaverse; Artificial intelligence; Augmented reality; Virtual reality

Core Tip: Metaverse consists of a virtual environment created using technologies such as augmented reality, artificial intelligence, and virtual reality. This paper discusses the readiness of patients, therapists and interfaces for managing mental health using the metaverse.

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INTRODUCTION

The relevance of this paper's topic concerns the need for precise knowledge on how to deal with mental health in the increasingly growing and dominant new reality of metaverse around the world[1]. The advent of the metaverse, including virtual reality, augmented reality, and artificial intelligence, is an undeniable issue that needs to be updated by health care scientists[2]. It influences all fields of knowledge, interpersonal relationships, and health. Regarding mental health in the post-coronavirus disease 2019 (COVID-19) pandemic period, it is important to consider and understand the potential, possibilities, weaknesses, and consequences arising from and provided by this new scenario[3].

There is an increasing need for mental health monitoring and care[4]. Statistics show that there has been a barrier to mental treatment access due to several factors, such as: Shame and prejudice against seeking mental treatment; lack of confidence and trust to share their problems and becoming fragile in front of a stranger; treatment abandonment; financial limitations[5]. Therefore, mental disorders such as depression, compulsive behavior, addictions, anxiety, and deep social phobias are underdiagnosed, and their treatments are neglected[6].

CLINICAL IMPLICATIONS

Mental health treatment requires in-depth training of therapists and long-term preparation. Time and experience are crucial to properly learn how to conduct a session. The therapists need to develop a bond and earn the patient´s trust. Also, it is important to understand patient's subliminal behavior variations, projections, verbal speech and non-verbal communication, action eminence and concealment of 'acting out' actions or even 'passage to the act' – suicidal attempt[7-9].

Psychological urgency and emergency state, crises, panic, and lack of control situations are difficult to detect and manage without prior training. Artificial reality programming needs previous input to acquire enough data to develop and apply strategies efficient enough to prevent an undesired outcome. Currently, actual therapists require at least five years of experiential professional knowledge to be able to deal with these matters, despite the chosen psychotherapeutic approach. Psychotherapeutic treatments, alone or associated with other treatments, have shown promising results in real life experience. Even so, there is a dropout rate and difficulty in maintaining results for prolonged periods when the treatment is discontinued, or follow-up might be lost[10,11].

METAVERSE RESOURCES

The metaverse represents a more accessible means on three fronts: Prevention, treatment, and long-term adherence to therapeutic monitoring[2].

Regarding prevention, access to the internet, artificial intelligence, and augmented reality can help educate a greater number of individuals regarding the signs and symptoms of mental disorders. This information can be available to read by any individual at any time *via* the internet or even downloaded for future off-line access. Many digital media outlets reach a population that represents more than 60% of the statistical data regarding mental illnesses[3,12].

In addition to the resources mentioned above, virtual reality and avatar representation can guarantee anonymity, which can provide the patient with more comfort in sharing and explaining problems in a non-judgmental communication[5,12]. On the other hand, this same action that offers comfort to the patient blinds the therapist to subliminal observations, thus making the supposedly unstable patient the only one responsible for controlling the therapy session [13].

Another particularity of the metaverse is the fact that people who are displaced from their locations of origin can be served in their languages, thus achieving more accuracy in their expression[5,14]. Through augmented reality and 'deepfake' using virtual reality to simulate traumatic situations it is possible to generate a realistic controlled experience and help treat trauma in a more optimized way[15,16]. Through the internet it is possible to reach those in need who are in remote or hostile places, enabling accessibility and treatment[17].

Finally, accessibility, confidentiality and anonymity favor adherence to treatment and may improve therapeutic results [9,17].

METAVERSE LIMITATIONS

Despite all these promising possibilities, very little is known about the effectiveness of remote mental health treatment for specific cases. Currently, therapists do not have the training in 'metaverse' practice, nor are they academically familiar with the appropriate therapies to use on such occasions, or even their limitations. Due to the COVID-19 pandemic period urgent guidelines were prepared and recommendations made regarding on-line therapy. These new vehicles and tools are particularly dangerous to use in cases of emotional instability, cognitive limitations, or therapeutic inexperience, and may even worsen the patient's condition in some cases[18].

There is no evidence that virtual reality surpasses face-to-face approaches, but it is certainly suggested that accessibility and the characteristics associated with the use of metaverse technologies may represent a new horizon of accessibility and approach tools. It is a promising framework, but not yet mature enough and still insecure regarding the object of study it proposes to focus on[19].

The fact that this reality is very recent is associated with the lack of studies and development on new mental health treatment approaches suitable for this scenario. Artificial intelligence, although gifted with the property of learning through the acquisition of experience, is still not able to perceive appropriately when lacking an active input, being subject to algorithms[15,20].

Although online care and remote medicine have already been used on an emergency basis since 2020; however, to make this modality more familiar in the modern world and open doors to new advances, psychologists require proper training. Any psychologist would need more than four years of academic maturity to graduate. Furthermore, there is insufficient safe scientific knowhow, or precise, feasible, and reliable training for therapists to be properly ready for metaverse mental health practice. Academic and scientific knowledge capable of being generalized on this topic are still not available at this time[21,22].

It can be inferred that the opportunity offered by the COVID-19 pandemic can be taken advantage of to develop the virtual modality as an option for prevention, detection and treatment of illnesses linked to mental health[23,24]. Nevertheless, to date, it is still only an optimistic and promising vision.

As progress is made in the development of tools to approach mental health *via* the metaverse, considering an immersive virtual experience in a safe environment, and qualified mature professionals, it is also necessary to consider the unknown possible side effects of this process[16,25].

At present, issues such as: Nomophobia; sleep circadian rhythm disorders, irritability; vision impairment; dependency; decreased interest in experiential experiences; frustration intolerance; reduction of physical activities; and development of postural conditions are attributed to the virtual environment[25,26]. However, when regarding mental functions and mental dysfunctions treated *via* a virtual environment, there is no scientific maturity, no evidence to prove safety, reproducibility, or feasibility.

It is necessary to develop research and observe the outcomes related to the influence of the metaverse on people and mental health so that this inevitable reality can be better utilized[27]. In mental health, taking into account the repercussions and sensitivity of the topic, systematic training and experimentation are extremely important before wide applicability. When more studies are carried out and more evidence is collected, accurate guidelines can be developed to guide conduct, develop safe training, therapeutic maturity, overcome limitations, and prevent undesirable effects[28].

ETHICAL IMPLICATIONS

Ethical concerns linked to mental health therapeutic care are specific and delicate. When addressing ethics in the metaverse, tools such as deepfake and artificial intelligence that can be used for treating and informing, can also disseminate fake news or release personal data, breaking privacy and confidentiality, thus presenting an acutely sensitive issue that needs development and stability[16,29]. Studies and development of containment methods could be the answer to reducing damage and eliminating potential risks. They are extremely necessary when entering this field of knowledge and clinical applicability.

The presentation of modern technologies does not replace other approaches. In mental health, there is no therapy that is sufficiently effective for all needs. All therapeutic approaches focus on tested systems within a theoretical rationale, a social and ontological method, clinical practical experience and generalizable evidence[30]. Some techniques are more suitable for certain conditions than others and the diversity of treatment options is welcome, opening space for a "fifth" therapeutic force to be potentially developed in the metaverse.

CONCLUSION

The metaverse is already a reality. Problems associated with mental health are a growing fact and a relevant concern around the world. Knowledge is the solution to better manage the risks of developing these diseases and increase adaptation to these new demands and contingencies. When opportunities present themselves to improve and use changes in favor of health and science, it is a win-win situation from any point of view, with advances in terms of mental health treatment in the metaverse era being of supreme urgency and relevance. Therefore, this knowledge needs to be developed, tested, trained, and applied in a responsible manner, with the patient and their safest well-being as the main point.

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FOOTNOTES

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Country of origin: Brazil

ORCID number: Patrícia Lordêlo 0000-0002-5487-3080.

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EDITORIAL

Optimizing outcomes: Implementing enhanced recovery after surgery in orthopedic surgery

Sathish Muthu, Madhan Jeyaraman, Naveen Jeyaraman, Swaminathan Ramasubramanian

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Sathish Muthu, Department of Orthopedics, Orthopedic Research Group, Tamil Nadu, Coimbatore 641045, India

Sathish Muthu, Department of Orthopedics, Government Medical College, Tamil Nadu, Karur 639003, India

Sathish Muthu, Department of Biotechnology, Karpagam Academy of Higher Education, Tamil Nadu, Coimbatore 641021, India

Madhan Jeyaraman, Naveen Jeyaraman, Department of Orthopedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Tamil Nadu, Chennai 600077, India

Swaminathan Ramasubramanian, Department of Orthopedics, Government Medical College, Omandurar Government Estate, Tamil Nadu, Chennai 600002, India

Corresponding author: Sathish Muthu, DNB, MS, PhD, Assistant Professor, Department of Orthopedics, Orthopedic Research Group, Ramanathapuram, Tamil Nadu, Coimbatore 641045, India. drsathishmuthu@gmail.com

Abstract

In the realm of orthopedics, the adoption of enhanced recovery after surgery (ERAS) protocols marks a significant stride towards enhancing patient well-being. By embracing a holistic approach that encompasses preoperative counseling, dietary optimization, minimally invasive procedures, and early postoperative mobilization, these protocols have ushered in a new era of surgical care. Despite encountering hurdles like resistance to change and resource allocation challenges, the efficacy of ERAS protocols in improving clinical outcomes is undeniable. Noteworthy benefits include shortened hospital stays and bolstered improved patient-safety measures. Looking ahead, the horizon for ERAS in orthopedics appears bright, with an emphasis on tailoring care to individual needs, integrating cutting-edge technologies, and perpetuating research endeavors. This shift towards a more personalized, streamlined, and cost-efficient model of care underscores the transformative potential of ERAS in reshaping not only orthopedic surgery but also the journey to patient recovery. This editorial details the scope and future of ERAS in the orthopedic specialty.

Key Words: Enhanced recovery after surgery; Orthopedic surgery; Perioperative care; Personalized care; Patient reported outcome measure; Complications

Core Tip: Enhanced recovery after surgery (ERAS) protocols in orthopedics significantly improve patient outcomes by reducing recovery time, the complication rate, and hospital stay through a multidisciplinary approach involving preoperative counseling, nutritional optimization, minimally invasive techniques, and early mobilization. Despite facing challenges in implementation, such as resistance to change and resource demands, ERAS protocols have proven their efficacy in improving clinical outcomes, including reduced hospital stay and enhanced patient safety. The future of ERAS in orthopedics is promising, with a focus on personalized care, technological integration, and ongoing research. The evolution towards more patient-centered, efficient, and cost-effective care underscores the potential of ERAS to revolutionize orthopedic surgery and patient recovery processes.

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INTRODUCTION

The evolution of perioperative care has been significantly influenced by enhanced recovery after surgery (ERAS) protocols that were initially developed for colorectal surgery and are now widely applied in orthopedic procedures[1]. ERAS signifies a departure from traditional methods, focusing on a multidisciplinary approach that includes surgeons, anesthesiologists, nurses, and physiotherapists, all working together to enhance patient outcomes[2]. This shift is particularly noteworthy in orthopedic surgery, a field historically reliant on conventional recovery protocols and now embracing ERAS to improve patient care. ERAS in orthopedics aims to reduce recovery time, lower the complication rate, and increase patient satisfaction through a series of strategic components. These include preoperative counseling, nutritional optimization, use of minimally invasive techniques, and early mobilization, each having a vital role in expediting patient recovery[3]. This comprehensive strategy contrasts sharply with previous practices that often resulted in longer hospital stays and a delayed return to normal activities. This editorial discusses the challenges and benefits of implementing ERAS in orthopedic surgery that are described by recent clinical studies. It also looks ahead at the potential future of ERAS in this field, particularly focusing on personalized care and the incorporation of digital health tools, hinting at how ERAS protocols might continue to transform postoperative recovery in orthopedic surgery.

The inception of ERAS protocols marked a pivotal shift in perioperative care, initially gaining traction in colorectal surgery and later extending to orthopedics[4]. Characterized by a comprehensive, multidisciplinary approach, ERAS drastically contrasts with traditional recovery methods, particularly in orthopedics, where longer hospital stays and recovery times were once standard. Integrating the expertise of surgeons, anesthesiologists, nurses, and physiotherapists, ERAS redefines patient management at all surgical stages[5]. ERAS signifies a significant evolution in surgical care, incorporating various components such as patient education, nutritional optimization, minimally invasive techniques, and early mobilization. These elements aim to minimize surgical stress and accelerate recovery, representing a shift towards patient-centered, evidence-based practices[6,7].

Originally prominent in colorectal surgery, the adoption of ERAS in orthopedics was a change from protracted, traditional recovery protocols to a streamlined, patient-focused approach[4]. The multidisciplinary essence of ERAS is crucial, transforming patient care from preoperative to postoperative stages[5]. ERAS originated in Europe during the 1990s, challenging conventional perioperative methods that often led to prolonged hospital stays and delayed recovery [1]. Its development is underpinned by the understanding that surgical stress and metabolic change significantly impact patient outcomes. Thus, ERAS embodies a holistic, patient-centered approach[2]. Contrasting traditional orthopedic protocols that involved extended bed rest and delayed feeding, ERAS advocates for early mobilization, nutritional support, and enhanced pain management. These practices have been shown to reduce complications, decrease hospital durations, and enhance patient satisfaction, marking ERAS as a notable departure from conventional orthopedic practice and a stride toward reducing surgical stress and speeding recovery[3]. The article underscores the transformative impact of ERAS on both patient care and healthcare economics, advocating for its continued evolution and adaptation in the field of orthopedic surgery.

ERAS COMPONENTS IN ORTHOPEDICS

ERAS in orthopedic surgery integrates various critical elements, each uniquely contributing to the optimization of patient recovery and outcomes as shown in Table 1 and Figure 1.

Table 1 Core components of enhanced recovery protocols after orthopedic surgery

Component	Description	Benefits
Preoperative counseling	Informing patients about the surgery and expectations	Reduces anxiety, sets realistic expectations
Nutritional optimization	Improving nutritional status pre-surgery	Enhances healing, reduces complications
Minimally invasive techniques	Employing less invasive surgical methods	Minimizes tissue damage, quicker recovery
Pain management	Multimodal strategy to control pain	Promotes early activity, reduces opioid dependency
Early mobilization	Encouraging movement post-surgery	Shortens hospital stays, reduces complication risks

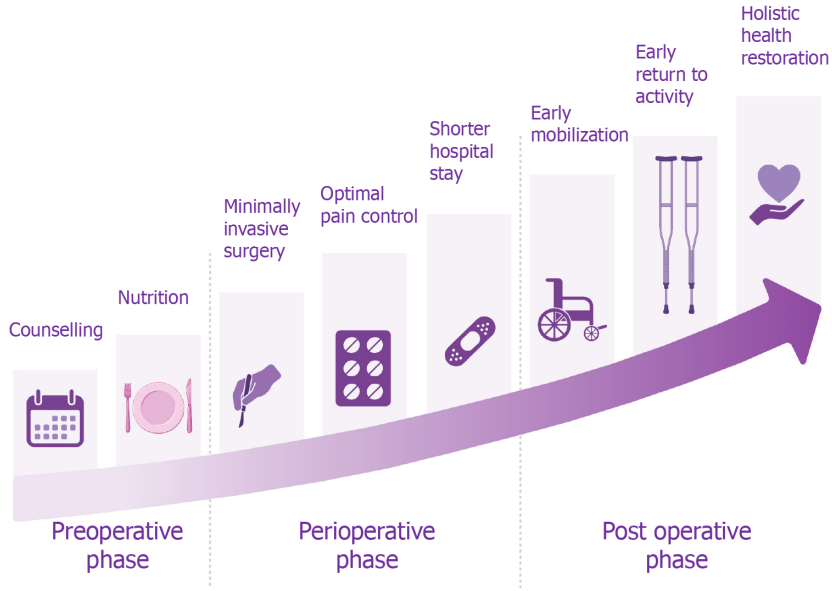

Figure 1 Phases of enhanced recovery after surgery management regimes.

Preoperative counseling

This key facet involves thorough patient education about the surgical procedure and recovery expectations. Informing patients comprehensively helps in mitigating anxiety and setting realistic expectations, which are pivotal for both mental and physical preparation before surgery. Such informed patients often have enhanced recovery outcomes and less anxiety, as indicated in studies[4].

Nutritional optimization

Assessing and improving patient nutritional status before surgery is an essential component of ERAS. Proper nutrition is crucial for fostering effective healing post-surgery, diminishing the risk of complications, and reinforcing the immune system. The link between adequate nutrition, improved wound healing, and reduced postoperative complications is well-established[5].

Minimally invasive techniques

ERAS emphasizes the use of state-of-the-art, less invasive surgical methods. These techniques are instrumental in minimizing tissue damage, leading to less postoperative pain and quicker recovery, thereby directly aligning with the objectives of ERAS to enhance patient outcomes. Such approaches are particularly beneficial in surgeries like joint replacement, offering faster recuperation and lower complication rates[6].

Pain management

A pivotal aspect of ERAS is the multimodal strategy for managing pain. This approach combines various methods to control pain, aiming to reduce reliance on opioids. Effective pain management is vital for promoting early physical activity and shortening the hospital stay. The use of regional anesthesia, non-opioid analgesics, and other pain control techniques not only provides effective pain relief but also curtails opioid-related adverse effects[7].

Early mobilization

Prompt mobilization post-surgery is a core element in ERAS. This practice is associated with shorter hospital stays, reduced risk of complications, and accelerated return to normal activities. Encouraging patients to move and ambulate

shortly after surgery has been linked to improved functional outcomes and decreased incidence of complications like deep vein thrombosis. The combination of minimally invasive surgery and efficient pain management facilitates early mobilization[2].

Each component of the ERAS protocol for orthopedic surgery plays a vital role in expediting patient recovery, minimizing the length of hospitalization, and augmenting overall patient satisfaction. This integrative approach showcases the multifaceted nature of patient care, underscoring the importance of addressing various aspects of the perioperative process to achieve optimal outcomes.

ERAS FOR ORTHOPEDIC SUBSPECIALTIES

Arthroplasty (hip and knee)

ERAS protocols in arthroplasty focus on minimizing perioperative stress and improving recovery times through various interventions like preoperative education, optimized fluid management, and the use of multimodal analgesia. Neuraxial anesthesia is preferred to general anesthesia owing to its association with reduced complications and faster recovery. Outpatient arthroplasty, facilitated by ERAS protocols, is becoming more prevalent, highlighting the efficacy of the protocol efficacy for enabling safe and effective recovery outside traditional hospital settings[8].

Adult reconstruction surgery

In the realm of adult reconstruction, particularly in surgeries involving the hip and knee, ERAS protocols emphasize early mobilization, pain management, and minimizing the length of hospital stay. For instance, maintaining normothermia and using goal-directed fluid therapy are critical components aimed at reducing postoperative complications and enhancing functional recovery[8].

Sport orthopedics

While the application of ERAS in sports orthopedics is not as extensively documented as in arthroplasty, key principles like reducing perioperative discomfort, early rehabilitation, and psychological support are integral. These components help athletes return to their sport at their pre-injury level more swiftly.

Trauma

The use of ERAS protocols in orthopedic trauma surgery focuses on rapid pain management and early physical therapy to reduce the duration of hospitalization and improve overall outcome. Effective fluid management and the prevention of hypothermia during surgery are also crucial elements tailored to meet the specific needs of trauma patients[8].

Spine surgery

ERAS in spine surgery incorporates specific strategies such as the selective use of minimally invasive techniques to reduce surgical stress and enhanced pain management protocols to facilitate quicker discharge and improved patient satisfaction[8].

The adaptation of ERAS protocols to specific surgical contexts within these subspecialties highlights their importance in enhancing patient recovery and the efficiency of care. Each component is carefully selected based on the surgical procedure and patient needs, demonstrating the versatile application of ERAS across orthopedic procedures[8,9].

Challenges to implementation

The integration of ERAS protocols into orthopedic settings faces several obstacles, with resistance to change being predominant. Healthcare professionals are often tied to conventional methods and may be reluctant to adopt ERAS protocols because of familiarity with existing practices and skepticism regarding new procedures[4]. Additionally, the demand for additional resources is a notable challenge. The implementation of ERAS requires substantial resources, including the need for thorough staff training and the procurement of necessary materials, which can be particularly taxing in settings with limited resources, as shown in Table 2[5].

A crucial component of successful ERAS integration is the extensive training of the multidisciplinary team. This encompasses not only the medical and surgical staff but also involves educating patients and their families about the ERAS protocols[6]. The complexities and variability inherent in orthopedic procedures further exacerbate these challenges. Convincing healthcare professionals to depart from established protocols and adopt ERAS requires substantial evidence of its benefits and a significant shift of institutional culture[2]. Initial resource intensiveness, including investments in training, patient education materials, and possibly new technologies, is another hurdle to ERAS implementation[3].

Several strategies can be employed to address these challenges,. Effective communication and education are key in mitigating resistance. Educating stakeholders about the advantages of ERAS, supported by clinical evidence and success stories, can facilitate a smoother transition to these new protocols[10]. Additionally, ensuring interdepartmental coordination of surgery, anesthesiology, nursing, and physiotherapy departments is crucial for the seamless adoption of ERAS protocols[2]. Furthermore, patient education regarding the ERAS pathway, their role in the recovery process, and setting realistic expectations can significantly improve compliance and outcomes[3]. Overcoming these barriers is essential for the successful implementation of ERAS in orthopedic surgery, which is instrumental in enhancing patient outcomes and operational efficiency.

Table 2 Clinical outcomes after implementation of enhanced recovery after surgery protocols

Outcome measure	Traditional approach	Enhanced approach	Impact
Postoperative complications	Higher	Reduced	Improved patient safety
Length of hospital stay	Longer	Shorter	Enhanced bed availability, cost savings
Patient satisfaction	Variable	Higher	Positive patient experience
Recovery time	Prolonged	Accelerated	Faster return to normal activities

Clinical outcomes and benefits

The integration of ERAS protocols in orthopedic procedures has yielded significant clinical advantages, as indicated in numerous studies. These protocols have been instrumental in minimizing postoperative complications, including lower incidences of infection and thromboembolic events. This decrease of complications is a key aspect of improving patient safety and overall health outcomes, as shown in Table 3[4]. Another notable advantage of ERAS is the reduction in the length of hospital stay. This benefit not only increases bed availability but also leads to a decrease in healthcare expenditures, making a strong case for the cost-effectiveness of ERAS[5,7]. Shorter hospital stays associated with ERAS primarily result from enhanced pain management, early mobilization, and optimal nutritional support, all of which contribute to faster recovery[10,11].

ERAS protocols have also improved patient satisfaction. Patients report higher contentment level, mainly because of expedited recovery, reduced discomfort, and the comprehensive care approach that includes detailed preoperative information. These factors collectively contribute to a positive patient experience[2,6]. Furthermore, the cost-effectiveness of ERAS cannot be overstated. By significantly curtailing the duration of hospital stays and diminishing the rate of postoperative complications, ERAS results in considerable savings for healthcare systems. This economic benefit, coupled with the aforementioned clinical outcomes, underscores the transformative impact of ERAS on both patient care and healthcare economics[3]. The success of ERAS in orthopedic surgery is largely attributed to its multimodal approach, which encompasses various aspects of patient care. However, its effective implementation necessitates the involvement of a committed multidisciplinary team and an ongoing commitment to enhancement through continuous research and feedback.

Future directions

The progressive trajectory of ERAS in orthopedic surgery is geared toward meticulous research and incremental enhancement of protocols. The focus is increasingly shifting towards personalized healthcare, where treatment is customized to meet the unique needs of each patient. This approach considers various patient-specific factors such as age, underlying health conditions and individual preferences[1,5]. The integration of cutting-edge technologies, especially digital health tools like wearable devices and telemedicine platforms, is anticipated to significantly improve patient monitoring and adherence to ERAS protocols[6,11]. Continuous research and development are fundamental to the evolution of ERAS, ensuring that protocols are not only up-to-date but also responsive to the diverse needs of different patient demographics and surgical procedures[2,4]. Moreover, there is an emphasis on enhancing the scope and efficacy of ERAS by incorporating feedback from patients and clinical outcomes, thereby fostering a cycle of perpetual improvement as shown in Table 4.

Interdisciplinary collaboration is another key factor in advancing ERAS[7]. This collaboration ensures a holistic approach to patient care, combining expertise from various medical disciplines. Together, these elements represent the dynamic nature of ERAS in orthopedic surgery, underscoring its potential to continually advance patient outcomes and healthcare efficiency. The future of ERAS thus lies in its ability to adapt and evolve by embracing personalized care, technological advancement, interdisciplinary teamwork, and a relentless pursuit of research and innovation.

CONCLUSION

ERAS protocols are a transformative approach in orthopedic surgery, with significant benefits in reducing recovery times, minimizing complications, and improving patient satisfaction. The formation of multidisciplinary teams and the adoption of components such as preoperative counseling, nutritional optimization, minimally invasive techniques, and early mobilization are central to its success. Despite facing challenges in implementation, such as resistance to change and resource demands, ERAS protocols have proven their efficacy by improving clinical outcomes, including reduced hospital stay and enhanced patient safety. The future of ERAS in orthopedics is promising, with a focus on personalized care, technological integration, and ongoing research. This evolution towards more patient-centered, efficient, and cost-effective care underscores the potential of ERAS to revolutionize orthopedic surgery and patient recovery.

Table 3 Challenges and solutions in implementation of enhanced recovery after surgery

Challenge	Description	Proposed solution
Resistance to change	Reluctance to adopt new protocols	Effective communication, education on benefits
Resource demands	Need for training, materials	Resource allocation, comprehensive staff training
Training requirements	Extensive training of multidisciplinary team	Developing structured training programs
Integration of teams	Coordination among various departments	Promoting interdepartmental collaboration

Table 4 Future directions of enhanced recovery after surgery in orthopedics

Area of focus	Description	Potential impact
Personalized care	Customized treatment per patient needs	Improved patient outcomes, enhanced satisfaction
Integration of digital tools	Use of wearables, telemedicine	Better monitoring, adherence to protocols
Continuous research and development	Ongoing updates to protocols	Keeping practices up-to-date, responsive to needs
Interdisciplinary collaboration	Collaborative patient care approach	Holistic patient management, improved care quality

FOOTNOTES

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Country of origin: India

ORCID number: Sathish Muthu 0000-0002-7143-4354; Madhan Jeyaraman 0000-0002-9045-9493; Naveen Jeyaraman 0000-0002-4362-3326; Swaminathan Ramasubramanian 0000-0001-8845-8427.

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EDITORIAL

Artificial intelligence and robotics in regional anesthesia

Nitin Choudhary, Anju Gupta, Nishkarsh Gupta

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Nitin Choudhary, Anju Gupta, Department of Anesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, New Delhi 110029, Delhi, India

Nishkarsh Gupta, Department of Onco-Anesthesiology and Palliative Medicine, All India Institute of Medical Sciences, New Delhi 110029, Delhi, India

Co-first authors: Nitin Choudhary and Anju Gupta.

Corresponding author: Nishkarsh Gupta, MBBS, Professor, Department of Onco-Anesthesiology and Palliative Medicine, All India Institute of Medical Sciences, Room No. 139 FF IRCH, New Delhi 110029, Delhi, India. drnishkarsh@rediffmail.com

Abstract

Artificial intelligence (AI) technology is vital for practitioners to incorporate AI and robotics in day-to-day regional anesthesia practice. Recent literature is encouraging on its applications in regional anesthesia, but the data are limited. AI can help us identify and guide the needle tip precisely to the location. This may help us reduce the time, improve precision, and reduce the associated side effects of improper distribution of drugs. In this article, we discuss the potential roles of AI and robotics in regional anesthesia.

Key Words: Artificial intelligence; Robotics; Regional anesthesia; Ultrasound; Anesthesia

Core Tip: Artificial intelligence (AI) technology has been incorporated in the medical field, including anesthesia. It is vital for practitioners to incorporate AI and robotics in day-to-day regional anesthesia practice. The literature is encouraging on its applications in regional anesthesia, but the data are limited. AI can help us identify and precisely guide the needle tip to the location. This may help us reduce the time, improve precision, and reduce associated side effects of improper distribution of drugs. We discuss the potential role of AI and robotics in regional anesthesia.

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INTRODUCTION

Artificial intelligence (AI) is the amalgamation of various algorithms that allows machines to generate the aptitude to analyze and perform complex functions such as problem-solving, object recognition, and decision-making[1]. With the growing advancements in the field of science and its application in medicine, AI-based technologies in medical science are on the rise. Therefore, all clinicians need to understand the application of these new technologies in medical science and use them appropriately to deliver more safe, efficient, and cost-effective patient care[2].

Anesthesiologists have been at the forefront in the initiation of patient safety initiatives. With the advent of advanced technology in the form of AI, these safety initiatives can be further refined to deliver improved quality of patient care[3]. The specialty of anesthesia can immensely benefit from recent developments in AI, as it has found applications in multiple elements of clinical practice, including perioperative and intensive care, pain management, airway management, and regional anesthesia (RA)[3,4]. Research has suggested that AI tools can have potential applications in various clinical scenarios in anesthesiology practice, including ultrasound guidance (USG) for RA and pain management[4]. Machine learning is a subset of AI characterized by improvements in performance through iterative tuning of weights or coefficients within mathematical models to identify patterns in complex data sets[5]. It can potentially provide scientific data on the role of RA in improvements of long and short-term patient-centric outcomes such as the length of in-hospital stay and patient mortality, which are otherwise challenging to furnish due to lack or incorrect data[3,4].

Despite mounting evidence in favor of AI in anesthesia, its role in RA practice is still preliminary. The utilization of AI in ultrasound-guided procedures is an essential integration of newer technology, which present-day clinicians are exploring[4]. The success of regional anesthesia relies on the sound knowledge of sonoanatomy and the expertise to carefully delineate the structure under ultrasound imaging. However, this may not appear as simple as it sounds because of varied sonoanatomy. Because ultrasound-guided nerve blocks rely on imaging, AI could potentially be used to improve image optimization and its interpretation in real-time during the procedure, which would help physicians identify the target nerve and avoid nerve block-related complications[1,4].

ROLE OF AI IN USG FOR RA

AI-assisted ultrasound-guided RA can facilitate the identification of anatomical structures, optimize the sonographic image, improve needle visibility, and help non-experts locate the correct USG anatomy to perform regional blocks[4]. The use of AI in USG-RA has been found to help increase the success rate of nerve blocks, improve safety, and decrease the complication rate. With the integration of AI in ultrasound, the safety profile of regional blocks can be further enhanced by detecting and labeling anatomical structures (*e.g.*, blood vessels) to reduce or avoid unwanted injury. AI can also be used as an educational tool to train novice anesthesiologists and trainees by helping identify sonoanatomy for USG-RA[4,5].

AI can significantly help decrease the risks and complications associated with injuring vital structures while performing a regional technique. AI can detect structures for various ultrasound-guided procedures, like nerves for nerve blocks and veins for central venous cannulation[1,4]. Convolutional neural networks are the most commonly employed method of achieving ultrasound image cataloging[6].

Bowness *et al*[7] examined NerveBlox® AI software for the identification of structures while performing regional techniques. AI models accurately identified the target structure in 93.5% of cases (1519/1624) with false-negative and false-positive rates of 3.0% (48/1624) and 3.5% (57/1624), respectively. Also, the risk of block failure decreased by 81.3% (585/720). In another study, authors built their neural network to identify the sciatic nerve as it was scanned over the posterior thigh[8]. The primary aim was to train the system to detect important information and ignore irrelevant information. The performance of the convolutional network was compared with that of a traditional 2D U-Net network, and the in-house study approach performed better than the standard 2D approach. The studies mentioned above demonstrate that nerve detection for RA is realistic using AI tools. Still, for widespread clinical application, further robust literature is required to develop a more efficient tracking system[8]. Scholzen and Schroeder[9] also evaluated the usefulness of the NerveBlox AI tool for training and teaching purposes. Eleven anesthesiologists and 25 students participated and worked on standardized patients. Both faculty and resident anesthesiologists rated NerveBlox® AI software's utility as a teaching aid with ratings of 9 (IQR: 7.5-10, n = 11) and 10 (IQR: 9-10, n = 25), respectively.

In addition to recognizing specific structures in ultrasound images, researchers have used these neural networks to assist in identifying correct vertebral levels and other anatomical landmarks to aid epidural catheter placement[10].

AI can help rapidly examine big data that is otherwise difficult to interpret, including patient, operator, procedure, and drug-related details. It may be used to speculate strategic steps required to correctly perform a given nerve block[2]. There is also potential for AI to act as a supervisor or assistant to a novice anesthesiologist and rapidly identify scenarios to improve block success. AI has been used in RA to detect the correct insertion site, track the needle insertion, and facilitate needle tip localization and length localization. Needle tracking is one of the most widely used functions in computer vision. Several AI models have been documented to improve monographic anatomical target perception quality. A multiple-model data association is applicable in detecting nerves and vessels[2,11].

AI technology could improve the interpretation of USG anatomy by identifying nerve block-relevant targets (such as peripheral nerves and fascial planes) and help map optimal insertion sites by detecting the pertinent landmarks and guidance structures[1,2]. Moreover, AI allows for the standardization of clinical procedures by providing ultrasound views for anesthetists, and a real-time representation of anatomical structures for immediate decision-making during blocks can potentially allow automated nerve block techniques to be performed using a remote control system[1,11].

ROBOTICS IN RA

There are three categories of robotics in anesthesia: Pharmaceutical, cognitive, and mechanical. Pharmaceutical robots are exemplified by target-controlled anesthesia using electroencephalogram (EEG) as a feedback loop. Mechanical robots have the advantage of better precision and dexterity than humans, and cognitive robots perform as decision support systems[12].

In RA, ongoing work on computer-assisted or even robotically autonomous ultrasound-guided procedures could become real possibilities with enough literature in the future. The first robotic ultrasound-guided nerve blocks in humans were described as early as 2013 using the Magellan System with a success rate of 100%[13]. In another study on training anesthetists using a robotic arm driven by a joystick to assess learning curves on a nerve phantom, learning curves were improved compared with manual insertion. The steeper learning curve in the said study was likely due to the novelty of the technology[14].

Furthermore, there is a potential danger of too much reliance on robotic assistance during training, and the overall competence of trainees may be inadequate, exposing them to any emergencies and equipment failure. Therefore, it is crucial to carefully design robotic techniques in training as a feedback system to aid and not supplant the training process [13,14].

Future cognitive robotic systems will be able to inform the anesthetist of a problem and may also be capable of suggesting or administering the treatment. Recent examples include devices such as Safer Injection for Regional Anesthesia, which eliminates the need for an assistant during nerve block. It can aspirate during injection and cut off flow when injection pressure is more than 117 kPa[15].

RECENT ADVANCES

AI and robotics have substantial potential applications in the field of anesthesiology. Advancements in augmented and virtual reality mixed reality technologies, including advanced sensing systems, display systems, and simulation platforms, will likely be informed by further advancements in AI[12]. Augmented and virtual environments will be more realistic in the future with the addition of sensory modalities such as motion, sight, and touch, as they will provide operator feedback and can even be incorporated into autonomous mode mechanical robots to perform tasks[16].

Motion analysis was used to guide the clinical performance of experts and novices regarding supraclavicular brachial plexus block and showed differences between time, number of movements, and needle path length. The feedback helped improve the performance of trainees[16].

Eye-tracking has recently been used in ultrasound-guided RA to objectively assess trainees' difficulties, performance levels, learning curves, and decision-making[17]. Furthermore, reflective feedback based on real-time performance can potentially accelerate the ultrasound-guided RA learning process. A novel system (RA simulator and assistant) system provides reflective feedback using combined virtual feedback using MRI or computed tomography images of actual patients with haptic feedback[12]. In addition to anatomical navigation, augmented reality may be helpful in RA training. Poor accessibility and high cost of high-fidelity cadaveric training are its main limitations, and alternatives like virtual training platforms to provide cadaver-like simulation training will be a big boon in the future. Another novel application of virtual reality to ultrasound-guided RA has focused on patient-centered anxiety reduction and training using virtual reality distraction but has had mixed results[16,17].

LIMITATIONS AND ETHICAL IMPLICATIONS OF AI

AI comes with its limitations. AI is a newly developed tool that we must install in the right circumstances to solve a clinical problem. AI-assisted USG-RA is a novel medical technology that has recently developed and is still growing with each passing day. As this technology is relatively new, most clinicians are learning to use it in their everyday practice. Therefore, beginners' use of these technologies in daily practice may be more time-consuming with a variable learning curve. Also, we must acknowledge that using AI–based techniques may not necessarily result in superior outcomes compared to conventional methods and skills[1,2].

There can be a risk of image misinterpretation in cases of abnormal anatomy (*e.g.*, spinal fusion or reduced interspinous distance) as AI image interpretation is operator-dependent. This may paradoxically increase the incidence of block failure and undesirable trauma to critical structures if the color on the screen misleadingly affirms the practitioner. So, AI-based tools are no replacement for clinical skills and understanding[10].

AI algorithms are susceptible to data bias. Beyond the fundamental research biases, there can be both implicit and explicit biases in the healthcare system that can impact the large-scale data fed to train AIs and meaningfully affect the types of predictions that an AI tool will make to influence clinical decisions. Therefore, clinicians must work with data scientists and engineers to ensure the appropriate interpretation of scientific data[2,18].

The practice of anesthesiology is a fusion of science and art, and much of the data that clinicians gather comes from the clinician-patient relationship that builds on patients' trust in their doctor. It won't be easy to account for these aspects, even by complex AI algorithms. Furthermore, the extent to which patients will be keen to trust these algorithms remains to be seen. Therefore, further research should focus on better understanding the ethical, societal, and cultural implications of integrating AI into clinical systems. Furthermore, reducing inter-operator variability has been a critical driver of robotics technology. However, this may be achieved with simulation training, along with the appropriate objective

performance metrics[1].

Cost remains a significant barrier to robotic use in RA on a wide scale. Still, in the long term, they can be cost-effective if fewer complications occur with robotic assistance. Regulatory processes can be another barrier to AI technology[12].

Lastly, AI models will not understand the data's implications for specific patients; therefore, anesthesiologists should partner with other specialties and patients to help develop the strategy for the optimal use of AI[19].

CONCLUSION

The field of anesthesiology has enormous potential for applying AI-based tools, and anesthesiologists are actively pursuing research incorporating AI technology in various procedural and patient management programs. At present, there is minimal literature in this regard, so it will be vital for clinicians to incorporate these techniques into routine practice to assist in the practical translation of AI. However, future projections point towards using robotics in autopilot mode instead of real-time physicians, but clinical decision-making will likely remain in the human domain. There is limited data on the application of AI in RA, but the available literature is encouraging and should be explored further. Its application in ultrasound-guided nerve blocks improves the identification of structures and needle tips during in-plane needling. Mechanical robots assisting or automatically performing nerve blocks is also a realistic possibility with further technological advances and the availability of sound data.

FOOTNOTES

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Country of origin: India

ORCID number: Nitin Choudhary 0000-0002-8933-1222; Nishkarsh Gupta 0000-0002-8444-2564.

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EDITORIAL

Exploring the limited use of transdermal medications in psychiatry: Challenges and potential solutions

Mandeep Kaur, Meera Patel, Elizabeth Monis

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Mandeep Kaur, Meera Patel, Elizabeth Monis, Department of Psychiatry and Behavioral Health, Cape Fear Valley Medical Center, Fayetteville, NC 28305, United States

Corresponding author: Mandeep Kaur, MD, Assistant Professor, Staff Physician, Department of Psychiatry and Behavioral Health, Cape Fear Valley Medical Center, 711 Executive Place, 4th Floor, Fayetteville, NC 28305, United States. mandy.drmandeep@gmail.com

Abstract

Transdermal medications are an useful yet underutilized tool in the field of psychiatry. Despite numerous advantages of using this route of medication delivery, transdermal medications remain less popular compared to other routes of medication administration such as oral and intramuscular routes in the management of various psychiatric conditions. In this editorial, we examine the advantages of transdermal medications with a brief overview of transdermal being used in psychiatry and other medical specialties. We discuss the factors that play a role in their limited usage in psychiatry. We highlight certain patient categories who can specifically benefit from them and discuss potential solutions that can broaden the perspective of treating clinicians making this an intriguing avenue in the field of psychiatry.

Key Words: Transdermal medications; Psychiatric medications; Psychopharmacology; Treatment options; Potential solutions

Core Tip: The field of psychiatry is advancing at an exponential rate. The advancements made in the diagnostic and treatment modalities for various psychiatric conditions is exemplary. Transdermal route of medication delivery has been around for past few decades, however, this route has not been a favorable route in psychiatry practices due to various biochemical, patient as well as clinician preferences. In this editorial article we discuss this issue and bring forward some potential solutions to make transdermal medication delivery as a viable option in the area of psychiatry.

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INTRODUCTION

In today's 'instant and QR code culture' anything that can help to save time and effort is usually well-received. With skin being the largest organ of our body, the use of transdermal creams, ointments, and patches is a convenient route for delivery of medications. The need for further innovative methods and routes of delivery of mostly non-medicinal agents has been a driving force for scientific and pharmaceutical fraternities to do more groundbreaking research in this arena. The discovery that extent of absorption could be controlled by modifying the diffusion area of the cell and controlling the level of skin hydration was the key point for the development of transdermal patches[1]. In this review article, we explore why transdermal medications are still not considered to be a popular route of medicine delivery in clinical psychiatric practices. We also discuss the type of patients are more likely to benefit from transdermal route of medication delivery in psychiatry.

USE OF TRANSDERMAL MEDICATIONS IN OTHER MEDICAL SPECIALTIES

Before discussing the limited use of transdermal medications in psychiatry we review some of the factors that make this route of medication administration more acceptable and prevalent in other medical specialties. In addition to being convenient this route of medication administration is minimally invasive[2,3]. Pharmacokinetically, the frequent dosing of the medications is not necessary especially for the medications with a short half-life due to sustained steady-state blood levels[2]. It is a safer option for patients with hepatic impairment due to the avoidance of hepatic first-pass metabolism[2, 3]. The gastrointestinal side effects are reduced and the concerns for potential gastrointestinal drug-drug interactions and effects of food on absorption of medications are lower[3]. The delivery method is cost-effective when compared with other medication forms, as transdermal patches can deliver medications from 1 to 7 days[2,3].

Over the last few decades with further advancements in technology, the use of transdermal medications has come a way long ranging from the novel transdermal patch of scopolamine to treat motion sickness to the smart technology utilizing insulin patch that delivers insulin least invasively *via* the subcutaneous route with high accuracy for treatment of diabetes mellitus[4]. Similarly, transdermal estrogen and progesterone patch has been used for contraception and the management of menopausal symptoms in women such as hot flashes and night sweats since the 1980s. Transdermal estrogen products including patch and gel products have been approved for the prevention of postmenopausal osteoporosis by producing physiological estradiol levels[5]. The advantages include decreased side effects compared to the oral formulations, improved compliance and convenience of use.

CURRENT TRANSDERMAL MEDICATIONS USED IN PSYCHIATRY

Though limited, psychiatric transdermal medications have been utilized in management of some conditions in psychiatry [3,6]. One of the first available transdermal patch Scopolamine patch is used to treat sialorrhea, a side effect of psychotropic medications. The alpha-adrenergic Clonidine patch is utilized for control of impulsivity and hyperactivity in attention-deficit hyperactivity disorder (ADHD), Autism spectrum disorder, and Oppositional Defiant Disorder. Additionally, the clonidine patch is used to assist with sleep disorders, anxiety related to post-traumatic stress disorder, tics in Tourette syndrome and management of opioid withdrawal. For management of ADHD, the methylphenidate-based patch Daytrana allows for ease of use in children during the school hours. Xelstrym is an amphetamine-based transdermal patch more recently approved by the US Food and Drug Administration (FDA) in 2022 for management of ADHD.

Monoamine oxidase inhibitor Selegiline in patch form is effective with less side effects in the treatment of major depressive disorder and Parkinson's disease due to avoidance of first pass metabolism and helps to evade the associated dietary restrictions[3,6]. Estrogen and Testosterone patches have been shown to be effective in the treatment of depression, specifically in the elderly males and in women suffering from premenstrual dysphoric disorder and postpartum depressive disorder. Partial opioid agonist Buprenorphine transdermal patch is used for management of chronic pain. Rotigotine, a dopamine agonist, is used for management of Parkinson's disease.

Antipsychotics available in transdermal formulation include Asenapine patch that was approved by the FDA in 2019 for the treatment of schizophrenia. Several short and long-term trials have established the efficacy and tolerability of Asenapine patch, with its tolerability being similar to the more metabolically favorable second-generation antipsychotics [7]. Cholinesterase inhibitor Rivastigmine patch has shown benefits of convenient administration by the care givers of patients suffering with dementia. The new transdermal formulation of Donepezil has benefited Alzheimer's dementia patients with the advantage of decreasing the medication's gastrointestinal side effect profile[8].

One notable factor is that the pharmacokinetics of certain medications differ significantly when taken by another route as opposed to transdermal use. One example of this is Asenapine which when taken by the sublingual route escapes rapid hepatic metabolism with the advantage of rapid onset of action but still has limited bioavailability of only 35% by this route[9]. The transdermal route of delivery of Asenapine not only allows the by-pass of first pass metabolism it also results in steady and sustained release over a long period of time thus increasing its bioavailability. Similarly, Blonanserin is a second-generation antipsychotic used in Asian countries such as Japan and Korea. The Blonanserin transdermal patch was developed in Japan and launched in 2019. As compared to oral route, when the medication is delivered transdermally, steadier release of medication allows for stable plasma levels of the medication and lowers the risks for side effects such as extrapyramidal side effects[10].

WHY ARE TRANSDERMAL MEDICATIONS UNDER-UTILIZED IN PSYCHIATRY?

Transdermal medications remain less popular compared to other routes of medication administration such as oral and intramuscular routes in the management of various psychiatric conditions.

The variability in absorption resulting in questionable outcomes is a critical factor in the clinical use of medications *via* this route. The absorption rates of medications depend on skin permeability, area, temperature and the metabolic activity of the skin[6,11]. The development of an effective transdermal delivery system directly co-relates with the biochemical properties of each drug molecule being targeted[6,12]. In order to adequately penetrate through the skin barrier the drug molecule has to be non-ionic and lipophilic in nature[6]. The medications with lower molecular weight and lower melting points can be easily formulated into a transdermal patch as they permeate the skin more efficiently[11].

Another factor playing a role in their low popularity is the slower onset of action compared to intramuscular or intravenous routes which makes them less efficient for rapid symptom control such as a panic attack or episode of acute agitation[11]. Therefore, the use of transdermal medications are not utilized in emergency department and acute inpatient settings.

Limited psychoeducation of patients and caregivers is another crucial reason resulting in lower use of transdermal medications in routine clinical practices. Hot temperatures can impact the efficacy of the transdermal medication delivery [11]. The discussion and education of patients regarding choosing the appropriate site of application and maintaining skin temperature is important. Avoiding hot showers or baths needs to be discussed.

Medication errors and misuse is another concern[11]. Case reports of fentanyl patch overdoses due to chewing and transmucosal absorption have been documented. Most common medication error associated with transdermal medications reported has been application of more than one Rivastigmine patch at one time without removal of the previous one in patients with dementia. There is always the potential for development of localized skin irritation or in rare cases development of contact dermatitis.

Patients with sensory sensitivities in conditions such as autism spectrum disorder may find the sensation of wearing transdermal medications to be uncomfortable. The adhesive or texture of the patch could be overwhelming and could cause distress in this patient population.

PATIENTS WHO CAN BENEFIT FROM TRANSDERMAL MEDICATIONS

Pediatric population

Adherence to treatment for chronic conditions is challenging and ADHD in pediatric age range is not any different in that regard. The Daytrana patch was the first long-acting methylphenidate transdermal delivery system that was introduced into the market in May 2006. Since its launch it has been utilized in younger pediatric patients due to their challenges of taking oral medications such as difficulty in swallowing pills or resistance to comply[13]. A review of clinical trials evaluating the use of a methylphenidate patch in the treatment of ADHD in children and adolescents found this route of medication delivery to be safe and showed improved adherence to treatment[14]. This route was found to offer additional practical advantages to the patients and caregivers including once-daily dosing and flexible wear times with visual confirmation of compliance. The review noted that this medication delivery system had a side-effect profile similar to that of other stimulants.

Interestingly, a gap of 16 years was noted in the development of another transdermal patch for the management of ADHD in pediatric populations. Xelstrym is an amphetamine-based transdermal medication and a recently available treatment option for ADHD. The availability of an amphetamine-based transdermal medication option is helpful for patients who respond better to amphetamine-based medications as compared to methylphenidate-based medications.

Geriatric population

Controlled use of transdermal psychotropic medications exists in general clinical practice for geriatric populations to date. Of the available transdermal treatment options, several exist for treating psychiatric and neurologic disorders including dementia, depression, and pain associated with post-herpetic neuralgia[15]. In the geriatric population, where cognitive reserves are frequently limited and adherence to oral medication regimens is often unlikely given resistance, misunderstanding, or other deficits, a patch option can be simpler for patients and/or caregivers to manage regularly. The involvement of caregivers in this population is a unique consideration, and having a visual indicator of medication compliance in the form of a patch can serve as an immense benefit.

Rivastigmine transdermal patch has been approved for utilization since 2007 to treat mild to severe Alzheimer's dementia and mild to moderate Parkinson's dementia[16]. The rivastigmine patch has shown reasonable tolerance and efficacy while eliminating some adverse side effects of its capsule counterpart such as gastrointestinal side effects[17]. Notably, in the IDEAL RCT study examining safety, tolerability, and efficacy of the rivastigmine patch compared to the capsule and placebo treatments, more than 70% of caregivers reported preference of patches for reasons of ease of scheduling, self-sufficiency, and minimal side effects[17,18].

Rotigotine is a dopamine agonist which aids in Parkinson's treatment. However, it is only available in transdermal format due to poor oral bioavailability and extensive first pass metabolism, highlighting a unique advantage of the transdermal delivery system[15]. Transdermal administration avoids the more pulsatile dopaminergic stimulation of repeated oral dosing that predisposes to dyskinetic complications; this transdermal medication has utility in a perioperative setting when oral agents cannot be administered. Additionally, it can also treat restless leg syndrome making it a versatile treatment option for geriatric patients[15].

POTENTIAL SOLUTIONS

Ongoing research and publications on the safety and effectiveness of transdermal psychotropic medications will help to build further credibility. Increasing awareness among healthcare professionals as well as patients is crucial. Continuing educational programs, highlighting benefits such as improved treatment adherence with lower associated side effects and collaboration with mental health organizations can contribute to widespread acceptance. Emphasizing the convenient and consistent release of medication will help to promote transdermal medication options as viable alternatives in management of psychiatric conditions. Partnering with pharmaceutical companies to invest in developing transdermal medications for various psychiatric conditions will broaden the available choices. Incorporating patient testimonials and success stories into promotional materials will provide real-world perspectives and help to alleviate concerns about the use of transdermal medications in the field of psychiatry.

CONCLUSION

Transdermal medications have shown to be a useful, yet underutilized tool in the field of psychiatric disorders. Despite biochemical limitations, there are several psychiatric medications that could be beneficial in this administrative form. Certain patient population subsets have proven benefit from transdermal patches and more could likely benefit with the further education, awareness, and collaborative care.

FOOTNOTES

Author contributions: Kaur M designed the research study; Kaur M, Patel M, Monis E performed the research and wrote the manuscript; Kaur M revised the manuscript.

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Country of origin: United States

ORCID number: Mandeep Kaur 0000-0002-2795-6198.

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EDITORIAL

Maintenance of stem cell self-renewal by sex chromosomal zinc-finger transcription factors

Katsuhiro Kita, Celine Morkos, Kathleen Nolan

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Katsuhiro Kita, Celine Morkos, Kathleen Nolan, Department of Biology, St. Francis College, Brooklyn, NY 11201, United States

Corresponding author: Katsuhiro Kita, PhD, Assistant Professor, Department of Biology, St. Francis College, 179 Livingston Street, Brooklyn, NY 11201, United States. kkita@sfc.edu

Abstract

In this Editorial review, we would like to focus on a very recent discovery showing the global autosomal gene regulation by Y- and inactivated X-chromosomal transcription factors, zinc finger gene on the Y chromosome (ZFY) and zinc finger protein X-linked (ZFX). ZFX and ZFY are both zinc-finger proteins that encode general transcription factors abundant in hematopoietic and embryonic stem cells. Although both proteins are homologs, interestingly, the regulation of self-renewal by these transcriptional factors is almost exclusive to ZFX. This fact implies that there are some differential roles between ZFX and ZFY in regulating the maintenance of self-renewal activity in stem cells. Besides the maintenance of stemness, ZFX overexpression or mutations may be linked to certain cancers. Although cancers and stem cells are double-edged swords, there is no study showing the link between ZFX activity and the telomere. Thus, stemness or cancers with ZFX may be linked to other molecules, such as Oct4, Sox2, Klf4, and others. Based on very recent studies and a few lines of evidence in the past decade, it appears that the ZFX is linked to the canonical Wnt signaling, which is one possible mechanism to explain the role of ZFX in the self-renewal of stem cells.

Key Words: ZFX; ZFY; Self-renewal; Stem cell; Sex chromosome regulators

Core Tip: This review article mainly focuses on stem cell self-renewal controlled by a sex chromosomal zinc-finger transcriptional factor, zinc finger protein X-linked (ZFX). We begin the review with the most recent paper reporting the autosomal gene regulation by ZFX, then we would like to shed light on missing links between ZFX and self-renewal signaling. Based on a line of evidence from very recent studies, it appears that the ZFX-canonical Wnt signaling (linked to c-Myc) emerged as one key pathway. Although ZFX plays an important role in stem cell self-renewal, it may be certain stem/progenitor cell-specific, and further studies will be necessary.

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INTRODUCTION

Transcription is the process of synthesizing an RNA strand using one template DNA strand of the genomic DNA using RNA polymerase II (RNA pol II) in eukaryotes[1,2]. It is one main rate-limiting processes in gene expression, and understanding transcriptional regulation is critical to elucidating the diversity in biological processes. Eukaryotic mRNA synthesis requires the assembly of the general transcription factor complex[3,4] prior to the recruitment of RNA pol II. Such mRNA transcriptional processes are the centerpiece of central dogma to produce functional protein molecules to orchestrate cellular signaling, including stem cell (SC) self-renewal, and a variety of transcription factors assist in fine-tuning of mRNA synthesis.

The complete human genome contains 19969 protein-coding genes[5]. Although the majority of genes are autosomal, there is sex divergence based on differential gene expression between males and females, as recently analyzed systematically[6]. Besides sex hormones, there are many genes involved in transcription on the X and Y chromosomes. One human X chromosome carries 829 protein-coding[7] (835 genes as of 2024; Supplementary Table 1) and the human Y chromosome contains 196 protein-coding genes[8] yet 107 out of 196 proteins have not been characterized. Although this number was published in 2009, still only 66 protein-coding genes on the Y chromosomes are listed with their loci as of 2024 (Supplementary Table 2). The middle region of the X and Y chromosomes are non-recombined regions (these are called non-pseudoautosomal regions, NPX and NPY, respectively). Shortening of the Y chromosome over 100 million years resulted in the loss of genes, thus, the Y chromosome only carries approximately 1/8 of the known protein-coding genes contained in the X chromosome. Even if all 196 protein-coding genes on the Y chromosome were characterized, it still would be 25% of those found on the X chromosome. Despite this divergent evolution of the X and Y chromosomes, many paralogs exist between the X and Y chromosomes. And more importantly, certain genes on these sex chromosomes are transcriptional regulators. A study published last year revealed that 10 X chromosomal genes have been discovered as candidates driving sex differences in common diseases and sex chromosome aneuploidies[9] The following study by the same group showed the autosomal gene regulation by X and Y chromosomes[10], implying that some of X- or Y-linked transcription factors may govern (SC self-renewal signals. Zinc-finger transcription factors have been reported in their role in the self-renewal of SCs; for example, KLF4[11], zinc-finger protein X-linked (ZFX; in glioblastoma SCs)[12], and Sall4B[13]. Some of the listed X and Y chromosomal transcriptional regulators are likely to play a pivotal role in the maintenance of self-renewal. The outstanding hypothesis from the line of studies is that some of the transcription factors on the X or Y chromosome (*i.e.*, ZFX) may activate the transcription of the gene(s) necessary for the self-renewal of SCs.

In this review, we would like to open the topic with a very recent paper describing autosomal gene regulation by X and Y chromosomes, then develop the discussion to be centered around zinc finger protein X-linked (ZFX) and its role in the self-renewal of SCs and possible subsequent pathways. We would like to conclude the discussion with newly emerging, biological questions.

REGULATION OF AUTOSOMAL GENE EXPRESSION BY SEX CHROMOSOME GENES (QUESTION: ZFX EXPRESSION ON THE ACTIVE X CHROMOSOME)

Both X and Y chromosomes are responsible for the expression of approximately half of autosomal genes in lymphoblastoid and dermal fibroblast cell lines. A very recent study by the Page lab highlighted the role of several genes in the NPX and NPY genes on the X and Y chromosomes as potential candidates; *ZFX/ZFY*, *DDX3X/DDX3Y*, *KDM5C/KDM5D*, and *KDM6A/UTY*)[10]. Using extensive analyses including X-isochromosomes and X-Y translocated chromosomes, the study confirmed that the dose-dependent autosomal gene activation is not caused by the pseudoautosomal region of the sex chromosomes – but rather, a missing part of the NPX/NPY negatively impacted autosomal gene regulation. Although both *KDM6A* and *ZFX* escape X chromosome inactivation, the role of *ZFX* as a transcription factor certainly makes sense to explain global autosomal transcriptional regulation. Intriguing to find out if there were differences between ZFX and zinc finger gene on the Y chromosome (ZFY) in autosomal gene regulation.

THE STRUCTURAL DIFFERENCE BETWEEN ZFX AND ZFY

Both ZFX and ZFY are encoded on the sex-linked part of the mammalian X- and Y-chromosomes, respectively. Both gene products are Zinc-finger transcriptional factors[14-16]. As uncovered from studies in the 1990s, indeed both ZFX and ZFY function as transcriptional activators. ZFX's target sequence is AGGCCTAG[17] and ZFY's target sequence is AGGCCY [18]. So, essentially both transcription factors share a similar consensus sequence as the target.

Structurally, ZFX and ZFY are fairly similar, paralog, and show 64% homology in their DNA alignment[19]. When ZFX and ZFY sequences are aligned at the protein level, 92% of the amino acids are identical (Figure 1). Human ZFX is composed of 805 amino acids (NP_003401.2) and ZFY is 801 amino acids (NP_003402.2), respectively. Thus, both proteins are structurally almost identical. However, as described later, the majority of research exclusively revealed the cellular function of ZFX. The role of ZFY in cellular functions might be similar to what ZFX does, although it remains elusive.

ZFX AND ZFY IN SELF-MAINTENANCE OF STEM CELLS

The first study describing the role of ZFX in the self-renewal of stem cells (SCs) was published by the Reizis lab in 2007 [20]. One significance of this study is the revelation of the role of ZFX as a self-renewal factor in both embryonic stem cells (ESCs) as well as hematopoietic stem cells (HSCs) using mouse model systems. This study was soon followed by a report that ZFX was one of the 13 sequence-specific transcription factors[21]. Interestingly, ZFX deficiency only affected adult HSCs but not fetal HSCs and erythromyeloid progenitors[20]. Although it is not difficult to imagine the global role of ZFX in SC self-renewal, there is only one more study reporting the confirmation of ZFX in SC self-renewal several years later using human ESCs[22]. As induced pluripotent SCs can be established with three minimum transcription factors, Klf4, Oct4, and Sox2[23], it is logical to predict the induction of these three factors by ZFX. Nevertheless, to date, the direct link of ZFX to Klf4, Oct4, and Sox2 has been poorly understood. Therefore, such a pathway may be unlikely to explain the contribution of ZFX in the self-renewal of SCs. As the initial reports of induced pluripotent SCs used c-Myc in addition to Klf4, Oct4, and Sox2[24,25], the other possibility is that ZFX may induce c-Myc expression to enhance the capability of SC self-renewal. ZFX can regulate the expression of c-Myc as well as a few other embryonic stem cell-specific, self-renewal regulators such as Tbx1 and Tcl1 directly[20], ZFX regulation of c-Myc may make much more sense. Although this study focused on glioblastoma, it was shown that ZFX specifically binds to the GGGCCCCG sequence on the human c-Myc promoter region[12]. Around the same time, ZFX was shown to act as a preventive factor for the differentiation of acute T-lymphoblastic and myeloid leukemia SCs[26].

Thus, one possible downstream pathway of ZFX regulation in SC self-renewal may be the direct induction of c-Myc expression (Figure 2A). Nevertheless, there are still limited numbers of studies that have been done to dissect the transcriptional mechanism of c-Myc mRNA expression by ZFX. We should note that the putative ZFX binding sequence, GGCCCCG[12] is apparently quite different from the ZFX sequence discussed in the previous section[17], and still slightly different from the other sequence discussed in the next section. Despite such controversy, it is possible that ZFX contributes to the SC self-renewal, probably *via* c-Myc expression. In addition, the genome-wide nucleosome occupancy study employing chromatin immunoprecipitation and DNA sequencing demonstrated that the nucleosome occupancies at c-Myc and ZFX sites do not show similar trends when compared between mouse embryonic fibroblasts, ESCs, and neural progenitor cells[27]. Besides the target sequence found in the c-Myc promoter, one remaining unanswered question in humans may be whether or not ZFX is a specific self-renewal factor for adult HSCs. If the case in mice is the same in humans, we can assume that the same mechanism governs the self-renewal of adult HSCs in humans, although there is no experimental proof showing it so far. Regarding this point, the commentary published in 2007 is very insightful[28]. Although ZFX is illustrated as an anti-apoptotic factor, the other factor(s) cooperating with ZFX is/are different between HSCs and ESCs. It would be interesting to investigate if such different factors can be found between fetal and adult HSCs.

The role of ZFY in the self-renewal of SCs has not been described as an independent study yet, although the most recent study by the Page lab[10] demonstrated similar autosomal gene regulation by ZFX on the inactive chromosome(s) and ZFY on the Y chromosome. Thus, additional studies may eventually reveal the similar (or differential) functions of ZFY. Because many fewer individual studies are dissecting the role of ZFY in self-renewal or other roles, we will focus on ZFX in the following sections. In short conclusion, it may be more reasonable to hypothesize indirect control of c-Myc expression by ZFX.

ZFX AND WNT SIGNALING

A very recent study reported that the overexpression of ZFX can promote Wnt3 expression and thus the growth of chronic myeloid leukemia stem/progenitor cells[29]. Although this study used cancer SCs, it clearly showed the link between ZFX and Wnt3 signaling in self-renewal. It should also be noted that this study conducted a comparable biological analysis and found that all tested vertebrates (human, mouse, rat, cattle, and dog) share the 100% conserved consensus ZFX-binding sequence (GGGCCGGGCGG) in the promoter region of the Wnt3a gene. There is no other study showing the link between ZFX and other Wnt genes to date, however, the outcome of this study really supports the pioneering discovery showing the role of Wnt (Wnt3a) as an SC growth factor[30,31]. In fact, the Wnt3a knockout was an embryonic lethal due to a reduction of HSCs and progenitor cells in the fetal liver[32].

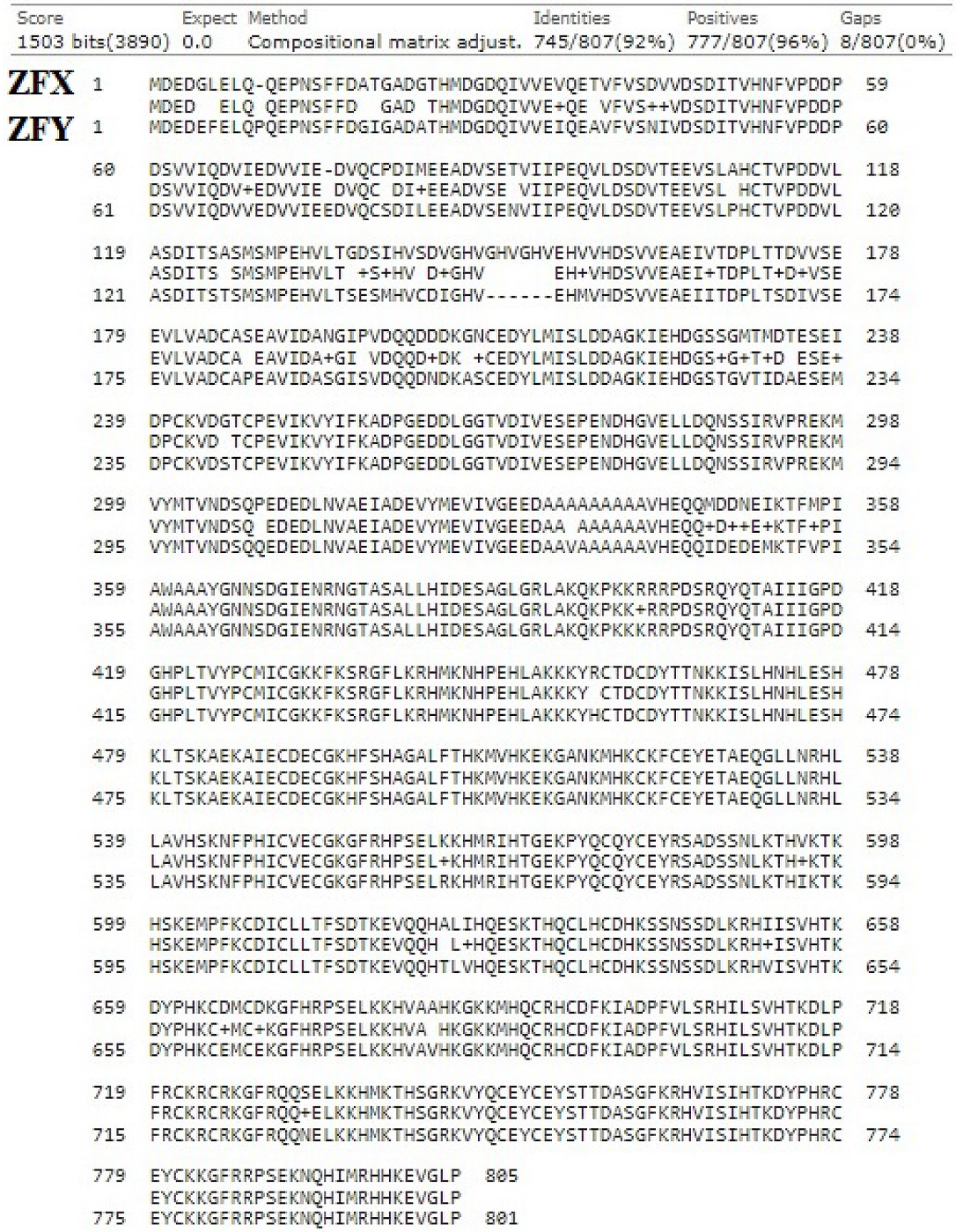

Figure 1 The sequence alignment of human ZFX (top) and ZFY (bottom). Protein BLAST for two sequences (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins&PROGRAM=blastp&BLAST_PROGRAMS=blastp&PAGE_TYPE=BlastSearch&BLAST_SPEC=blast2seq&DATABASE=n/a&QUERY=&SUBJECTS=) was used.

Wnt signaling has been well-documented as one of the key-signaling pathways in regulating the fate of SCs through asymmetric cell division of SCs. The study by the Weissman lab[30] would be the first that demonstrated the role of Wnt signaling in SC (in this case, HSCs) self-renewal. The role of Wnt in asymmetric cell division and self-renewal is well-explained in a review by Clevers *et al*[33]. The binding of Wnt to the cell surface receptor, Frizzled, prevents b-catenin from degradation and thus promotes transcription controlled by TCF/LEF. Interestingly, a cell on the side of Wnt binding keeps the progenitor, losing the capability of SCs to divide

In humans, there are a total of 19 Wnt genes[34]. Among them, the role of Wnt in self-renewal seems to be specific to Wnt3a, at least in the self-renewal of ESCs. One study showed that Wnt3a, but not Wnt11, specifically supports ESC renewal[35]. Note that this study used mouse ESCs and feeder cells expressing Wnt3a. In the same year, a different study also showed the role of Wnt3a in mouse ESC renewal[36]. This study confirmed that recombinant Wnt3a is not effective in maintaining the pluripotency of mouse ESCs. However, one key point in this study was that the synergistic action of LIF can maintain the pluripotency of mouse ESCs, if both ZFX and ZFY are added as supplements in the media.

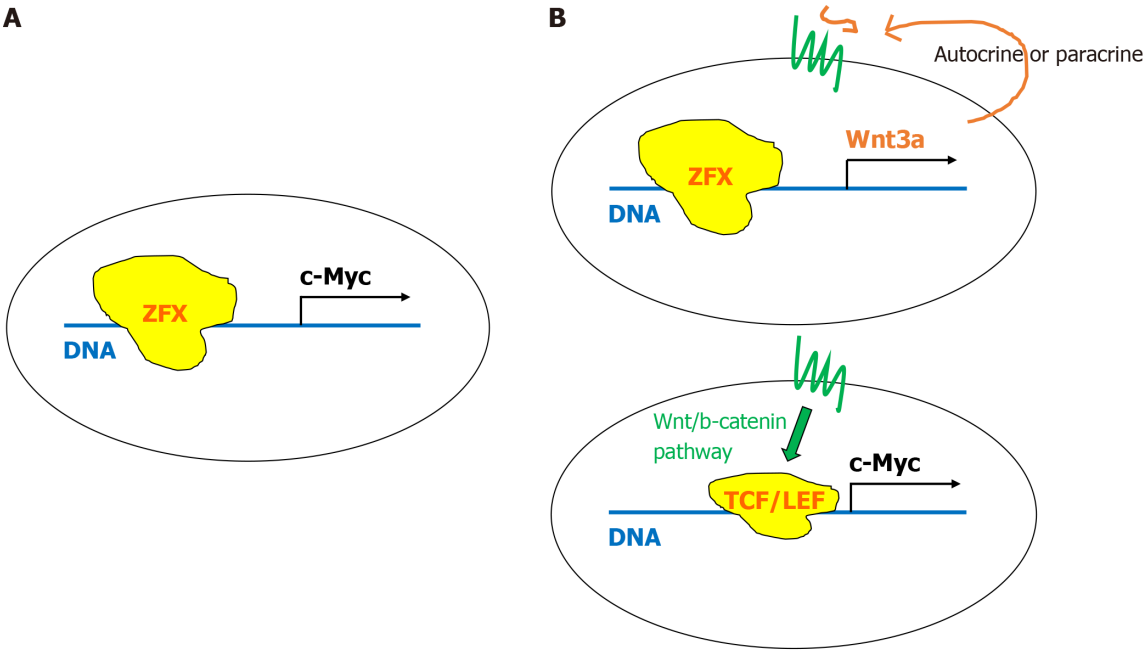

Figure 2 The schematic figure summarizes the potential self-renewal signaling driving c-Myc expression. A: Direct control of c-Myc expression by ZFX; B: Indirect control of c-Myc expression through canonical Wnt/-catenin signaling. ZFX first binds the consensus sequence upstream of the Wnt3a gene to induce the expression of the Wnt3a protein. Secreted Wnt3a binds to its receptor by either autocrine or paracrine. TCF/LEF: T-cell factor/lymphoid enhancer factor.

It is not surprising to imagine the correlation between Wnt3a and cancer SCs—In fact, there are several studies reporting the role of Wnt3a in colorectal and breast cancer[37,38].

In summary, the ZFX-Wnt3a axis appears to be a key pathway in maintaining the stemness of certain SCs as well as some cancer cells. Because it is relatively well-acknowledged in the field of the link of Wnt/b-catenin signaling with c-Myc expression[39-41] and the role of Wnt3a[42], it may be more reasonable to presume that ZFX-induced expression of Wnt3a causes either autocrine or paracrine activation of canonical Wnt/b-catenin signaling, leading to the induction of c-Myc (Figure 2B). Additional studies would still be informative to confirm the ZFX-Wnt3a axis in SCs, especially in HSC self-renewal and potential roles in cancer. As mentioned in the introduction, we would like to focus on SC self-renewal in this review.

CONCLUSION

ZFX has emerged as a global transcriptional regulator[10], and it has already been shown as a key transcriptional factor for the self-renewal of SCs[20,22]. Based on published studies, c-Myc and Wnt3a have emerged as molecules linking ZFX with SC self-renewal. Although ZFX appears to be a key factor in assisting SC self-renewal, additional time and studies will be necessary to see if ZFY also shares the same role as ZFX. This is currently one unanswered question. Besides the difference between ZFX and ZFY, there would be a few potentially novel biological questions associated with these studies: (1) Is the transcriptional activity of ZFX maintained in the same way between males and females? (2) If there is a chromosome dosage-dependent difference in ZFX activity; does it affect the self-renewal capability between females and males? and (3) What may be the difference between ZFX on active and inactive X chromosomes?

There are a few points that might command our attention. Although the ZFX target sequence(s) may need to be further investigated, the ZFY target sequence is AGGCCY, which is different from reported ZFX target sequences[12,29], maybe except the closest one[17]. Thus, ZFY may still not have the same capacity, such as SC self-renewal, that ZFX has. Supporting this notion, ZFY was not listed as one of the 13 sequence-specific transcriptional factors in genome-wide, chromatin immunoprecipitation-coupled DNA sequencing[21]. Although the structure of ZFY in solution was reported using nuclear magnetic resonance three decades ago[43], there is no experimentally confirmed structural information on ZFX protein. Therefore, despite very similar primary structures between the two proteins (Figure 1), it might be still worth revisiting and comparing both protein structures with more advanced technologies.

Females probably could express (slightly) more proteins that are regulated by ZFX, as ZFX can escape X chromosome inactivation. Does this mean that females may have higher regeneration potential, especially in the reconstruction of the hematopoietic system?

FOOTNOTES

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Country of origin: United States

ORCID number: Katsuhiro Kita 0000-0001-7392-1722.

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OPINION REVIEW

Point-of-care ultrasound in nephrology: A private practice viewpoint

Rajiv Sinanan, Afsheen Moshtaghi, Abhilash Koratala

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Rajiv Sinanan, Arizona Kidney Disease and Hypertension Centers, Phoenix, AZ 85016, United States

Afsheen Moshtaghi, Department of Medicine, Verde Valley Medical Center, Cottonwood, AZ 86326, United States

Abhilash Koratala, Division of Nephrology, Medical College of Wisconsin, Milwaukee, WI 53226, United States

Corresponding author: Abhilash Koratala, FASN, MD, Associate Professor, Division of Nephrology, Medical College of Wisconsin, 8701 W Watertown Plank Road, Room A 7633, Milwaukee, WI 53226, United States. akoratala@mcw.edu

Abstract

Point-of-care ultrasound (POCUS) is a limited ultrasound examination performed by the clinician at the bedside, emerging as a complement to physical examination across various medical specialties. In the field of nephrology, its integration has been gradual, primarily limited to guiding procedures like temporary dialysis catheter placement or, in some cases, diagnostic kidney ultrasounds. In reality, the assessment of hemodynamic status at the bedside holds immense value for nephrologists, yet there exists limited awareness among practitioners regarding its implementation. While there is a growing trend towards incorporating multi-organ POCUS training in fellowship programs, private practice nephrologists remain relatively uninformed. This discussion explores the untapped potential of POCUS as a valuable diagnostic tool in everyday nephrology practice, demonstrating its effectiveness in diverse clinical settings, ranging from medical wards to outpatient dialysis units. Additionally, we delve into the challenges hindering its widespread adoption and consider the future trajectory of this innovative approach.

Key Words: Point-of-care ultrasound; Bedside ultrasound; Nephrology; Hemodynamics; Cirrhosis; Acute kidney injury

Core Tip: The integration of point-of-care ultrasound (POCUS) into nephrology practice offers significant potential to streamline diagnosis and enhance patient care. Despite some barriers to implementation, such as time constraints and initial costs, the benefits of POCUS in improving diagnostic accuracy and practical outcomes are substantial. By leveraging available resources and gradually incorporating POCUS into practice, nephrologists can overcome these barriers and harness the full potential of this valuable diagnostic tool.

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INTRODUCTION

Physical examination has long been regarded as a vital component of bedside diagnosis and medical decision-making, involving the interpretation of physical findings alongside medical history and laboratory data. In recent decades, point-of-care ultrasonography (POCUS) has emerged as a valuable adjunct to physical examination across various medical specialties. POCUS entails clinician-performed focused ultrasound examinations at the bedside to address clinical queries, aiming to quickly establish diagnosis, narrow the differential, or guide a bedside procedure[1,2]. While the use of imaging guidance for procedures like central venous catheter placement is well-established, diagnostic POCUS remains relatively overlooked and poorly understood by many physicians. The current scope of POCUS in nephrology is wide, as illustrated in Figures 1 and 2. Although some nephrology fellowship programs are incorporating efforts to teach multi-organ POCUS[3], training in diagnostic POCUS and expertise among nephrologists beyond kidney ultrasound remain rudimentary at present. Particularly in private practice settings, which often have a heavier clinical workload compared to academic environments, the uptake of POCUS is additionally hindered by a lack of awareness and limited training opportunities. However, we firmly believe that the substantial clinical load in this setting positions POCUS as an even more advantageous tool to streamline diagnosis, reduce cognitive burden on the physician, and enhance patient care. To gain a better understanding of POCUS, it is essential to recognize its clinical utility. In this review, we will delve into real-life scenarios that demonstrate various POCUS applications, drawing from the experiences of a private practice nephrologist (author RS) and additional insights provided by an academic nephrologist (author AK). Author AM is RS's trainee in a community hospital setting. Our aim is to convincingly present the case that integrating this highly effective bedside diagnostic modality into one's busy practice is a worthwhile investment.

CLINICAL CASES

The clinical cases presented below are not meant to provide exhaustive case presentations, but rather to emphasize the pivotal role played by POCUS in diagnosis and management for each scenario. We will endeavor to succinctly explain the significance of abnormal findings. Regarding equipment, all images shown were captured using a multipurpose handheld ultrasound device. Of note, the image quality and available features vary widely depending on the cost of the ultrasound device. While handheld devices (often connectible to tablets or cell phones) do not match the image quality of traditional cart-based ultrasound machines, they offer enhanced portability for private practice nephrologists who typically round in multiple clinical facilities and settings. The key is to understand the limitations of the equipment being used and the images obtained in a given patient; for instance, "Do these images sufficiently answer the focused clinical question(s) I am asking?"

Case 1: Mitigating a frequent hospitalization trigger among chronic kidney disease patients

We have an elderly female with stage 3b chronic kidney disease (CKD) and a history of chronic obstructive pulmonary disease (COPD) presenting for routine clinic follow-up. She complains of shortness of breath on exertion but is otherwise doing well. There is no chest pain. Her blood pressure is well-controlled on two antihypertensive medications, including a calcium channel blocker, and exhibits trace to 1 + edema.

Now, the questions for the nephrologist are - Is the exertional dyspnea of cardiac origin, or is it attributable to COPD? Could the edema signify congestive heart failure (CHF), or might it be related to her calcium channel blocker? Outpatient evaluation with an echocardiogram, chest X-ray (CXR), brain natriuretic peptide (BNP) measurement, stress testing, pulmonary function testing, *etc.*, could entail weeks of waiting. Lung auscultation yields no notable findings making COPD exacerbation less likely, and her oxygen saturations are normal on room air.

POCUS enhanced physical exam findings: Lung POCUS revealed diffuse B-lines, indicative of an interstitial pattern (often observed with pulmonary edema, pneumonia, fibrosis). Focused cardiac ultrasound depicted a qualitatively normal ejection fraction without gross regional wall motion abnormalities but demonstrated left ventricular hypertrophy and an abnormal mitral Doppler pattern of elevated E/A ratio > 2, along with an L-wave consistent with diastolic dysfunction and elevated left atrial pressure[4]. Based on these findings, a diagnosis of cardiogenic pulmonary edema

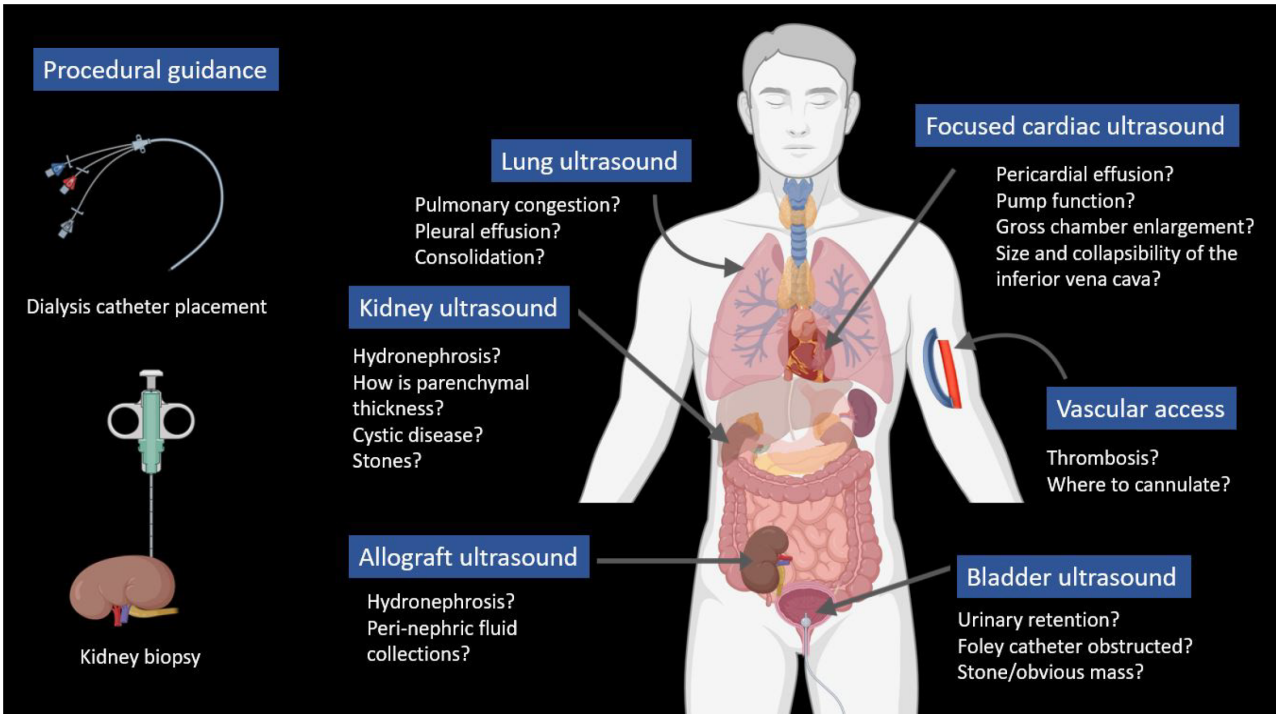

Figure 1 Basic nephrology-related point-of-care ultrasonography: This figure illustrates the organs examined and common clinical questions encountered[2]. Basic POCUS includes greyscale ultrasound and color Doppler but excludes spectral Doppler, which assesses blood flow patterns and velocities. Citation: Koratala A, Kazory A. An Introduction to Point-of-Care Ultrasound: Laennec to Lichtenstein. *Adv Chronic Kidney Dis* 2021; 28: 193-199. The authors have obtained the permission (Supplementary material).

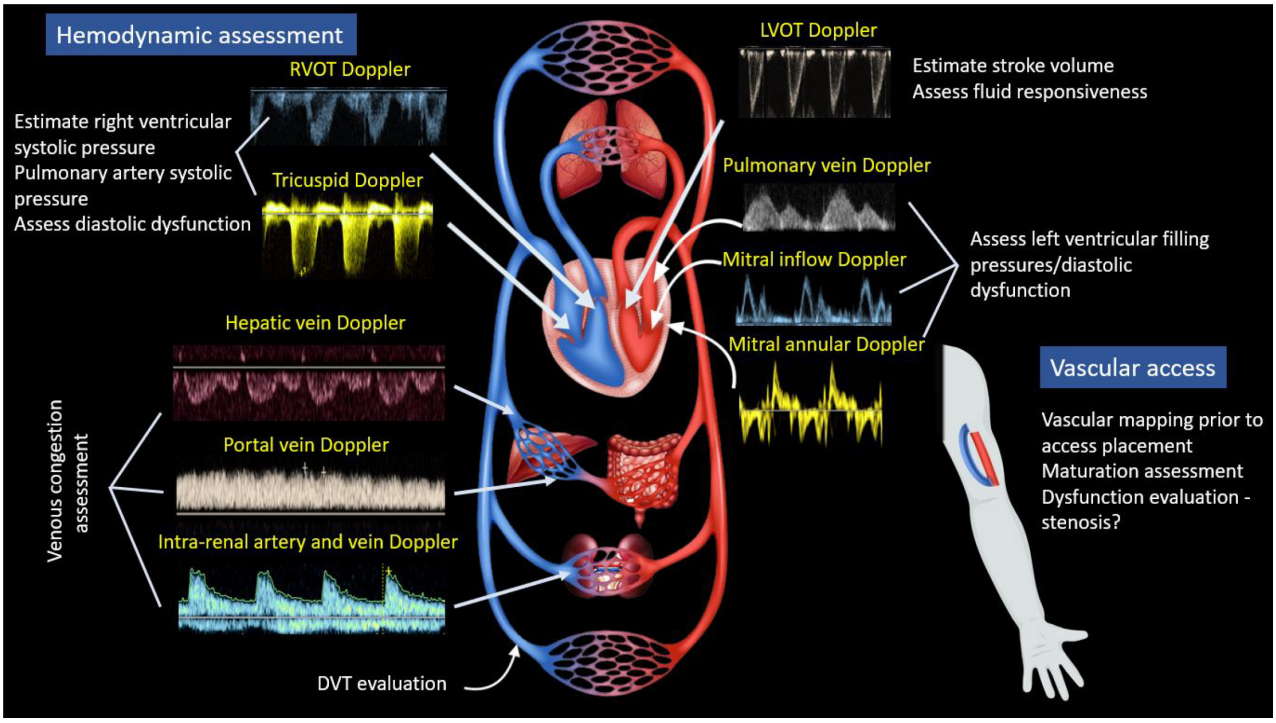

Figure 2 Advanced nephrology-related point-of-care ultrasonography applications involving spectral Doppler[2]. RVOT: Right ventricular outflow tract; LVOT: Left ventricular outflow tract; DVT: Deep vein thrombosis. Citation: Koratala A, Kazory A. An Introduction to Point-of-Care Ultrasound: Laennec to Lichtenstein. *Adv Chronic Kidney Dis* 2021; 28: 193-199. The authors have obtained the permission (Supplementary material).

[heart failure with preserved ejection fraction (HFpEF)] was made. In addition to cardiology referral, diuretics were promptly initiated, leading to rapid improvement. Subsequent POCUS assessment during follow up visit revealed a normal A-line pattern in the lungs, indicative of response to diuretics (Figure 3). It's worth mentioning that lung ultrasound demonstrates greater sensitivity compared to both physical examination and CXR in detecting cardiogenic pulmonary edema, which explains normal auscultation findings in our patient[5].

How did POCUS help? Obtaining conventional diagnostics such as CXR, BNP, and formal echocardiography, which provide a definitive diagnosis, may take days to weeks. However, with POCUS, the diagnosis of cardiogenic pulmonary edema and HFpEF was swiftly made at the bedside, saving valuable time. POCUS also facilitated objective evaluation of treatment response and potentially averted hospital admission for acute decompensated heart failure.

Case 2: Avoiding 'obstructions' to kidney care

A middle-aged female, with a history of renal calculi, presents to the outpatient clinic with poorly localized abdominal pain and subjective fever. Urinalysis performed in the office revealed hematuria and pyuria. Despite her symptoms, she did not exhibit significant signs of illness during the office visit, and her serum creatinine was within her baseline range. The patient expressed reluctance to go to the emergency room (ER), which is understandable given the long wait times, inconvenience, high costs and her relatively stable condition. Moreover, outpatient imaging was not readily available, often requiring appointments scheduled several weeks out.

The dilemma arises: Should we refer a seemingly well patient with stable, near-normal kidney function to the ER? Or should we wait until diagnostic imaging is available as an outpatient, accepting the risk of potential clinical deterioration? Perhaps an alternative solution could involve POCUS.

POCUS enhanced physical exam findings: Right hydronephrosis was identified on POCUS (Figure 4). The images were promptly reviewed with the on-call urologist, and an intervention was scheduled while awaiting confirmatory imaging. Subsequently, a computed tomography (CT) abdomen confirmed the presence of right hydronephrosis along with a proximal 5mm ureteric stone.

How did POCUS help? The timely detection of hydronephrosis *via* POCUS facilitated the immediate scheduling of surgical intervention, obviating the need to wait for a formal ultrasound, which could have resulted in treatment delays. Consequently, an unnecessary ER visit, or hospitalization was also averted.

Case 3: Intercepting the empiric fluid bolus

This is the case of a middle-aged male with valvular heart disease who presented with weakness, lethargy, and bradycardia (heart rate in the 40s). He exhibited near-normal blood pressure and had no peripheral edema. Lung auscultation revealed clear breath sounds. Additionally, he was anuric, and his serum creatinine (SCr) had risen to 6.3 mg/dL from an apparently normal baseline, with associated hyperkalemia and markedly elevated serum transaminase levels. Serum lactate levels were found to be 14 mmol/L (ref: < 2). CXR did not demonstrate acute lung abnormalities and he was empirically initiated on aggressive intravenous fluids due to acute kidney injury (AKI), hyperkalemia and lactic acidosis. At this juncture, a POCUS examination was performed by the nephrology consultant.

POCUS enhanced physical exam findings: The inferior vena cava (IVC) was plethoric, indicative of elevated right atrial pressure (RAP). Furthermore, the portal vein Doppler displayed a pulsatile waveform with flow reversal, consistent with severe venous congestion (Figure 5). While cardiac ultrasound was limited by the presence of electrocardiogram leads and transcutaneous pacing pads, we managed to identify a normal left ventricular ejection fraction and a dilated right ventricle with interventricular septal flattening, predominantly evident during diastole, which suggests volume overload. Continued volume administration can exacerbate this compression on the left ventricle leading to a drop in cardiac output and hypotension.

POCUS directed management: Given the above findings, intravenous fluids were discontinued, and the decision was taken to initiate continuous renal replacement therapy (CRRT). Following volume removal, there was an increase in urine output, and the patient reported feeling better. Within 48 hours, he was successfully weaned off CRRT, and his serum creatinine stabilized around 1.7 mg/dL. Additionally, there was an improvement in transaminase levels, which correlated with the normalization of the inferior vena cava and portal vein parameters (Figure 6).

How did POCUS help? POCUS revealed severe venous congestion, contrasting with the absence of volume overload evident during the clinical examination. This shifted the diagnosis towards congestive nephropathy and hepatopathy, as opposed to renal and liver injury stemming from decreased arterial flow due to hypovolemia. Consequently, POCUS prompted a change in management strategy, transitioning from administering intravenous fluids to initiating and subsequently *via* diuresis. This approach facilitated rapid clinical and biochemical improvement. Without POCUS, continued fluid administration would have exacerbated venous congestion and right ventricular overload. Additionally, POCUS served as a valuable tool for monitoring the response to therapy. It is important to recognize that the absence of pedal edema does not necessarily rule out venous congestion, and hemodynamics are dynamic – the lack of fluid overload upon initial assessment does not ensure its absence following volume loading.

Case 4: 'AKI in cirrhosis. Just hold the diuretics and administer intravenous albumin?'

A middle-aged woman with autoimmune hepatitis/cirrhosis was referred to the ER by her primary care physician due to

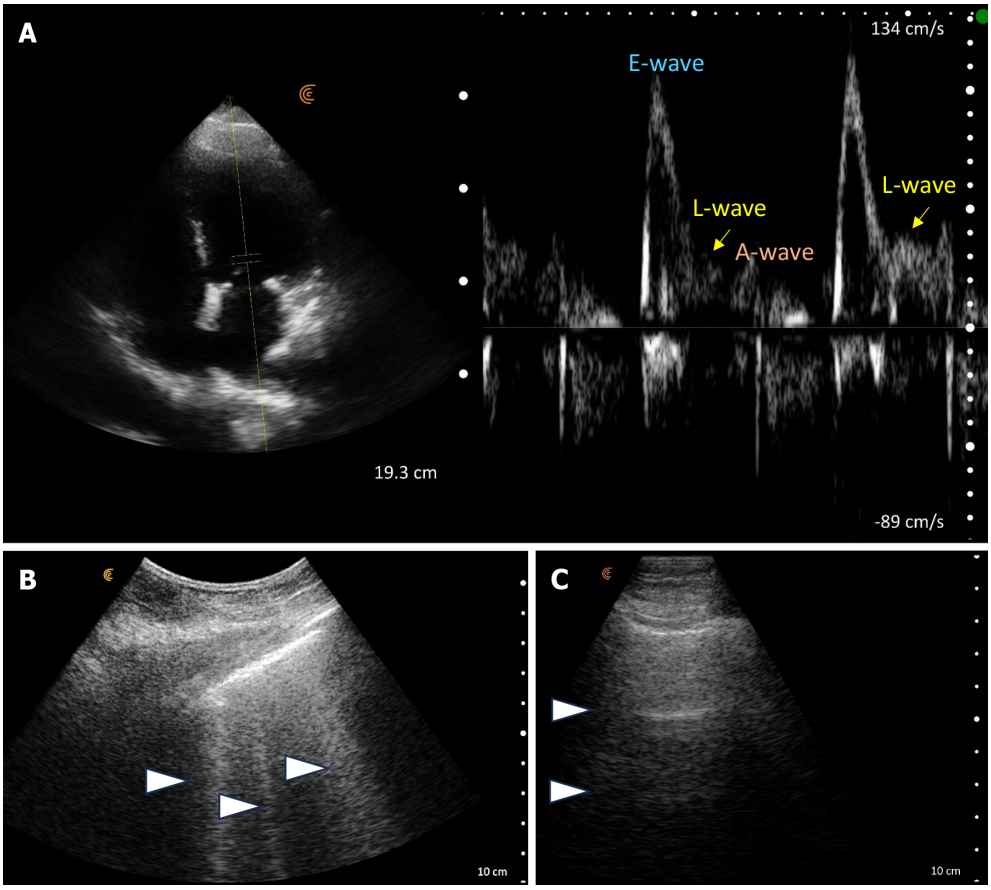

Figure 3 Point-of-care ultrasound images at the time of nephrology consult. A: An elevated E-wave to A-wave ratio and an L-wave on transmitral Doppler; B: Vertical B-lines on lung ultrasound at initial examination (arrowheads). Follow up lung ultrasound; C: Horizontal A-lines (arrowheads) on lung ultrasound - normal finding.

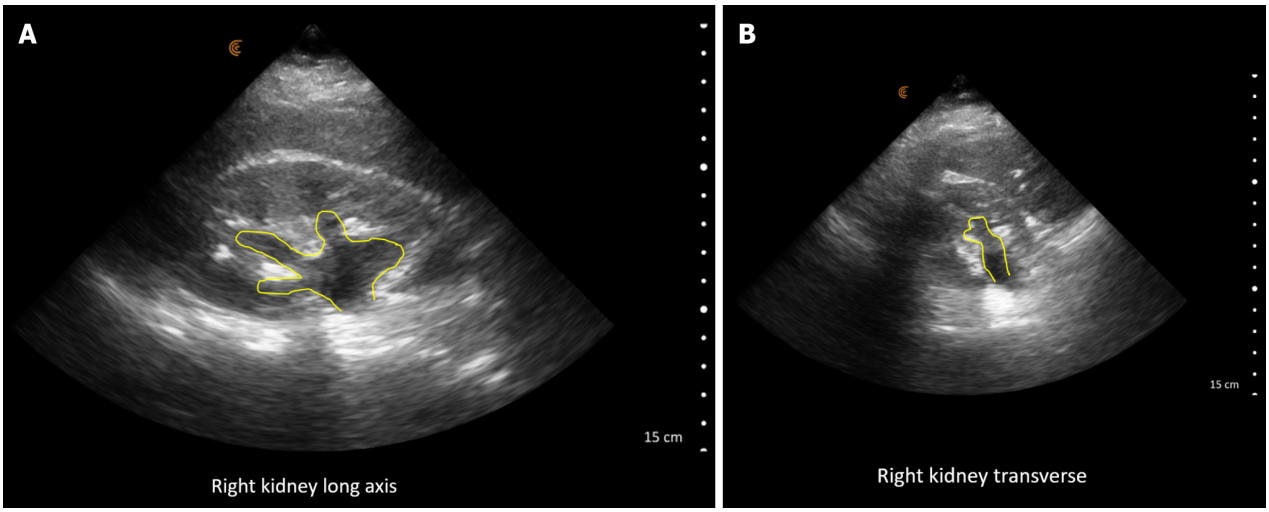

Figure 4 Renal ultrasound images demonstrating. A: Long axis views of right hydronephrosis (yellow outline); B: Short axis views of right hydronephrosis (yellow outline).

laboratory results demonstrating a serum creatinine increase to 5.7 mg/dL from a normal baseline two months earlier. Her blood pressure was 81/43 mmHg, with a heart rate of 65 beats per minute. Upon physical examination, there were no crackles, no pedal edema, and her abdomen appeared mildly distended. In the context of cirrhosis and AKI, the admitting physician ordered empiric intravenous fluids followed by midodrine, octreotide, and albumin. However, there was no improvement observed in renal function or clinical status after 24 hours of this treatment regimen.

POCUS enhanced physical exam findings: POCUS revealed several crucial findings that were missed or not detectable during the initial examination: Focused cardiac ultrasound revealed a normal left ventricular ejection fraction but

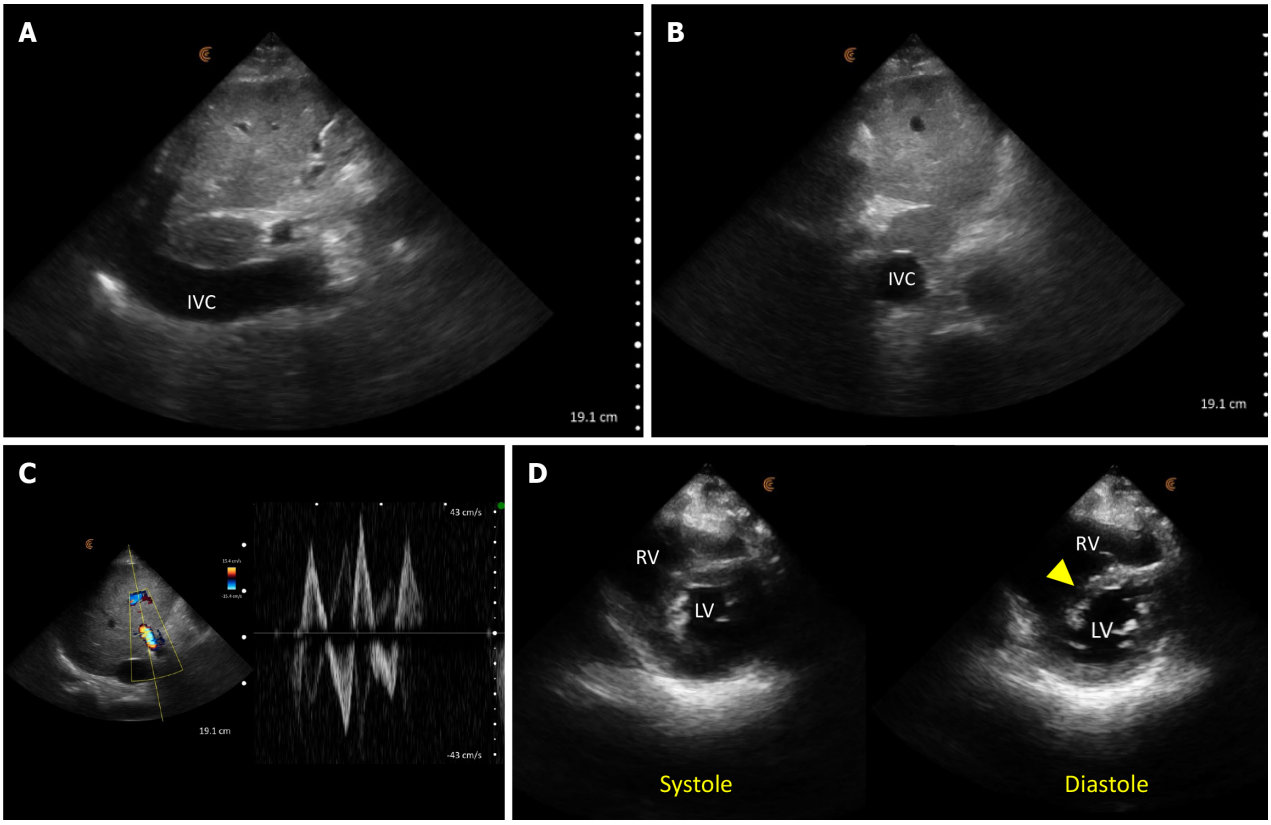

Figure 5 Point-of-care ultrasound images demonstrating findings suggestive of volume/pressure overload. A: A dilated inferior vena cava (IVC) in long axis; B: IVC transverse view shows a circular vessel as opposed to normal elliptical shape; C: Pulsatile portal vein Doppler with a to-and-fro pattern (normally it's continuous); D: Parasternal short axis cardiac view showing interventricular septal flattening (arrowhead) predominantly in diastole. RV: Right ventricle; LV: Left ventricle.

enlargement of both left and right atria suggestive of elevated cardiac filling pressures. Lung POCUS identified bilateral small pleural effusions and scattered B-lines suggestive of increased extravascular lung water. Abdominal assessment unveiled moderate to severe ascites accompanied by a shrunken liver. Ultrasound of the internal jugular vein showed that is distended with a collapse point at the angle of the jaw, consistent with significantly elevated jugular venous pressure/RAP (Figure 7). The collapse point is analogous to highest point of venous pulsations on the inspection method.

POCUS guided management: Based on the POCUS findings, a diagnosis of cirrhotic cardiomyopathy resulting in decreased renal perfusion was made. Volume expansion was halted, and diuretics were initiated. Additionally, a paracentesis was scheduled to relieve the intraabdominal pressure-related renal hypoperfusion. These interventions resulted in a substantial improvement in renal function and clinical condition. A formal echocardiogram later confirmed biatrial enlargement and reported an elevated pulmonary artery systolic pressure of 50-60 mmHg, further supporting the diagnosis.

How did POCUS help? Cardiac dysfunction often goes unnoticed in cirrhotic patients due to preserved systolic function. The left ventricle is usually hyperdynamic due to the high output cardiac state induced by splanchnic vasodilation, which can be misinterpreted as volume depletion when taken in isolation. This high output cardiac state eventually leads to elevated cardiac filling pressures and congestion, termed high output cardiac 'failure', a condition that remains underrecognized in cirrhosis[6]. Some authors describe this intricate interaction between the heart, kidneys, and cirrhosis-induced circulatory dysfunction as hepatocardiorenal syndrome[7]. In our case, POCUS altered the differential diagnosis from hypovolemia/hepatorenal syndrome to congestive nephropathy in the presence of cardiac dysfunction. This change in diagnosis prompted a shift in treatment strategy from continued volume expansion to diuresis and paracentesis. POCUS helped prevent prolonged hospitalization for AKI treatment, avoided the potential harm of volume overload, and likely mitigated the need for dialysis.

Case 5: The chest X-ray report is not invincible. POCUS can tease out those misleading reports!

An elderly man with a history of CHF presented with symptoms of reduced oral intake, encephalopathy, and hypoxia. Notably, he had a recent hospitalization for heart failure exacerbation a few weeks prior. At the time of presentation, he was normotensive and afebrile. Auscultation revealed crackles in the right lower zone, while the rest of the physical examination was unremarkable. Laboratory results showed an elevated serum creatinine of 2.4 mg/dL compared to his normal baseline. Other notable findings included a normal white cell count and procalcitonin level but with an elevated C reactive protein (CRP) of 129 mg/dL. COVID19 testing was negative. The CXR reported "cardiomegaly, mild interstitial

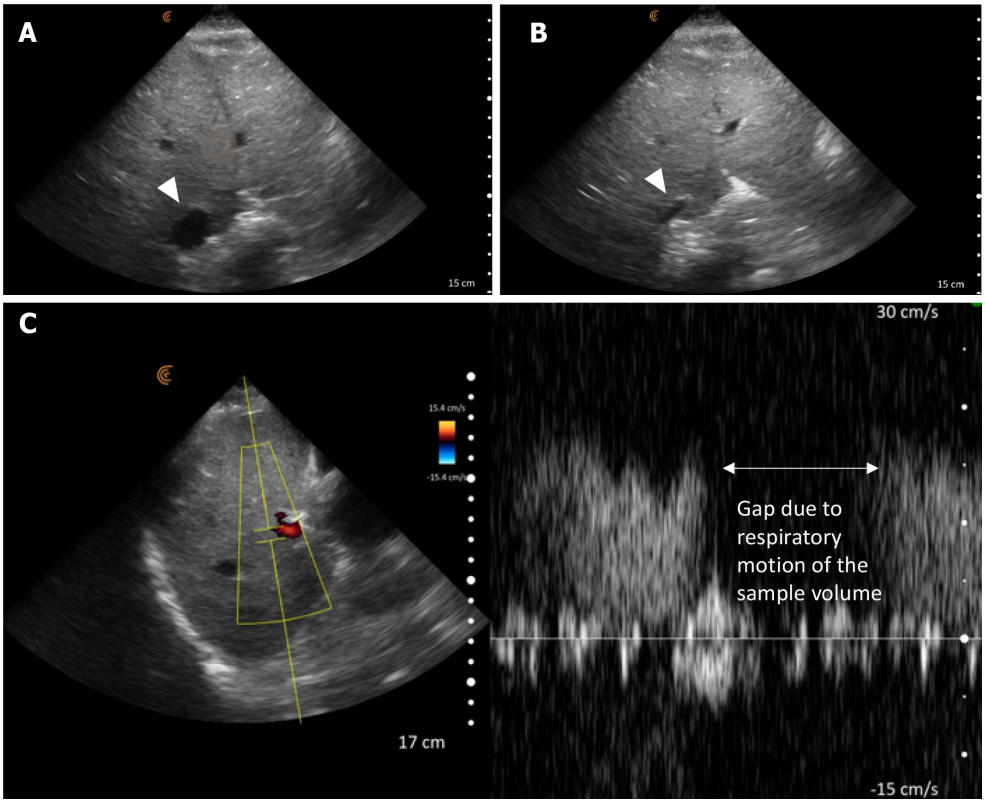

Figure 6 Follow up ultrasound examination demonstrating resolution of congestion. A: The inferior vena cava (indicated by the arrowhead) appearing elliptical in the transverse view with a decreased diameter compared to the initial examination; B: Near-complete collapse of the inferior vena cava (arrowhead) during a sniff, indicative of normal right atrial pressure; C: Continuous waveform observed in the portal vein on Doppler imaging.

opacities bilaterally, and small pleural effusions consistent with congestive heart failure". Although the physical examination findings were nonspecific, the chest X-ray report and the patient's recent hospitalization for pulmonary edema raised concerns for the primary service. As a result, they initiated intravenous furosemide, and the elevated CRP was attributed to a possible urinary tract infection.

POCUS enhanced physical exam findings: POCUS demonstrated a collapsible IVC, hyperdynamic left ventricle, and markedly irregular pleura/subpleural consolidations, accompanied by B-lines (Figure 8). These observations leaned more towards an infectious or inflammatory lung condition rather than acute decompensated heart failure contrary to what was inferred from the CXR. Generally, the pleural line is smooth and regular in cases of cardiogenic pulmonary edema unless the patient has pre-existing lung or pleural disease.

POCUS guided management: The diuretics were discontinued, and intravenous fluids were administered, resulting in the serum creatinine returning to within normal limits within 48 hours. Antibiotics were titrated to cover possible pneumonia.

How did POCUS help? In this instance, the patient's medical history and clinical examination didn't strongly indicate CHF. However, the CXR report and recent hospitalization for acute pulmonary edema caused diagnostic uncertainty, resulting in the incorrect treatment approach for the patient's AKI. Although the data gathered through POCUS wasn't sufficient to definitively rule out CHF, the observed features pointed towards a more probable alternative diagnosis in this clinical context, guiding a more suitable intervention. Unlike radiologists, who frequently interpret images with minimal clinical context provided to them, POCUS, being clinician-performed, allows for immediate integration of relevant clinical information with the images.

Case 6: A straightforward case of euvolemic hyponatremia?

An elderly woman underwent bowel surgery and experienced symptoms of nausea, vomiting, and fatigue one day following the procedure. She was normotensive and showed no signs of respiratory distress. Lung auscultation revealed clear breath sounds, and there was no peripheral edema observed (clinically euvolemic). Laboratory results showed a serum sodium level of 118 mmol/L. Urine sodium was 40 mmol/L, urine osmolality was 516 mOsm/kg, and serum osmolality was 256 mOsm/kg. Her sodium level was within the normal range four days prior to admission. Based on this information, it appeared to be a straightforward case of postoperative syndrome of inappropriate antidiuretic hormone secretion (SIADH).

POCUS enhanced physical examination findings: POCUS revealed severe enlargement of the left atrium suggestive of elevated left sided filling pressures, along with mild enlargement of the right ventricle. Lung examination showed diffuse

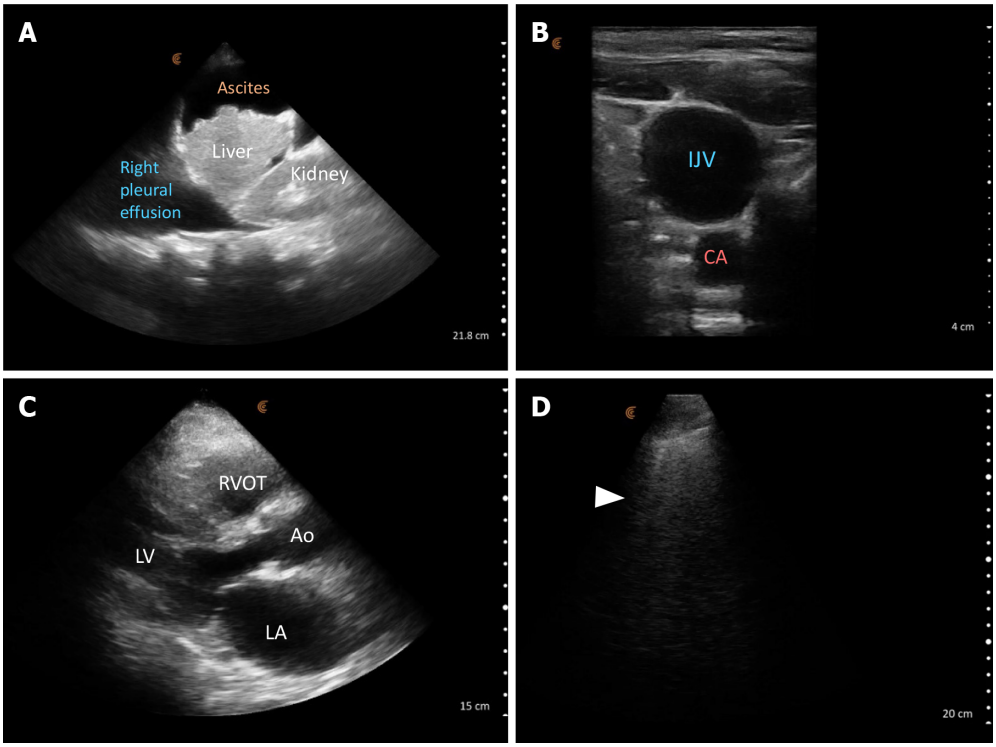

Figure 7 Point-of-care ultrasound images demonstrating findings suggestive of elevated cardiac filling pressures. A: Right pleural effusion and ascites as seen on right upper quadrant lateral scan plane; B: A dilated internal jugular vein (IJV) at the cricoid cartilage level with a head angle of approximately 45 degrees consistent with elevated right atrial pressure. Adjacent carotid artery (CA) is seen: C: Parasternal long axis cardiac view showing a qualitatively dilated left atrium; D: Lung ultrasound image demonstrating vertical B-lines (arrowhead) indicative of elevated extravascular lung water. LA: left atrium; Ao: Aorta; LV: Left ventricle; RVOT: Right ventricular outflow tract.

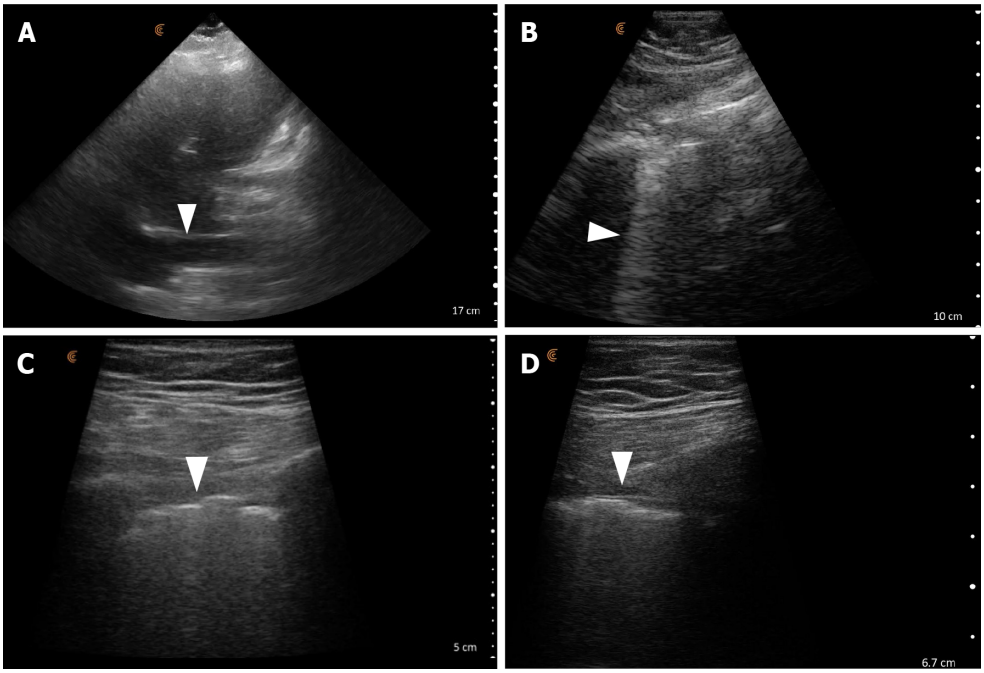

Figure 8 Point-of-care ultrasound findings favoring primary lung pathology over congestive heart failure. A: A relatively small IVC (< 1.5 cm maximal diameter); B: Confluent B-lines on lung ultrasound (arrowhead); C and D: Irregular pleural line imaged using a high frequency-low depth setting.

B-lines indicating elevated extravascular lung water. The IVC appeared plethoric, and the portal vein exhibited more than 50% pulsatility, indicating elevated RAP and venous congestion (Figure 9).

POCUS guided management: Considering the findings, the diagnosis of concurrent CHF was established. The patient received treatment with intravenous diuretics and tolvaptan, resulting in improvement of sodium levels. A follow-up POCUS examination performed 48 hours after treatment demonstrated almost complete resolution of B-lines. Additionally, improvements were observed in both IVC and portal venous pulsatility.

How did POCUS help? This case initially seemed to indicate a typical postoperative SIADH scenario. With the POCUS-assisted identification of heart failure, the treatment approach shifted from salt tablets/urea supplements to tolvaptan and furosemide. While furosemide may also help with SIADH, the case likely involved a mixed etiology, and POCUS played a crucial role in diagnosing clinically silent heart failure, potentially averting the need for rehospitalization.

BARRIERS TO IMPLEMENTING POCUS IN PRIVATE PRACTICE NEPHROLOGY AND POTENTIAL SOLUTIONS

Here are some of the common concerns nephrologists may have when considering the integration of POCUS into their practice. We aim to offer reasoned explanations and practical suggestions based on our experience for each of these barriers.

"I don't have the time to perform POCUS-enhanced physical examination on every patient"

Firstly, not every patient requires a POCUS-enhanced physical examination. Moreover, once a certain level of proficiency is achieved, the additional time required is often minimal. For instance, assessing the lungs for effusions or pulmonary edema, examining the IVC, and ruling out hydronephrosis can be accomplished in about 5 minutes[8]. Surprisingly, in some instances, POCUS can even expedite the examination process! Consider the following scenarios to illustrate this point: To diagnose a pleural effusion conventionally involves auscultating for reduced breath sounds, eliciting reduced vocal/tactile fremitus, and assessing dullness to percussion, which is more time-consuming than simply placing an ultrasound probe at the dependent lung zone and visualizing an effusion. Similarly, diagnosing ascites typically requires demonstrating shifting dullness or a fluid thrill, which also takes more time than merely positioning the ultrasound probe on the abdomen to identify fluid between the liver and the kidney. Thus, while it may initially appear time-consuming, POCUS can ultimately streamline the examination process.

Our suggestion: Our recommendation is to begin practicing POCUS examinations initially on hospitalized patients with their consent. They are easier to position in a hospital bed, and there is less time pressure compared to clinic settings. Start with simpler examinations such as lung, IVC, and ruling out hydronephrosis, as they require less technical expertise. These examinations can be performed almost immediately after attending a well-structured POCUS workshop and watching a few online tutorials. The findings can be compared with the formal imaging report, where available. Clinical integration should not be a hurdle for practicing physicians in most scenarios. For instance, a plethoric IVC presents a similar diagnostic implication as an elevated jugular venous pressure, and a B-line pattern is analogous to crackles on auscultation, albeit more sensitive. Once comfortable with these basic POCUS applications, one can gradually integrate more complex examinations such as cardiac ultrasound and Doppler studies.

"At this point in my career, I don't have the time and energy to dedicate to mastering POCUS"

As physicians, our commitment to lifelong learning is fundamental. While certain procedures may be best handled by specialists with dedicated training (*e.g.*, dialysis access interventions, kidney biopsy), the essence of physical examination remains a cornerstone of our practice. Therefore, it's essential that we embrace the POCUS-enhanced physical examination to provide better patient care. However, not everyone needs to master advanced techniques like stroke volume assessment or diastology. Simple POCUS applications such as estimating RAP through IVC POCUS and lung ultrasound offer significant benefits and are relatively easy to learn. Learning any new skill requires time commitment, but the motivation to serve our patients better should drive us to adopt POCUS into our practice. Additionally, many private practice physicians play a role in teaching trainees at community hospitals. Incorporating POCUS could reignite interest in nephrology as a career choice, which currently faces some challenges. Studies have shown that POCUS can enhance the interest of medical students in pursuing nephrology electives[9].

Our suggestion: Take advantage of freely available online resources, such as NephroPOCUS.com. Attend live workshops whenever feasible to gain hands-on experience. Given that the scope of nephrologist-performed POCUS aligns with that of hospitalists and intensivists, it's acceptable to participate in workshops and certification programs designed for these physicians until dedicated nephrology courses become more widespread[10]. Some larger private practice groups arrange for POCUS experts from academic institutions to conduct exclusive workshops for their members. This setup allows the workshop to utilize the equipment that the group is already using or familiar with and ensures a favorable learner-to-faculty ratio. Consequently, physicians can benefit from specialized training without the need to travel to attend conventional workshops elsewhere. Additionally, some ultrasound devices feature image-sharing capabilities, allowing experts to provide feedback on your scans. Certain devices also offer artificial intelligence-based real-time image guidance, which can be beneficial for novice users. If you have your own handheld device, consider scanning yourself at home to further

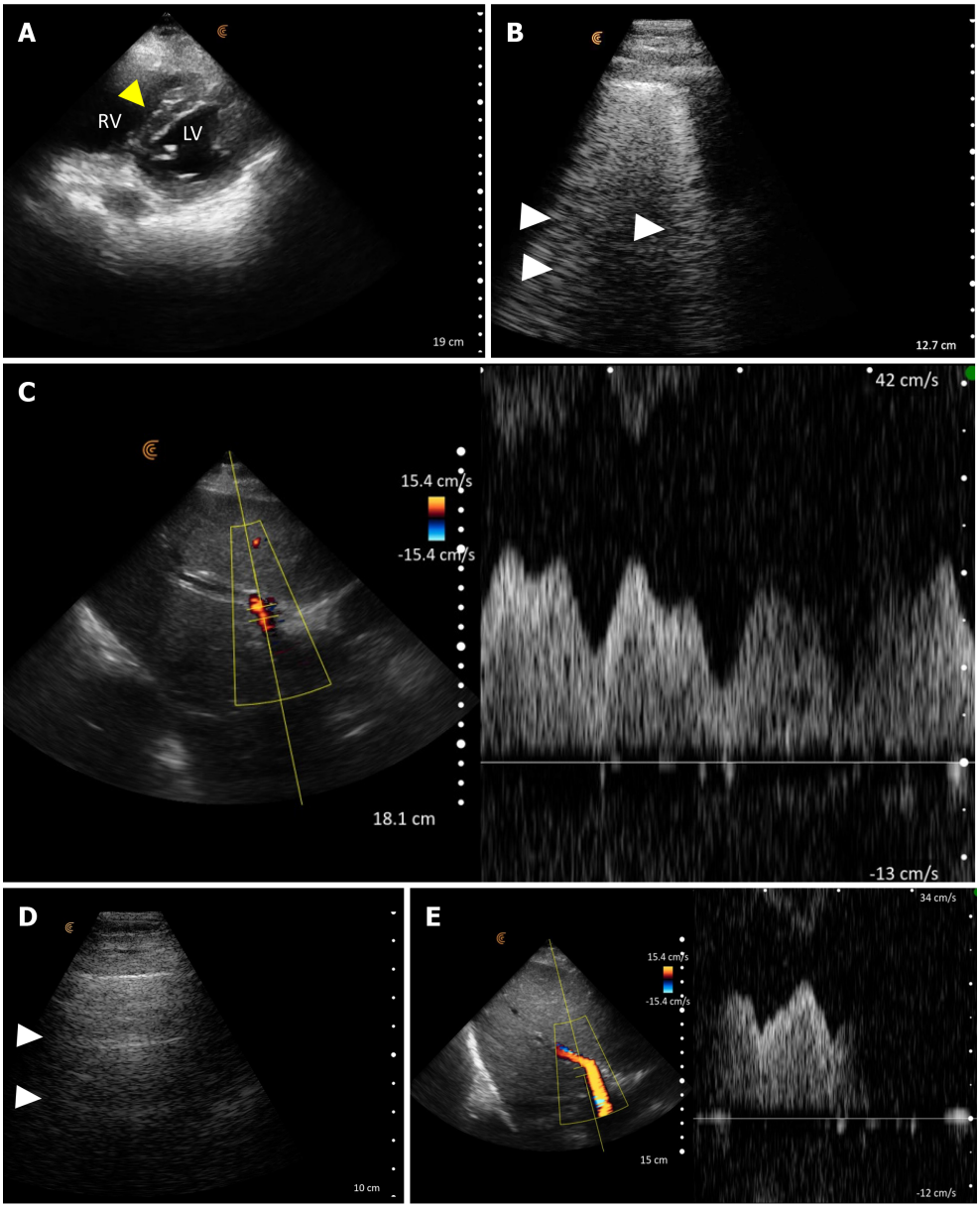

Figure 9 Point-of-care ultrasound images demonstrating stigmata of elevated cardiac filling pressures at the time of nephrology consult. A: Interventricular septal flattening (arrowhead) on parasternal short axis cardiac view suggestive of elevated right heart pressures; B: B-lines on lung ultrasound (arrowheads); C: Increased portal vein pulsatility > 50% (asterisks represent highest and lowest points in one cardiac cycle); D and E: Represent follow up examination. Normal horizontal A-lines seen on lung ultrasound (D), improved portal vein pulsatility (E).

refine your skills.

"Incorporating POCUS into my practice would be too costly!"

Advancements in ultrasound technology in recent years have led to the development of smaller, more portable devices with improved image quality and ergonomics. The availability of handheld ultrasound devices, in particular, has revolutionized portability, which is crucial for private practice nephrologists who may need to travel to multiple facilities to see patients. These devices typically range in price from approximately $4000 to $12000, depending on factors such as image quality and options like spectral Doppler. While cart-based machines generally offer superior image quality compared to handheld devices, they may be more suitable for advanced users who have less need for mobility and primarily see patients in specific wards or clinics. For instance, qualified users can perform comprehensive hemodynamic scans with high-quality Doppler and EKG guidance using such machines in the nephrology clinic[11]. POCUS-certified physicians with appropriate credentials can bill for these studies, which helps offset the equipment costs. The reimbursement rates vary depending on factors such as insurance type and the specific scans performed, as detailed elsewhere[3,12,13].

Our suggestion: Discuss with your practice or hospital leadership the potential acquisition of handheld or cart-based ultrasound machines tailored to your imaging requirements. Highlight the ability to bill for POCUS procedures, which can lead to financial reimbursement. Most commercially available handheld devices can be integrated with the hospital's

picture archiving and communication system, ensuring secure storage of patient data, which is necessary for billing purposes. If your practice offers a continuing medical education allowance, inquire about using it to procure an ultrasound machine. Additionally, many ultrasound companies provide financing options to mitigate the initial cost. However, it's essential to exercise caution and acknowledge the limitations of the device being used, while also avoiding overestimation of one's skills.

"Physical exam has always worked fine for me. If I'm going to change, I need some outcome data!"

Regrettably, this perspective is prevalent among physicians who harbor skepticism about incorporating POCUS into their practice. However, it's important to recognize that while POCUS serves as a diagnostic aid, its impact on mortality is contingent upon being tied together with treatments that can enhance patient survival. As a diagnostic tool, POCUS is expected to offer superior diagnostic accuracy compared to traditional methods, which it has shown to do in multiple clinical settings[2,14,15]. Yet, its findings significantly influence various clinically relevant outcomes such as time to diagnosis, need for additional imaging, healthcare expenditure, and patient satisfaction. For example, in a systematic review involving 5393 dyspneic patients, those managed with POCUS experienced notably shorter times to correct diagnosis and treatment compared to conventional care recipients (mean difference -63 min and -27 min, respectively). Moreover, the odds of receiving appropriate therapy were substantially higher in the POCUS group, with a corresponding reduction in intensive care unit length of stay[16]. This scenario holds relevance for nephrologists tasked with addressing dyspnea linked to fluid overload, underscoring the importance of promptly discerning its cause to guide interventions effectively. Similarly, POCUS-guided management has proven effective in reducing subsequent imaging needs, including chest radiographs, echocardiograms, and CT scans, thereby positively impacting healthcare expenditure [17]. In hemodialysis patients, POCUS-based ultrafiltration titration has resulted in notable reductions in left ventricular filling pressures, cardiac dimensions, and ambulatory blood pressure, indicating its efficacy as a treatment guiding tool [18,19]. Regarding patient-reported outcomes, mounting evidence suggests that POCUS enhances patient satisfaction and facilitates better comprehension of their diagnosis[20,21], a particularly relevant aspect for nephrologists tasked with conveying dietary restrictions and medication adherence to asymptomatic patients. In this context, sharing and discussing POCUS images with patients could be beneficial.

Our suggestion: POCUS complements conventional physical examination, significantly enhancing the accuracy of bedside diagnosis and positively influencing practical outcomes, as outlined above. The primary duty of a physician is to ensure accurate diagnoses by thoughtfully integrating historical and physical examination data. Therefore, it would be irrational to disregard the utilization of enhanced bedside diagnostic tools simply due to the absence of treatments directly impacting mortality.

"I am concerned about medicolegal implications!"

The concern about misinterpreting or missing important findings, which might result in legal consequences, often acts as a barrier to the integration of POCUS in nephrology practice[22]. Numerous studies have investigated lawsuits related to POCUS across different specialties. However, none of these studies have shown that missed findings on focused ultrasound scans led to legal action against physicians. Rather, the research indicates that legal action is more frequently associated with not conducting POCUS when necessary and in a timely manner[23-27].

Our suggestion: To further reduce the risk of medicolegal action related to the use of POCUS, we recommend the following:

Avoid replacing definitive diagnostic testing with POCUS, unless there is absolutely no indication for further testing.

Ensure thorough documentation of findings and securely archive images.

Recognize your level of competency and understand the capabilities and limitations of the equipment. Acknowledge that while POCUS can be effective for confirming a suspected diagnosis or narrowing the differential, it may not always definitively rule them out. Exercise clinical judgment accordingly.

Seek consultation and discuss images with institutional experts when in doubt. Image archiving facilitates this, as the experts can retrieve the images from the patient's chart instead of repeating the scan.

Manage patient expectations by clearly explaining the purpose of POCUS and its limitations. For instance, instead of stating "I will perform an ultrasound of your chest," say "This device allows me to examine the surface of your lungs for fluid or infection, but it does not allow me to visualize the entirety of your lungs like a CT scan." Similarly, when discussing findings, refrain from definitive statements like "Your heart looks normal" and instead, provide a nuanced explanation such as "I can observe that your heart is functioning well in terms of squeezing, and the sizes of the heart chambers appear grossly normal. However, for a complete assessment of valve function and pressures inside your heart, a formal echocardiogram is necessary."

CONCLUSION

POCUS presents significant opportunities to improve daily nephrology practice and enhance patient satisfaction when performed by adequately trained practitioners. In nephrology, a field heavily reliant on laboratory data, POCUS renews our connection with patients at the bedside. Please take a moment to consider this quote: "Like most new technologies, there is a risk that new practitioners will make mistakes based on their erroneous interpretations. This technology, therefore, must be restricted." Interestingly, this statement wasn't referring to POCUS but was a reaction to the invention

of the stethoscope, which has become a cornerstone of the physical examination. Another similar instance occurred in the surgical field with the introduction of laparoscopic surgery. In the 1980s, Dr. Kurt Semm faced significant resistance, stating, "Both surgeons and gynecologists were angry with me, they virtually stoned me. All my initial attempts to publish a report on laparoscopic appendectomy were rejected with the comment that such nonsense does not, and will never, belong in general surgery."

Like the stethoscope and laparoscope during their early days, POCUS represents a new and promising technology to aid us in patient care, regardless of location. So, how will today's nephrologists perceive this modern diagnostic tool? Will we embrace the change, or will we reject it due to our familiarity and comfort with the status quo?

FOOTNOTES

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Country of origin: United States

ORCID number: Abhilash Koratala 0000-0001-5801-3574.

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REVIEW

Role of molecular imaging in prognosis, diagnosis, and treatment of gastrointestinal cancers: An update on new therapeutic methods

Mobina Fathi, Hayder Jasim Taher, Sabah Jassim Al-Rubiae, Shirin Yaghoobpoor, Ashkan Bahrami, Reza Eshraghi, Hossein Sadri, Mahsa Asadi Anar, Ali Gholamrezanezhad

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Mobina Fathi, Shirin Yaghoobpoor, Mahsa Asadi Anar, Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran 1983969411, Iran

Hayder Jasim Taher, Sabah Jassim Al-Rubiae, Department of Radiology, Hilla University College, Babylon 00964, Iraq

Ashkan Bahrami, Reza Eshraghi, Hossein Sadri, Faculty of Medicine, Kashan University of Medical Sciences, Kashan 1617768911, Iran

Ali Gholamrezanezhad, Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, United States

Corresponding author: Ali Gholamrezanezhad, MD, Associate Professor, Department of Radiology, Keck School of Medicine, University of Southern California, 2051 Marengo ST, Los Angeles, CA 90033, United States. gholamre@usc.edu

Abstract

One of the leading causes of cancer-related death is gastrointestinal cancer, which has a significant morbidity and mortality rate. Although preoperative risk assessment is essential for directing patient care, its biological behavior cannot be accurately predicted by conventional imaging investigations. Potential patho-physiological information in anatomical imaging that cannot be visually identified can now be converted into high-dimensional quantitative image features thanks to the developing discipline of molecular imaging. In order to enable molecular tissue profile *in vivo*, molecular imaging has most recently been utilized to phenotype the expression of single receptors and targets of biological therapy. It is expected that molecular imaging will become increasingly important in the near future, driven by the expanding range of biological therapies for cancer. With this live molecular fingerprinting, molecular imaging can be utilized to drive expression-tailored customized therapy. The technical aspects of molecular imaging are first briefly discussed in this review, followed by an examination of the most recent research on the diagnosis, prognosis, and potential future clinical methods of molecular imaging for GI tract malignancies.

Key Words: Molecular imaging; Personalized medicine; Gastrointestinal cancers; Positron emission tomography-computed tomography

Core Tip: In this study, we explored the important role of molecular imaging methods including single-photon emission computed tomography, positron emission tomography, magnetic resonance spectroscopy, photoacoustic imaging, magnetic resonance imaging in gastrointestinal cancers (GIC). These techniques require a forward-looking attitude and clear objectives, which will ultimately guarantee the efficient utilization of these promising tools for identifying GIC characteristics, assessing treatment effectiveness, and providing guidance for therapy and monitoring. By incorporating these sophisticated imaging and molecular technologies into the therapeutic process, medical professionals can customize treatment approaches for each patient, track the effectiveness of treatment, and make well-informed choices on ongoing care.

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INTRODUCTION

The World Health Organization reported that gastrointestinal (GI) malignancies account for 26.3% of diagnosed cancers and 35.4% cancer-related deaths globally. Colorectal, stomach, liver, esophagus, and pancreatic neoplasms account for 10.2%, 5.7%, 4.7%, 3.2%, and 2.5% of new cancer cases, respectively. In terms of mortality, GI malignancies account for one-third of all cancer fatalities. Colorectal, stomach, liver, esophageal, and pancreatic cancers (PC) account for 9.2%, 8.2%, 8.2%, 5.3%, and 4.5% of cancer mortality, respectively[1].

"Molecular Imaging" refers to a non-invasive medical imaging technique that allows for the characterization, visualization, and assessment of biological activities in malignancies at both molecular and cellular scales[2-6]. Molecular imaging, unlike anatomic imaging techniques, focuses on the expression status or physiological activity of certain molecules inside of an organ or tissue[7]. Single-photon emission computed tomography (SPECT)[8,9], positron emission tomography (PET)[10,11], magnetic resonance spectroscopy[12], photoacoustic imaging[13,14], magnetic resonance imaging (MRI)[15], optical imaging (optical bioluminescence, optical fluorescence)[16,17], chemical exchange saturation transfer[18], near-infrared fluorescence[19,20], and multimodal imaging[21] including PET-magnetic resonance and also PET-computed tomography (CT)[22,23], are some of the techniques used for molecular imaging.

With the advancement of molecular imaging in recent years, molecular imaging has become a crucial technique for diagnosing, assessing, and treating GI cancer cases. It can identify lesions and define the type of early lesions more precisely than conventional anatomic imaging since cancerous cells have a high metabolic rate, cell surface markers, cell cycle regulators, growth factors, or DNA-binding transcription factors[24,25]. For instance, PET-MRI has higher accuracy compared with CT and endoscopic ultrasound for staging and detecting occult metastases of gastric cancer (GC)[26,27]. Also, PET-CT has a better accuracy than contrast CT for evaluating the stage of liver cancer[28]. Accordingly, the Centers for Medicare and Medicaid Services in the United States reimburse most oncological indications of PET. These indications include staging or restaging gastric, colorectal, esophageal, and other GI malignancies[29].

Personalized medicine (PM) is a concept that attempts to provide the proper management to the appropriate patient at the ideal moment[30]. PM might be closely tied to molecular imaging, considering molecular imaging has the potential to help in determining therapeutic targets and choosing patients to identify individuals likely to benefit from targeted treatment[31]. It can also be used in assessing drug pharmacokinetics and directing doses to guide medication dosing and minimize harmful effects by evaluating drug transport, delivery, and clearance in cancerous or normal cells[32]. During the last few years, molecular classifications have progressed from histology-based to genomic, epigenomic, and transcriptome data, revealing novel prognostic indicators and assisting in therapy selection[33-35]. Understanding the complicated molecular alterations associated with abdominal malignancies, particularly colon and pancreatic tumors, is progressing. Molecular imaging agents can detect changes in cancer induced by genetic mutations[36].

Regardless of the number of papers or meta-analyses published on this topic, a complete review in narrative form addresses the significance of molecular imaging and personalized treatment in GI tumors. This article tries to illuminate the ever-changing landscape of GI cancer research by digging into the nuances of classifications, advances in genomics, and the correlation between agents and genetic variables. Finally, the study aims to bridge the gap between imaging, individualized care, and the complexity involved with cancer. It provides insight into accuracy, therapy techniques, and their possible impact on patient outcomes.

IMPACT OF MOLECULAR IMAGING ON PROGNOSIS AND DIAGNOSIS OF GI CANCER AND THE ROLE IN PM

PM is a new branch of medicine that attempts to improve diagnosis accuracy and treatment efficacy. Molecular imaging, a visualization of the metabolic activity and localization of the lesions that are not evident at the structural imaging level, is widely employed in numerous illnesses, notably cancer treatment. Imaging is often divided into three categories: functional, molecular, and anatomical imaging. Tumors are visualized and measured using anatomical imaging methods including ultrasound, CT, and MRI. In contrast, such procedures do not offer information and can be difficult when tumors share physical properties with adjacent tissues[37]. Functional imaging measures processes such as blood flow changes, allows us to greater comprehend disease dynamics in angiogenic cancer therapy[38-41]. On the one hand, molecular imaging enables us to visualize processes at the cellular and molecular levels. It gives information regarding activities such as enzyme processes and receptor numbers, allowing for a more in-depth understanding of cancer development. With advances in genomes, proteomics, and targeted drug discovery, molecular imaging has emerged as a tool for cancer detection, staging, therapy response prediction, and effectiveness monitoring. Despite laboratory approaches that provide snapshots of cancer biology, molecular imaging offers a dynamic understanding of how tumors progress in laboratory settings[42].

The utilization of imaging modalities, particularly integrating anatomical and molecular or functional data, has considerably increased diagnostic accuracy, specificity, and sensitivity. PET-CT, SPECT-CT, PET-MRI, and MRI-optical imaging are some examples of this method[43-47]. A retrospective investigation showed that PET-CT performed well in tumor staging, with an 84% accuracy rate. In comparison, PET-CT obtained 76% accuracy, whereas CT alone achieved 63% and PET alone achieved 64%[44]. Although anatomic imaging has limitations, functional imaging can shed light on them, and molecular imaging could enhance cancer diagnosis and treatment monitoring. The use of modal imaging is a significant advancement since it provides a more comprehensive and accurate view of malignancies[48].

The development of imaging techniques, plays an important role in improving diagnostic skills. It emphasizes the importance of biomarkers and advanced detection methods while distinguishing between two types of probes: Exogenous probes and genetically encoded probes. Exogenous probes for PET imaging, such as 18 F labeled fluorodeoxyglucose (FDG), are designed to target cancer biomarkers. When there is inflammation, the specificity may be reduced. Various types of molecules, including antibodies and peptides, are being studied for their potential as imaging agents in techniques such as ultrasound, CT, MRI, SPECT, and PET methods[49-53].

Molecular imaging has enormous potential in clinical oncology, going beyond laboratory applications to play a crucial part in early cancer detection, and prognosis. It has the greatest impact on tumors that can be treated using non-invasive or minimally invasive approaches, boosting traditional imaging methods by highlighting minor abnormalities and detecting molecular alterations in tissues. This increased sensitivity enables more precise staging, prognostic predictions, and tailored treatment methods. As a cornerstone in clinical oncology, molecular imaging considerably improves 5-year survival rates by allowing for early detection and diagnosis of tumors, particularly in cases such as colorectal cancer (CRC), where screening programs have been implemented to reduce mortality rates. The changing landscape of genetic markers linked to tumor biology and medication responsiveness highlights molecular imaging's expanding role in influencing the future of cancer care[48].

Significantly, malignancies that can be diagnosed without surgery, such as GI cancers, benefit greatly from the use of imaging. This innovative approach gives information about the biology and progression of the lesions. It is a prognostic tool that highlights anomalies and aids in the differentiation of normal or inflammatory tissues from malignant tissue based on early molecular changes rather than evident morphological distinctions. The great precision of biomarkers is critical for collecting data from repeated investigations and comparing before and after therapy. Furthermore, molecular imaging approaches adds information to colonoscopy, while increases sensitivity and diagnostic capacities[48].

As sequencing and proteomic data, tumor vessels, and tumor stroma assessments become available, new targets may emerge for both imaging and targeted therapies. For example, fibroblasts present in tumors are potential targets worth exploring. This expanding knowledge enhances our understanding of subsets within diseases like colon and PC, which opens up possibilities for more precise targeted therapies. Changes in proteins found in tumors and the surrounding tumor environment are used as points for therapies that target molecular processes, immunotherapies, and other precision treatments. Finally, PM seeks to improve the accuracy of diagnosis while decreasing treatment failures. Molecular imaging plays a significant role in PM. Despite many parts of molecular imaging in their early stages, the ultimate aim is to use these approaches to reach superior diagnoses and treatment decisions and determine patient outcomes. Molecular imaging technologies are expected to improve much more technologically over the next few years, substantially influencing PM[54] (Figure 1, Table 1).

LIVER NEOPLASMS

Liver cancer is one of the current global health challenges not only because of its growing incidence but also because of its prognoses[55,56]. The five-year survival of liver cancer is about 21 percent. Therefore, liver cancer is one of the most lethal GI neoplasms[57].

The most common type of liver cancer is hepatocellular carcinoma (HCC), which accounts for approximately 90 percent of liver cancer cases[58]. HCC is the second most fatal tumor, with a 20.3 percent five-year survival rate, according to the surveillance, epidemiology, and results program of the National Cancer Institute (Figure 2, Table 1).

Table 1 Summary of the molecular imaging in gastrointestinal cancers

	Imaging modalities		Diagnosis	Staging	Prognosis/survival	Metastasis	Recurrence	RtT
Liver	PET	18F-FDG-PET-CT			Independent prognostic factor			
		11C-acetate *vs* 18F-FDG-PET	Dual-tracer PET had better sensitivity and specificity *vs* FDG PET alone	Dual-tracer PET-CT was superior in staging *vs* contrast CT		18 F-FDG PET-CT has higher	Dual-tracer can predict recurrence after TACE	
		Choline *vs* 18F-FDG PET-CT						
		11C-choline *vs*. 18F-FDG PET-CT	Dual-tracer had higher sensitivity compared w/each one alone		Dual-tracer had better prognostic value compared w/each one alone			Dual- tracer was a better tool for selecting patients for resection or LT
		68Ga-FAPI PET-CT *vs* 18F-FDG PET-CT	68Ga-FAPI PET-CT is more sensitive *vs* 18F-FDG PET-CT					
		18F-FAPI PET-CT *vs*. 18F-FDG PETCT	18F-FAPI PET-CT was superior	18F-FAPI PET-CT was superior		18F-FAPI PET/CT was superior in lymph node metastasis *vs*. distant metastasis	18F-FAPI PET-CT was superior for local recurrence	
		68Ga-LNC1007 *vs* 68Ga-FAPI and 18F-FDG PET-CT	68Ga-LNC1007 PET-CT was superior			68Ga-LNC1007 was superior in skeletal metastases, and peritoneal metastases		
	MRI	DWI		Use in staging				Determining response after CT-guided HDR- B
		DWI *vs* DCE MRI						Can evaluate responses to radiotherapy
Colorectal	PET	18F-FDG PET/CT			Could predict the prognosis			
						Dual-time-point 18F-FDG PET/CT could liver metastasis		
		68Ga-FAPI PET/CT *vs* 18F-FDG PET/CT	68Ga-FAPI PET/CT was superior			68Ga-FAPI PET/CT was superior		
		Ga-DOTA-FAPI-04 PET/CT *vs* FDG PET/CT	Ga-DOTA-FAPI-04 PET/CT was superior			Ga-DOTA-FAPI-04 PET/CT was superior		
	MRI	Whole body DWI/MRI *vs* CT				WB-DWI/MRI significantly outperformed CT		
		Whole body DWI/MRI	Could improve diagnostic accuracy					

		FDG-PET/CT *vs* MRI *vs* CT				MRI had highest sensitivity in detecting liver metastasis		
	SPECT	99mTc-MAA SPECT/CT				Could detect liver metastasis		
Pancreas	PET	FDG-PET						Could predict RtT
		FDG-PET (CT) *vs* CA-19-9			FDG-PET was univariate preoperative predictor of OS			FDG-PET was superior in predicting pathologic treatment response
			FDG-PET/CT was superior in diagnosis					
		FDG-PET/CT			Independent prognostic factor of PFS and OS			
					Could predict prognosis			
					Independent prognostic values for OS			
		FDG-PET/CT and ceCT	Equal potential in Diagnosing			FDG-PET/CT was superior in metastasis detection		
				ceCT was superior at nodal staging		FDG-PET/CT was superior		
					F-FDG PET/CT was superior	F-FDG PET/CT was superior in predicting LN metastasis		
							FDG-PET/CT was superior	
		FDG-PET/CT and FDG-PET/MR	Equal diagnostic performance					
				18F-FDG PET/MR was superior in TNM staging			18F-FDG PET/MR was superior in liver metastasis	
		FDG-PET/CT *vs* EUS					EUS was superior in detection of locoregional and isolated locoregional recurrences	
		68Ga-FAPI PET/CT *vs* ceCT		68Ga-FAPI PET/CT was superior				
		FAPI PET/(CT) *vs* ^{18}F-FDG PET/CT	Equivalent detection ability	Al18F-NOTA-FAPI-04 PET/CT was superior in TNM staging				
			68Ga-FAPI PET was superior in diagnosis					
			Ga-FAPI PET/CT superior	Ga-FAPI PET/CT was superior		Ga-FAPI PET/CT superior		

		FDG-PET/CT *vs* CA19-9				Both potent predictors for determining the lymph node status		
Esophagus	SPECT	C-Met targeted fluorescence molecular endoscopy	It did not improve endoscopy					
		99mTc-3PRGD2 SPEC *vs* [18F] FDG PET/CT	SPECT was superior	SPECT was superior		FDG-PET/CT was superior		
		99mTc-3PRGD2 SPEC *vs* CT				SPECT was superior		
	PET	18F-FDG PET/CT			Showed prognostic ability			
						Could identify interval metastasis		
					Could predict prognosis		Could predict recurrence	
							Could predict recurrence	
					Could predict prognosis			
		68Ga-FAPI-04 PET/CT				Could predict lymph node metastasis		
		[68Ga] Pentixafor-PET/CT *vs* (FDG)-PET/CT	[68Ga] Pentixafor-PET/CT can be complementary to (FDG)-PET/CT				[68Ga] Pentixafor-PET/CT can be complementary to (FDG)-PET/CT	
	MRI	CT *vs* MRI *vs* EUS		MRI had better diagnostic performance for tumor staging				
		DW-MRI						Could predict pathologic complete response
		DCE-MRI						Could predict response to treatment
		FDG-PET/CT *vs* DWI-MRI			DWI-MRI was independent prognostic factor	DWI-MRI was superior in predicting lymph node metastasis		
Stomach	PET	FAPI PET/CT *vs* FDG PET/CT				FAPI PET/CT is more effective than FDG PET/CT		

TNM: Tumor-node-metastasis; PFS: Progression-free survival; FDG: Fluorodeoxyglucose; PET: Positron emission tomography; CT: Computed tomography; DWI-MRI: Diffusion-weighted imaging magnetic resonance imaging; DCE: Dynamic contrast-enhanced; EUS: Endoscopic ultrasound; HCC: Hepatocellular carcinoma; SPECT: Single photon emission computed tomography; TACE: Transarterial chemoembolization; CCRT: Concurrent chemoradiotherapy; OS: Overall survival.

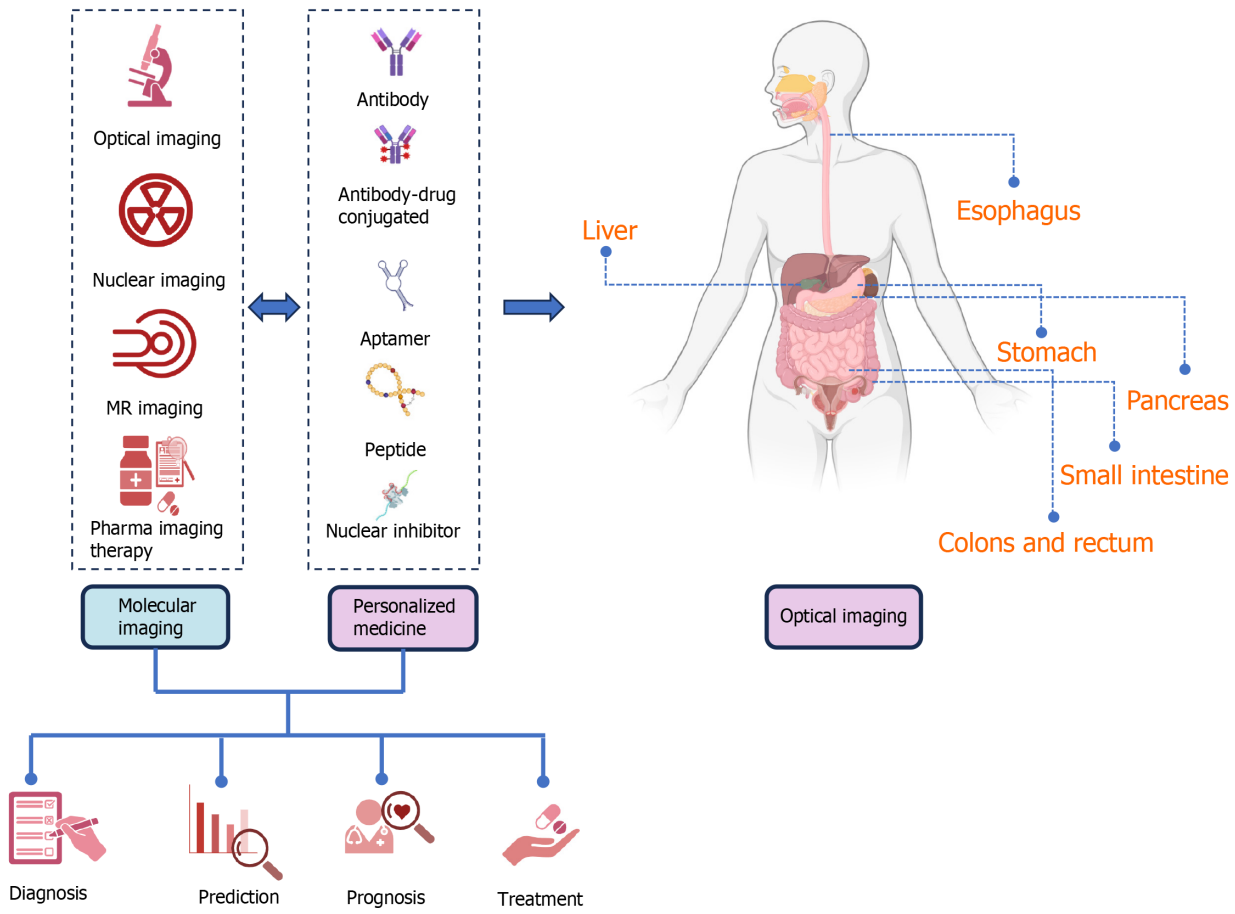

Figure 1 The function of molecular imaging along with personalized medicine in the diagnosis, screening, prognosis, treatment and also follow-up of gastrointestinal cancers, including the organs of the esophagus, stomach, intestines, colons, rectum, pancreas, and liver, is schematically shown. With the use of molecular imaging and personalized medicine in recent years, the possibility of presenting the function and role of these two concepts in the form of priority and delay is generally not proposed and can be used in parallel or earlier and later according to each organ, and finally to benefit the patients. Molecular imaging including optical imaging (submodalities, including fluorescence, bioluminescence imaging, near infrared, surface-enhanced raman scattering and chemiluminescence), nuclear imaging [positron emission tomography (PET), PET/computerized tomography (CT), and single-photon emission CT], magnetic resonance imaging, imaging and pharma imaging Therapy can be used in the stage of screening, diagnosis, prognosis, treatment, and follow-up separately or in combination with personalized medicine (PM). PM can help patients and clinicians by intervening and taking into account the differences and considerations at the molecular level of various organs of digestive cancer, including aptamer, peptide, nuclear inhibitor, and antibodies. When necessary, PM aims to treat the appropriate patient. PM may be effective in molecular imaging since it helps in the identification of therapeutic targets and persons in need of therapy. It may assess drug transport, administration, and clearance in malignant or healthy cells to reduce side effects and prescribe medication dosage. By evaluating tumor drug activity, molecular imaging can analyze medication pharmacodynamics and uncover promising therapeutic responses and early malfunction. GI: Gastrointestinal.

PET imaging using FDG

FDG-PET has a 50%-55% sensitivity for diagnosing and characterizing HCC[59-61]. A study found that 18F-FDG PET-CT has 59% accuracy, 60% specificity, and 76.5% sensitivity in identifying primary HCC and its metastases[62].

The prognostic use of FDG-PET in HCC appears to be connected to particular gene expressions. HCC cells with high expression of vinexin beta, vascular cell adhesion molecule-1, and the natural killer cell inhibitory receptor, appear to have more aggressive biological properties. A substantial association was found between the grade of FDG uptake and the pathological grade. In an experiment by Lee and colleagues on surgical samples from ten patients with HCC showed that tumors with significantly higher 18F-FDG uptake activity were more biologically malignant compared to tumors with lower 18F-FDG uptake. The presence of FDG within a diagnosed HCC might be regarded as an imaging indicator of biological aggressiveness[63].

Furthermore, in a meta-analysis, researchers indicated that an elevated tumor maximal Standardized Uptake Value (SUV_{max}), as well as a high ratio of lesion SUV_{max} to average liver SUV_{max} was associated with a poor outcome in HCC cases. Furthermore, the uptake of FDG in the primary lesions can differentiate the extra-hepatic HCC from intrahepatic disease with a higher uptake in extra-hepatic tumors[64].

Choline, a phosphatidyl cellular membrane component, is upregulated in tumor cells, and radiolabeled choline PET-CT detects well to moderately differentiated HCC more accurately than FDG-PET-CT. FDG-PET-CT is however superior for poorly differentiated and advanced-stage HCC. Combining choline PET-CT and FDG-PET-CT improves the detection of HCC. A systematic review and meta-analysis found that the pooled detection rate per patient and lesion-based of HCC with dual tracer PET-CT was 91% and 89%[65].

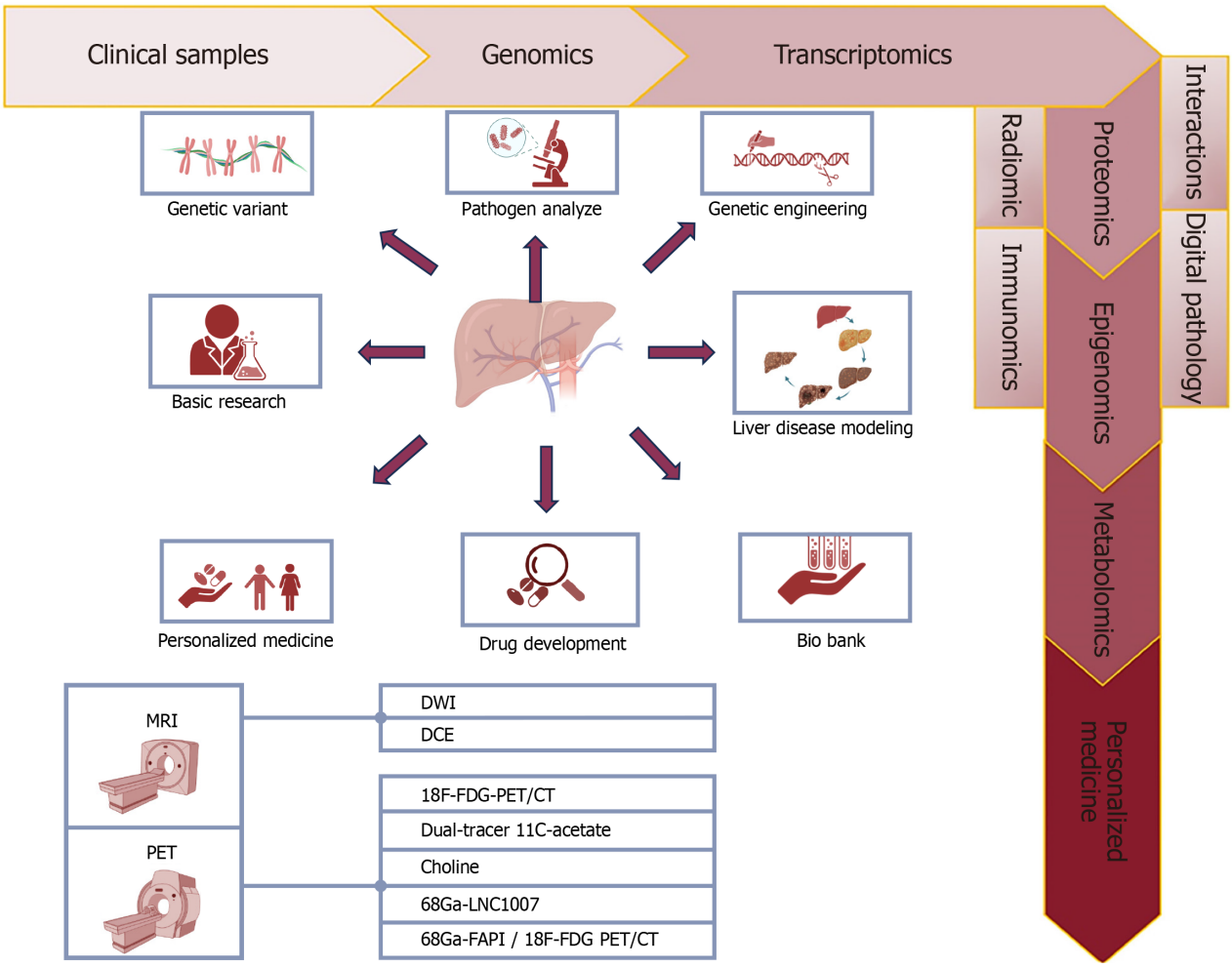

Figure 2 Role of personalized medicine and molecular imaging in liver cancers. The main diagnostic and treatment modalities for liver cancer include positron emission tomography (PET) and magnetic resonance imaging, which are specific types of PET modalities including types bound with 18F-F-fluorodeoxyglucose, 11C-acetate, Choline, and types combined with Ga such as fibroblast activation protein inhibitor. The diagram with arrows shows the general progress and considerations made based on genetic, molecular, immunohistochemistry, microscopy, examination of pathogens at the cellular and molecular level, and background information of patients suffering from various types of liver cancer, which ultimately lead to adopting the best and most accurate and most appropriate and personalized solution available. In fact, in the pre-screening stage, collecting patient information, examining samples, and taking images to diagnose and adopt the most appropriate laboratory and imaging methods, as well as the most appropriate and personalized treatment method including medical treatment (drugs, dose, and type of drug), radiation therapy, non-intervention includes all types of surgeries on liver cancer patients according to different types of liver cancer including hepatocellular carcinoma, cholangiocarcinoma, and angiosarcoma. MRI: Magnetic resonance imaging; PET: Positron emission tomography; CT: Computed tomography; FDG: F-fluorodeoxyglucose; DCE: Dynamic contrast-enhanced imaging; DWI: Diffusion-weighted.

Tumor cells accumulate acetate, a precursor for fatty acid production, as a tumor activity marker. In a study by Ho *et al* [66] dual-tracer PET with FDG-11C-acetate showed 87.3% sensitivity in biopsy-confirmed HCC patients, while FDG had a sensitivity of 47.3%. According to a large cohort study, combining FDG PET-CT with C-11-acetate PET-CT improved sensitivity for identifying primary HCC, yet there was no improvement in detecting metastatic lesions. Additionally, they noted that FDG-PET has a 64.4% sensitivity for detecting primary HCC, whereas 11C-acetate PET has 84.4% sensitivity. A study indicates that dual-tracer PET-CT was much more percise at determining tumor-node-metastasis staging than contrast CT in liver transplantation (LT) and partial-hepatectomy patients. It also accurately assessed tumor burden regarding the size as well as the number of HCC lesions. LT individuals who have 11C-acetate-avid HCC lesions may have more prolonged survival after LT. In advanced-stage patients, 11C-acetate PET-CT might provide valuable information in addition to 18F-FDG because it is related to tumor differentiation in advanced-stages lesions; whereas 18F-FDG uptake was prevalent in those advanced-stage patients. Treatment strategies might be more personalized based on dual radiotracer PET-CT measurements of tumor metabolism features[67].

Fibroblast activation protein (FAP), a serine protease in fibroblast membranes, is excessively expressed in most of the epithelial carcinomas, such as HCC[68]. 68 Ga-FAP inhibitor (FAPI), a fibroblast activating protein inhibitor, helps diagnose various types of cancers[69], with 18F-FAPI-PET-CT being more sensitive in identifying HCC lesions[70-73]. However, 18F-FAPI benefits from a longer half-life which is equal to 68 Ga-FAPI in identifying malignant tumors[74]. A prospective study found that 18F-FAPI-PET-CT was better in detection of primary tumors and lymph node metastases in HCC compared to 18F-FDG-PET-CT[75].

Ga-68 LNC1007 is a radiotracer, created by chemically combining two ligands that target FAP and tripeptide arginine-glycine-aspartic, two key targets in cancer cell growth. A study comparing 68Ga-LNC1007 with 18F-FDG-PET-CT discovered that 68Ga-LNC1007 identified all of the HCC cases (55 primary tumors) and was superior to 2-18F-FDG for diagnosing HCC[76].

PANCREATIC NEOPLASMS

By 2025, PC is expected to become the third most common cause of cancer-related deaths, potentially overtaking breast cancer[77]. Typically, the initial phase of PC lacks noticeable symptoms which justifies the significant number of cases diagnosed at advanced stages (80%)[78,79]. Similar to other cancers, the management of PC depends on early diagnosis, suggesting the curable one-third of PC, if diagnosed at early stages[80]. Imaging techniques are necessary for PC's early detection, staging, treatment, and surgical resection procedures[81].

PET imaging using PET-CT

A meta-analysis which comprised 3567 patients with PC indicated that PET-CT for PC has 89% sensitivity, 70% specificity, and 84% diagnostic accuracy[82]. Nonetheless, PET-CT provides detailed data in volume, size, and stage[83]. The combined use with CA19-9 enhanced the indicators to 96.25%, 63.64%, and 92.31%. The SUV_{max} combined with CA19-9 level had a 0.94 area under the curve (AUC), substantially greater than either alone[84]. Additionally, the integrated use of PET-CT and CT exhibited even better accuracy (90.0%) and sensitivity (97.6%) than either scan alone. The investigators found that the combination of PET-CT and CT enhances the identification of recurrence. The PET-CT scan was particularly beneficial in identifying recurrences in regions that had been missed by the CT scan[85].

Moreover, PET-CT has been demonstrated to predict PC prognosis[86,87]. Low SUV_{max} is associated with a PC survival rate at each stage. It has been discovered that PET-CT metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were independent predictive variables of overall survival (OS) in locally progressed PC patients who received Stereotactic Body Radiation Therapy. In another study, MTV independently provided valuable information on prognosis of locally advanced PC targeted with radiation and chemotherapy. Characteristics shown *via* volume-based PET-CT approach may assist in identifying patients who benefit from radiation therapy[88].

Additionally, MTV and TLG can improve prediction models of prognosis of patients who are candidate for surgical management. In a study of 89 individuals with PC who experienced surgical therapy, of whom 57 treated with neoadjuvant chemotherapy, the MTV and TLG were shown to have significant potential in predicting relapse-free survival (RFS) and OS, regardless of treatment[89]. In another study, MTV and TLG predicted RFS and OS better than baseline tumor size, SUV_{max}, and serum CA19-9[90]. The results of a comparison study between PET-CT images obtained three months prior to and three months post-radioembolization of hepatic metastases originated from PC indicated that differences in the SUV_{max} and TLG could serve as predictors of progression-free survival (PFS), OS, and the time to intrahepatic progression subsequent to hepatic metastases[91].

PET imaging using other PET tracers

Quinoline-based FAPIs have shown promising outcomes in both pre/clinical molecular imaging investigations[92,93]. The first published report of clinical research employing FAPI-PET to examine PC was released in 2018[94]. Alongside the findings of this study, pancreatic neoplasms exhibited increased 68Ga-FAPI (FAPI-02) PET-CT uptake, while its rate in normal tissues, unlike 18F-FDG, was low[95]. This low background activity enhances the image contrast and accuracy. Likewise, other observational case studies showed the superiority of 68Ga-FAPI-PET-CT to 18F-FDG-PET-CT in detecting pancreatic-related metastasis[96,97].

Using multiplex immunohistochemistry, a retrospective investigation was conducted to analyze the images of 215 treatment-naïve pancreatic ductal adenocarcinomas (PDACs). The results showed that patients with FAP-dominant and fibroblast-rich stroma had a worse prognosis compared to those with collagen-rich stroma[98]. Shi *et al*[99] found that there was a strong correlation between high FAP expression levels and poor outcomes in 134 individuals with PDAC. Hence, parameters obtained from FAPI-PET-CT could be potentially in correlation with the clinical prognosis of PC. Nevertheless, this necessitates additional investigations.

Antibody-mediated PET scan

Although the majority of studies using antibody mediated PET in PC s are at animal experiments, they have reported promising outcomes. For instance, Chen *et al*[100] recruited 89Zr-labeled Anti-Trop-2 antibody (AF650) to evaluate Trop-2 as an immunoPET target in three PC cell lines (BxPC-3, MIA PaCa-2, and AsPC-1). The use of 89Zr-DFO-AF650 showed a remarkable capacity to differentiate primary tumors in the orthotopic BxPC-3 cancer model. It suggests a strong association observed between PET imaging and great sensitivity and bio-distribution. They concluded that this method clearly demonstrates the significant promise of Trop-2-based method of non-invasive imaging in detecting PC and tracking the treatment response.

COLORECTAL NEOPLASMS

In 2020, CRC was attributed to around 150000 new cases and over 53000 fatalities[101]. Non-metastatic CRC has a good

prognosis, having an approximate 5-year survival rate of around 90[101]. Regrettably, the five-year survival rate for metastatic CRC stands at a mere 14%. The main treatment options for CRC are surgical removal of the primary tumor and metastasis, systemic chemotherapy, and neoadjuvant chemoradiation[102,103].

PET imaging using FDG

Despite the limitations of FDG-PET in inflammation, infection, and some non-neoplastic conditions[104], FDG-PET-CT is invaluable due to its capacity to evaluate the abnormal metabolic activity that occurs before any visible changes in structure, as well as its capability of detecting tiny malignant tumors within structures with normal morphology[105].

Several studies have tried to improve clinical management strategies of CRC by employing imaging prognostic parameters including depth of presence of malignant lymph nodes, tumor spread, extramural vascular invasion (EMVI), and tumor deposits[106]. In this direction, Lv *et al*[107] designed and validated a machine learning model of predicting the prognosis of primary CRC by 18F-FDG-PET-CT radiomic and clinical-biological features. They concluded that radiomics signature, including four clinical and four PET-CT characteristics, resulted in the most efficient prognostic prediction model (C-index 0.780, 95%CI: 0.634-0.877). In addition, they reported radiomics features to be associated with tumor metabolic markers, such as SUV_{max} and SUV_{mean}. This integrated model of bio-clinic and radiology depicts the potentials of 18F-FDG- PET-CT findings along other features in predicting CRC prognosis.

PET imaging using other PET tracers

Studying primary and recurrent GI malignancies, Pang *et al*[108] found that 68Ga-FAPI-PET-CT with a detection rate of 100% is superior in detecting primary tumors than 18F-FDG-PET-CT with a detection rate of 53%. Furthermore, the 68Ga-FAPI PET/CT scan revealed enhanced tumor delineation and increased contrast between the tumor and its surrounding background. The study revealed the significant absorption of primary CRC lesions in 18F-FDG-PET-CT and 68Ga-FAPI-PET-CT scans. The SUV_{max} of 68Ga-FAPI in the primary lesions was greater than that of 18F-FDG (15.9 *vs* 7.9). The superiority of 68Ga-FAPI-PET-CT over 18F-FDG-PET-CT was evident in the visualization and image quality of peritoneal metastases in CRC. Additionally, the average SUV_{max} value was significantly greater[109].

In 2022, Kömek *et al*[110] evaluated the patients with CRC and showed that [68 Ga]Ga-DOTA-FAPI-04 PET/CT had a sensitivity of 90% in detecting nodal involvement and a sensitivity of 100% in peritoneal seeding, while these values for 18F-FDG-PET-CT were 80% and 55%. These findings shed light on the promising efficacy of [68 Ga] Ga-DOTA-FAPI-04 PET-CT in evaluating patients with CRC, regarding the primary and secondary lesions.

Prashanth *et al*[111] examined 29 patients with CRC by 68Ga-FAPI-PET-CT and reported the sensitivity of FAPI in the detection of recurrence was 100%, which was higher than that of FDG-conventional imaging (88%). In another study on 68Ga-FAPI-PET-CT, moderate 68Ga-FAPI absorption in primary CRC tumors was seen (SUV_{max}, 8.6). In metastatic lesions, however, the SUV_{max} and SUV_{mean} were 7.95 and 3.96, respectively. Simultaneously, the activity levels of the background and normal tissues were extremely low. Consequently, the tumor-to-background ratio (TBR) exceeded 3, resulting in a significant contrast between normal and tumor tissue. Therefore, the study reported that FAPI-PET-CT has promising potential for detecting metastatic CRC, particularly in cases with lymph node and liver metastasis[112].

Dynamic contrast-enhanced imaging-MRI imaging

In 2022, Chen *et al*[113] explored the predictive and diagnostic potentials of dynamic contrast-enhanced imaging (DCE)-MRI in EMVI in 124 patients with rectal cancer. They reported the Ktrans and Ve values of EMVI-positive patients evaluated by DCE-MRI to be 1.08 ± 0.97 and 1.03 ± 0.93, while the values for conventional MRI were 0.68 ± 0.29 and 0.65 ± 0.31, respectively. These amounts were higher significantly in EMVI-negative patients ($P < 0.05$). In another study, Shen *et al*[114] applied DCE-MRI in 40 individuals with rectal cancer and 15 controls. The time-signal intensity curve of lesions presented in MRI exhibited an outflow pattern. In addition, a moderate association between Ktrans and iAUC, and pathological differentiation was highlighted ($0.3 < r < 0.8$, all $P < 0.05$), which provides new insights to preoperative diagnosis of rectal cancer.

ESOPHAGEAL NEOPLASMS

Although there have been advancements in therapeutic approaches and an increase in survival rates for esophageal cancer (EC) patients in the last twenty years, the prognosis of EC remains unfavorable, with an overall five-year survival rate of less than 20%[115,116] (Figure 3).

PET imaging using FDG

Tustumi *et al*[117] evaluated 113 patients with EC by 18F-FDG-PET-CT and demonstrated that TLG and MTV in the primary tumor and the SUV_{max} in the suspicious lymph nodes were correlated with survival after surgery ($P \leq 0.05$). They concluded that pre-neoadjuvant 18F-FDG-PET-CT parameters can independently predict the prognosis (Figure 4).

PET imaging using other PET tracers

In a prospective analysis of 45 patients with locally advanced EC, the prognostic value of 68 Ga-FAPI was evaluated. Regarding the importance of T stage as a significant prognostic factor in patients with EC, groups with different T stages showed significantly different PET parameters; higher stages were associated with higher SUV_{max}-FAPI ($P = 0.009$) and GTVFAPI ($P < 0.001$). In addition, GTVFAPI values lower than 33.9 cm^3 were correlated with better PFS. In this pilot

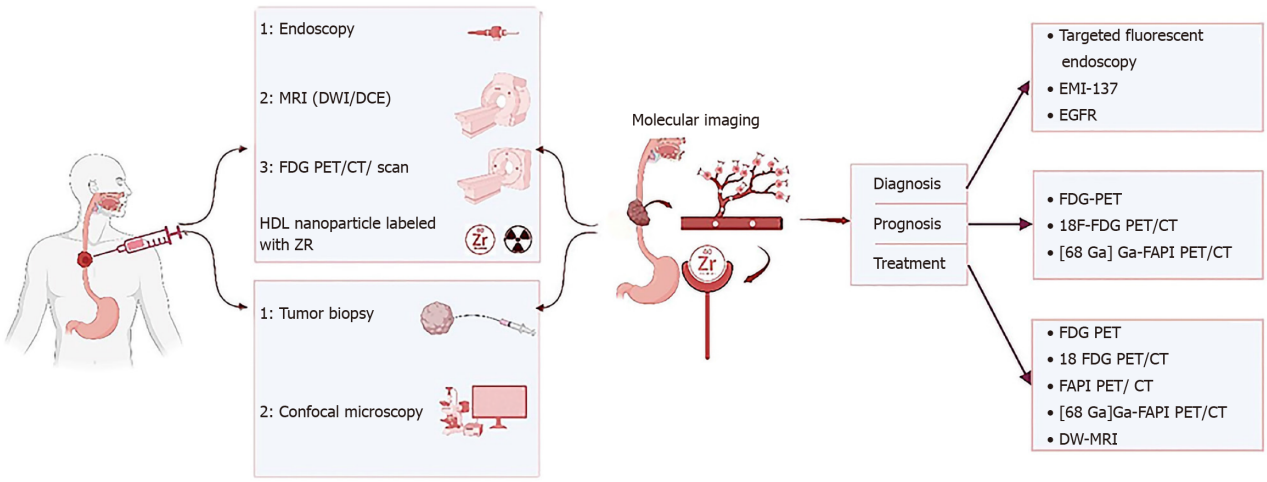

Figure 3 Role of personalized medicine and molecular imaging in esophagus cancers. The function of molecular imaging and personalized medicine in esophageal cancers such as squamous cell carcinoma or adenocarcinoma including simultaneous or even initial and final examinations in the way of collecting temporal and personal information (specific to each person) in the diagnosis process including the collection of human samples, biopsy and blood samples and so on, all kinds of imaging modalities like endoscopy, magnetic resonance imaging (MRI) [diffusion-weighted (DWI)/dynamic contrast-enhanced imaging], [positron emission tomography (PET), PET computed tomograph (CT) and bound with F-fluorodeoxyglucose (FDG)] and also in the path of determining disease prognosis with PET types including FDG-PET, [68 Ga] Ga-FAPI PET/CT, and 18F-FDG PET/CT. Treatment with dedicated modalities FDG-PET, [68 Ga] Ga-FAPI PET/CT, 18F-FDG PET/CT, and DWI-MRI and it is tried in each stage of the currency, from the beginning of data collection to diagnosis, determining prognosis, treatment, response to treatment, assessment of relapse and follow-up, is the most appropriate and accurate and personalized solution possible based on personalized medicine in determining the dose of the substances used in the modalities imaging, choosing the most suitable imaging modality and binding element, the amount of medical treatment (drugs, amount and type of drug), and even all kinds of combined solutions with surgery and radiation therapy should be used. MRI: Magnetic resonance imaging; DW: Diffusion-weighted; PET: Positron emission tomography; CT: Computed tomography; FDG: F-fluorodeoxyglucose; EGFR: Epidermal growth factor receptor.

study, Zhao *et al*[118] concluded that 68Ga-FAPI- PET-CT may predict the response to treatment and OS.

GASTRIC NEOPLASMS

The absolute number of cases of stomach cancer is expected to remain stable or perhaps rise in the future despite a lowering incidence, given the anticipated growth of the global population and the rise in average life expectancies in many countries. While there has been considerable progress in the clinical therapy of stomach cancer, most nations still have a 5-year survival rate of less than 30%, and reported death rates are in line with the disease's frequency. As a result, facilitating an early diagnosis are crucial.

PET imaging using FAPI

Pang *et al*[108] have recently demonstrated that FAPI-PET-CT is more effective than FDG-PET-CT in identifying primary and malignant lesions in a diverse group of patients, including GC. The significant detection rate observed for FAPI in primary gastric tumors with varying levels of differentiation, coupled with the recognized limitations of FDG in detecting certain subtypes of gastric carcinoma, like mucinous, poorly differentiated, and signet ring tumors[119], suggests the potential use of FAPI as a preferred radiotracer for assessing GC. The notably higher ratio of tumor uptake compared to background in primary GCs demonstrates the potential of FAPI-PET-CT for accurately identifying tumors for radiotherapy, as has been previously demonstrated in other tumor types[120] (Figure 5).

ImmunoPET and ImmunoSPECT

Radiotracers based on antibodies are used in the imaging procedures of immunoPET and immunoSPECT. In both preclinical and clinical trials, non-invasive imaging of GC has been accomplished using immunoPET and immunoSPECT. The following examines the application of immunoPET in GC that targets the antigens CDH17, PD-1, and MG7. For PET or SPECT imaging of stomach tumors, antibodies that were either newly developed or approved by the FDA and that targeted membrane antigens were radiolabeled with gallium-68 (68 Ga), technetium-99m (99m Tc), indium-111 (111 In), copper-64 (64 Cu), zirconium-89 (89 Zr), and bromine-76 (76 Br).

The expression of MG7, an antigen specific to GC, is strongly linked with the advancement of the disease[121]. More than 90% of GC patients have MG7, which may serve as a biomarker for the disease because it is overexpressed in GC tissues as compared to benign lesions or normal mucosa[121]. Afterwards, the NOTA-MG7 compound was utilized as a probe for *in vivo* imaging of BGC-823 stomach xenografts after being radiolabeled with the short-lived radioisotope gallium-68. Effective labeling at room temperature is made possible by using NOTA as a bifunctional chelator to radiolabel biomolecules with gallium-68. This is crucial for maintaining the immunoreactivity of the antibody. At 60

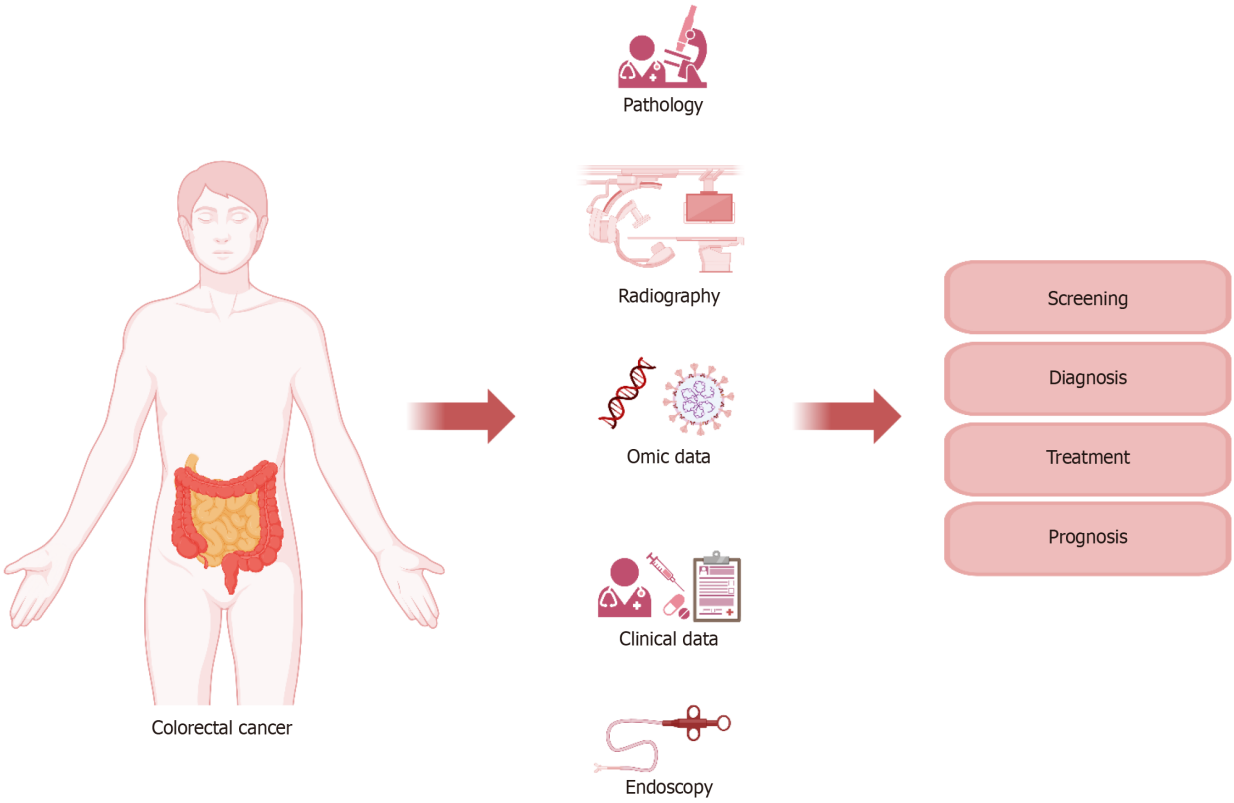

Figure 4 Role of personalized medicine and molecular imaging in colorectal cancers. The function and role of molecular imaging and personalized medicine in charge of management of colorectal cancers is shown schematically in the picture, and the possibility of playing the role of these two concepts does not have any special priority or delay and can be simultaneous and parallel. The role of these two concepts is to adopt the most accurate, appropriate, and personalized mode for patients with colorectal cancers, including the basic steps of collecting individual demographic information of patients, collecting human samples, including blood, urine, and biopsy samples *etc*, and examination and analysis, screening, in the diagnostic path using common and novel imaging and anatomical laboratory methods and even at the cellular and molecular level, determining the most suitable and targeted treatment method including various medical methods (drugs, type and amount), and types of surgical methods, radiation therapy or combined methods, determining the rate of response to treatment, recurrence, prognosis and follow-up of patients according to the characteristics of each patient. Imaging modalities including positron emission tomography (PET), 18F-fluorodeoxyglucose (FDG) PET, FDG-PETPET, 68[Ga]Ga-DOTA-fibroblast activation protein inhibitor (FAPI)-04 PET/computed tomography (CT), 68Ga-FAPI PET/CT, magnetic resonance imaging (MRI), including dynamic contrast-enhanced imaging (DCE) MRI and CT perfusion imaging in determining the course diagnosis, prognosis and FDG-PET/CT, 18F-FDG PET/CT, 68Ga-FAPI PET/CT, and DCE-MRI in treatment.

minutes following intravenous (tail vein) injection of 68 Ga-NOTA-MG7, the 68 Ga-labeled immunoconjugate showed a tumor absorption of 2.53 ± 0.28 percent ID/g. 68 Ga-NOTA-MG7 accumulated in the liver and kidneys in addition to the tumor, most likely as a result of the probe's metabolism in these organs. Antibodies have a delayed biodistribution profile and comparatively extended biological half-life when administered systemically. Because of this, they are frequently marked with radiometals that have longer half-lives, such zirconium-89 (half-life of 3.3 days). Given that gallium-68 has a short half-life of 67.7 minutes, tagging the antibody with a radioisotope with a longer half-life could result in a larger TBR. The high expression of MG7 in Helicobacter pylori-associated stomach illnesses, which may skew patient immunoPET data, is another restriction on the use of 68 Ga-NOTA-MG7[121].

CONCLUSION

The use of cutting-edge biological technology in precision medicine allows for precise diagnosis and therapy by considering a patient's living environment in addition to their clinical data, molecular imaging methods, and bioinformatics. The inconsistent biological properties across the human genome make it challenging to pinpoint the exact clinical and biological importance for each given patient.

In terms of care, we anticipate that reducing the pool of potential patients in accordance with dosage and scheduling guidelines and choosing concurrent medications based on the molecular targeted agents' mechanisms would result in efficient therapy tailored to each patient. FDG-PET-CT and other PET Tracers are becoming a crucial component of the first diagnosis in patients with GI malignancies. Additionally, there is growing interest in studying various radiotracers, especially those that assess hypoxia and other significant characteristics of the tumor micro-environment. These techniques require a forward-looking attitude and clear objectives, which will ultimately guarantee the efficient utilization of these promising tools for identifying GI cancer characteristics, assessing treatment effectiveness, and providing guidance for therapy and monitoring. By incorporating these sophisticated imaging and molecular techno-

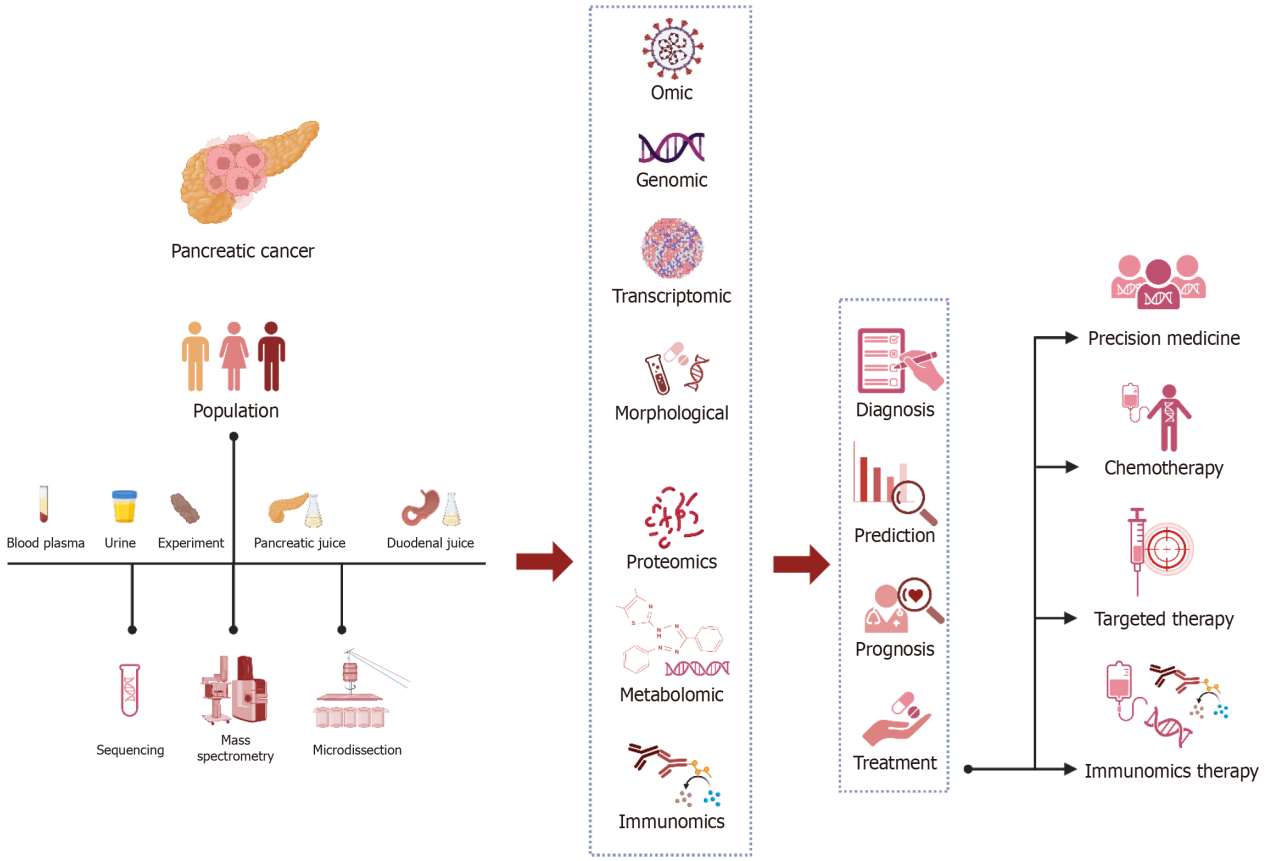

Figure 5 Role of personalized medicine and molecular imaging in pancreatic cancers. The function and role of molecular imaging and personal medicine in the management of pancreas is shown in a semantic way, and the possibility of playing the role of these two concepts does not have any special priority or delay, and it can be both concurrent and concurrent, and it is changing day by day. The role of these two concepts is to adopt the most accurate, appropriate and personalized mode possible for pancreatic cancer patients from the initial stages of collecting individual demographic information of patients, collecting human samples including blood, urine and biopsy samples, *etc.* and checking and their analysis, in the path of individualization using the common methods of novel imaging and anatomical laboratory and even at the cellular and molecular level to determine the most appropriate and targeted treatment including various medical methods (drugs, type and amount) and various surgical methods, radiation Treatment or combined methods is to determine the rate of response to treatment, recurrence, prognosis and follow-up of patients according to the conditions and characteristics of each patient. Imaging modality in determining the course of diagnosis and determining prognosis includes endoscopy, computed tomography (CT), positron emission tomography (PET) and their combination with chemical agents such as 68Ga- fibroblast activation protein inhibitor (FAPI) PET/CT, 18F-fluorodeoxyglucose (FDG) PET/CT and even FAPI PET/CT alone, and Gd-enhanced magnetic resonance imaging (MRI) with diffusion-weighted along contrast-enhanced CT and adopting a treatment plan based on CT, PET, PET/CT, 18F-FDG PET/CT, FDG-PET/contrast-enhanced CT, FDG-PET/non-contrast-enhanced CT, FAPI PET/CT, single-photon emission CT/CT and dynamic contrast-enhanced-MRI are utilized to select chemotherapy, endohistochemical therapy or medical treatment based on personalized medicine.

logies into the therapeutic process, medical professionals can customize treatment approaches for each patient, track the effectiveness of treatment, and make well-informed choices on ongoing care. This holistic strategy has significant potential for enhancing patient outcomes in the treatment of GI cancers.

FOOTNOTES

Author contributions: Gholamrezanezhad A contributed to the supervision and conceptualization of the topic; Fathi M conceived and designed the data; Al-Rubaei SJ and Taher HJ searched the databases and extracted data; Yaghoobpoor S, Eshraghi R, Sadri H and Asadi Anar M contributed to the writing and editing paper; Bahrami A designed the Tables and gathered Figures. All authors have read and approved the final version of the manuscript.

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Country of origin: United States

ORCID number: Mobina Fathi 0000-0002-4811-3982; Ali Gholamrezanezhad 0000-0001-6930-4246.

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REVIEW

Diabetic retinopathy: A review on its pathophysiology and novel treatment modalities

Arvind Kumar Morya, Prasanna Venkatesh Ramesh, Prateek Nishant, Kirandeep Kaur, Bharat Gurnani, Aarti Heda, Sarika Salodia

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Arvind Kumar Morya, Head of the Department, Department of Ophthalmology, All India Institute of Medical Sciences, Hyderabad 508126, Telangana, India

Prasanna Venkatesh Ramesh, Glaucoma Medical Officer, Department of Glaucoma and Research, Mahathma Eye Hospital Private Limited, Trichy 620017, Tamil Nadu, India

Prateek Nishant, Department of Ophthalmology, ESIC Medical College, Patna 801103, Bihar, India

Kirandeep Kaur, Department of Pediatric Ophthalmology and Strabismus, Gomabai Netralaya and Research Centre, Neemuch 458441, Madhya Pradesh, India

Bharat Gurnani, Cornea and Refractive Services, Gomabai Netralaya and Research Centre, Neemuch 458441, Madhya Pradesh, India

Aarti Heda, Department of Ophthalmology, National Institute of Ophthalmology, Pune 411000, Maharashtra, India

Sarika Salodia, Global Medical Safety, Lundbeck, Singapore 569933, Singapore, Singapore

Co-first authors: Arvind Kumar Morya and Prasanna Venkatesh Ramesh.

Corresponding author: Arvind Kumar Morya, MS, Doctor, Neurosurgeon, Professor, Researcher, Senior Lecturer, Senior Researcher, Surgeon, Head of the Department, Department of Ophthalmology, All India Institute of Medical Sciences, Bibi Nagar, Hyderabad 508126, Telangana, India. bulbul.morya@gmail.com

Abstract

Diabetes mellitus (DM) is a chronic metabolic non-communicable disease with the ability to cause serious microvascular and macrovascular complications throughout the body, including in the eye. Diabetic retinopathy (DR), present in one-third of patients with diabetes, is a vision-threatening complication caused by uncontrolled diabetes, which greatly affects the retinal blood vessels and the light-sensitive inner retina, eventually leading to blindness. Several epidemiological studies elucidate that DR can vary by age of onset, duration, types of diabetes, and ethnicity. Recent studies show that the pathogenesis of diabetic retinopathy has spread its roots beyond merely being the result of hyperglycemia. The complexity of its etiopathology and diagnosis makes therapeutic intervention chal-

lenging. This review throws light on the pathological processes behind DR, the cascade of events that follow it, as well as the available and emerging treatment options.

Key Words: Diabetes; Diabetic retinopathy; Diabetic macular edema; Intravitreal injection; Laser photocoagulation

Core Tip: Diabetic retinopathy (DR) is a complication of diabetes mellitus that is a potential threat to the vision of patients. In patients with diabetes, regular ocular examination is essential to diagnose the disease at an early stage, and timely screening and diagnosis play an important part in a better prognosis. Non-proliferative diabetic retinopathy (NPDR) requires regular follow-up and treatment as and when needed. In proliferative diabetic retinopathy (PDR), the effectiveness of laser photocoagulation is time-bound: the earlier the better. Advanced DR stages require a more intensive approach such as vitreoretinal surgery, and PDR is associated with limited visual prognosis. Despite the multiple therapeutic approaches that are currently available for DR patients, such as intravitreal injections and sutureless pars plana vitrectomy, an interdisciplinary approach remains a mandate to treat these patients. Diabetic patients require good glycemic control as well as blood pressure control to reduce the risk of associated ophthalmic complications.

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INTRODUCTION

Diabetes mellitus (DM) is a globally growing epidemic affecting more than 400 million adults and is likely to affect 650 million by 2040[1-3]. Uncontrolled and long-standing diabetes affects every organ of the body, including the eye.

Arguably the most popular ocular complication of DM is diabetic retinopathy (DR). DR is classically characterized by gradually progressing changes that occur in the microvasculature. These changes include alterations in the retinal permeability, macular edema, retinal ischemia and neovascularization. Recent research, however, has explained that neurodegeneration of the retina is a crucial hallmark linked with the disease process. Retinal ganglion and axonal loss appear to be antecedent to microangiopathy[4-9], as various cell types show deviations in their functions on electrodiagnostic tests and other macular function investigations performed with reduced illumination and contrast[10-15]. The functional abnormalities are attributable to vascular injury, as well as toxicity to the integrated neurovascular unit by products of direct inflammation causing slow but relentless neurodegeneration[16]. Further, the idea that neurovascular complex lesions precede the angiopathic lesions suggests that innovative management modalities targeting these pathways ought to be carefully investigated. This is likely to guide us to better understand this problem and ultimately develop practical treatment modalities[17-19].

DR is a leading cause of blindness in the adult working populace. Poor patient compliance with annual ocular screening (only 35%–55% compliance) is an important factor for late diagnosis of the disease. Screening of the retina or retinal photography focused on vascular abnormalities is usually delayed, and the disease is often left undetected. In instances where severe damage has occurred, it was found that treatments are not able to effectively restore vision, with only 25%–28% demonstrating improvement of ≥ 3 early treatment DR study (ETDRS) lines[20-25]. Additionally, retinal examination alone, or with artificial intelligence-assisted photographic identification of hemorrhagic and vascular lesions, is currently limited by its capacity to overwhelmingly detect gross retinal abnormalities that cause visual impairment, and is not yet adept at identifying inner retinal ischemia, the histological levels of exudates with hemorrhages in the retina, and retinal pigment epithelium abnormalities[26-28].

Management of DR involves a combination of strategies aimed at controlling the underlying diabetes and directly treating retinal complications. Primarily, it involves a combination of strategies, including glycemic control, blood pressure management, and lipid-lowering therapies to slow the progression of the disease. For advanced stages of DR, treatment modalities are laser photocoagulation, intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents, and corticosteroids to treat macular edema and proliferative DR. Vitrectomy is reserved for severe cases involving vitreous hemorrhage or tractional retinal detachment.

Retinopathy is best understood if approached from the point of view of being an integrated pathophysiological construct of diabetes and its associated complications. This review manuscript presents newer perspectives regarding the etiology and pathophysiology of the domino-like progression of DR, and its candidate targets, highlighting the role of the inter-professional team in diagnosing and treating patients with these diseases.

METHODOLOGY

The authors looked up highly cited articles from PubMed, Scopus, Google Scholar, Web of Science, Cochrane Library, and Embase databases, focusing on publications from 1990 to 2022. The specific keywords used in the search included "Diabetic Retinopathy," "Retinal Neurodegeneration," "Anti-VEGF Therapy," "Macular Edema," and "Neurovascular Unit." These keywords were selected to cover critical aspects of DR, ensuring a focused and detailed examination of the condition's underlying mechanisms and treatment strategies.

We diligently used Reference Citation Analysis to search the articles, based on the Impact Index per article. Five independent reviewers selected the latest highlighted articles, based on their relevance, recency, and impact on the understanding and management of DR. This selection includes recent reviews and meta-analyses that offer comprehensive overviews, clinical trials, studies on new treatment modalities like anti-VEGF therapies and corticosteroids, and basic science research that delves into the neurodegenerative aspects of DR and the function of the neurovascular unit. Additionally, articles discussing technological advances in diagnosing and managing DR, particularly the use of artificial intelligence in retinal imaging, were included. All articles published in English were included.

PREVALENCE AND CLINICAL CHALLENGE OF DR

DR is an ever-rising public health problem, with the increasing burden of DR-related visual impairment and blindness [29-32]. Many epidemiologic studies state that DR is more frequent in younger patients with type 1 DM. Thus, DR is a burden to the socio-economic system, owing to its significant impact on the global workforce[33]. The prevalence of DR in pediatric age groups is variable. Few studies have published that mild DR occurs in children, with the duration of the disease as short as 1–2 years. However, many studies reveal that the duration is 3 years or more, with the typical duration being 8–10 years before the inception of retinopathy[34-37].

Among adults, the prevalence of DR has been found to range from 4%–32% in various studies[38-46]. The International Centre for Eye Health, London, has included the prevalence of DR in the Rapid Assessment of Avoidable Blindness (RAAB + DR) study, as a much faster and less expensive way to determine the burden of diabetes and DR in the over-50 population. This will help plan and prioritize diabetic eye care services to that population group, for early detection and treatment of the disease[34].

RISK FACTORS

Development of DR is proportionate to the age of the patient, the duration of diabetes, poor glycemic control, and fluctuating serum lipid and blood pressure levels. The etiological risk factors for DR are shown in Table 1.

PATHOPHYSIOLOGY OF DR

Although the core pathophysiological factor responsible for the development of DR is hyperglycemia, the natural history of DR arises from increased vascular perfusion and leakage, retinal inflammation, edema, expression of cytokines and cell adhesion molecules, glial reaction, apoptosis of the inner retinal structures, and neovessel formation (Figure 1)[47].

Hyperglycemia

Hyperglycemia is a primary biochemical disturbance of diabetes and implies an increased level of plasma glucose owing to insulin inadequacy. Various metabolic pathways have been involved in hyperglycemia-induced vascular changes, including advanced glycation end products (AGEs) accumulation, the polyol pathway, and the protein kinase C (PKC) pathway. Oxidative stress due to hyperglycemia has also been implicated in the development of DR.

AGEs: Accumulation of AGEs occurs secondary to non-enzymatic protein glycation pathogenic mechanisms due to raised glucose levels. AGE formation causes various secondary complications, such as triggering the reactive oxygen species (ROS), which subjects retinal cells to oxidative stress by one of three primary pathways: as altered serum proteins, as endogenous adducts produced secondary to glucose metabolism, or as extracellular matrix-immobilized alterations of structural proteins. Additionally, the increased amount of AGEs cause a decrease in the standard mRNA levels of pigment epithelium-derived factor (PEDF), which has a protective role[48-50]. Simultaneously, this cascades nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nuclear factor-B (NF-κB), causing inflammation and retinal cell damage, leading to DR[48,51,52].

Polyol pathway: Hyperglycemia activates the metabolic polyol pathway, leading to the production of sorbitol with NADPH (Figure 2)[53]. Sorbitol dehydrogenase converts sorbitol into fructose as cellular membranes are impermeable to sorbitol. In addition, NADPH reduces the antioxidant capacity of the cells. So, the accumulation of sorbitol causes multiple forms of damage in retinal cells including osmotic damage and leads to DR.

PKC: Of the 10 enzymes in the PKC family, the β1/2 isoform seems to be particularly connected to the onset and progress of DR[54]. PKC is a serine/threonine kinase that participates as a signal transducer in response to extracellular stimuli.

Table 1 Etiological risk factors for diabetic retinopathy

Non-modifiable risk factors	Modifiable risk factors	Newer risk factors
Puberty	Hypertension	Inflammation
Pregnancy	Obesity	Apolipoproteins
	Dyslipidemia	Hormonal influence
	Poor glycemic control	Leptin and adiponectin vitamin D
	Nephropathy	Oxidative stress
		Genetic factors

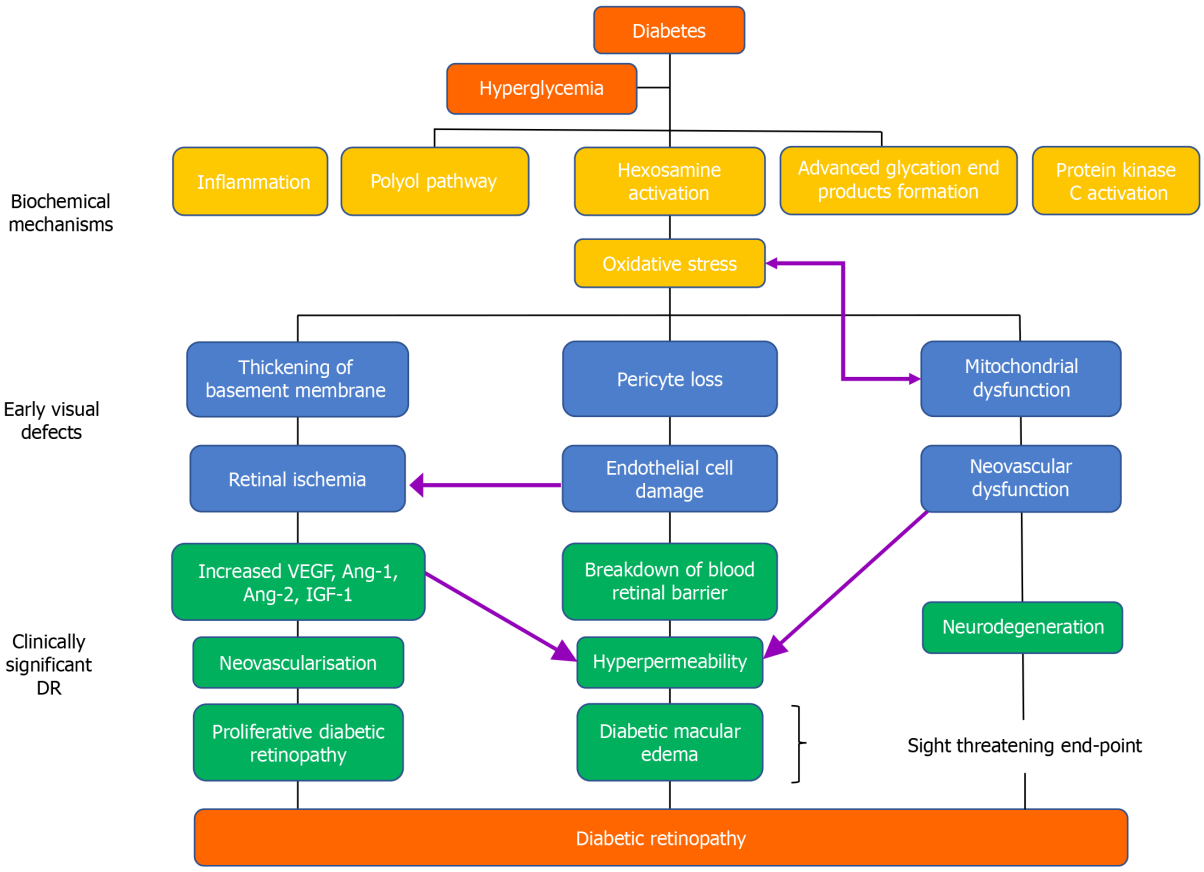

Figure 1 Pathophysiologic process of diabetic retinopathy. Ang: Angiotensin; IGF: Insulin-like growth factor; VEGF: Vascular endothelial growth factor.

The main PKC activator in physiology, diacylglycerol (DAG), is synthesized *de novo* because of increased glucose metabolism through the glycolysis pathway brought on by hyperglycemia. Clinical and experimental research has shown that the expression of DAG and PKC activation are both increased in the diabetes condition (Figure 3)[55]. PKC promotes DR by altering blood flow to the retina, causing changes in endothelial and leukocyte function that lead to capillary occlusion and leukostasis, and altering the synthesis of extracellular matrix (ECM) proteins and ECM remodeling. Because of this, the PKC pathway has a direct impact on other pathways, including those involved in inflammation, neovascularization, and abnormal hemodynamics, all of which play a role in the development of DR.

Oxidative stress: The increased ROS causes loss of neurons and pericytes, resulting in clogged capillaries (Figure 4). Escalating intracellular NADH levels increase the tricarboxylic acid cycle, thereby altering the tissue lactate:pyruvate ratio. This causes electron flux into the mitochondria, generating ROS, causing oxidative stress[48]. This potentially accentuates the nuclear enzyme poly-adenosine diphosphate-ribose polymerase and increases NF-κB activation, which influence production of TNF-α and NF-κB-dependent genes. This exacerbates stress, leading to capillary block and ultimately deforming alterations in the microvascular structure of the retina causing DR[49].

Other pathophysiological changes leading to DR

Renin-angiotensin-aldosterone system: The renin-angiotensin-aldosterone system (RAAS) regulates fluid balance and

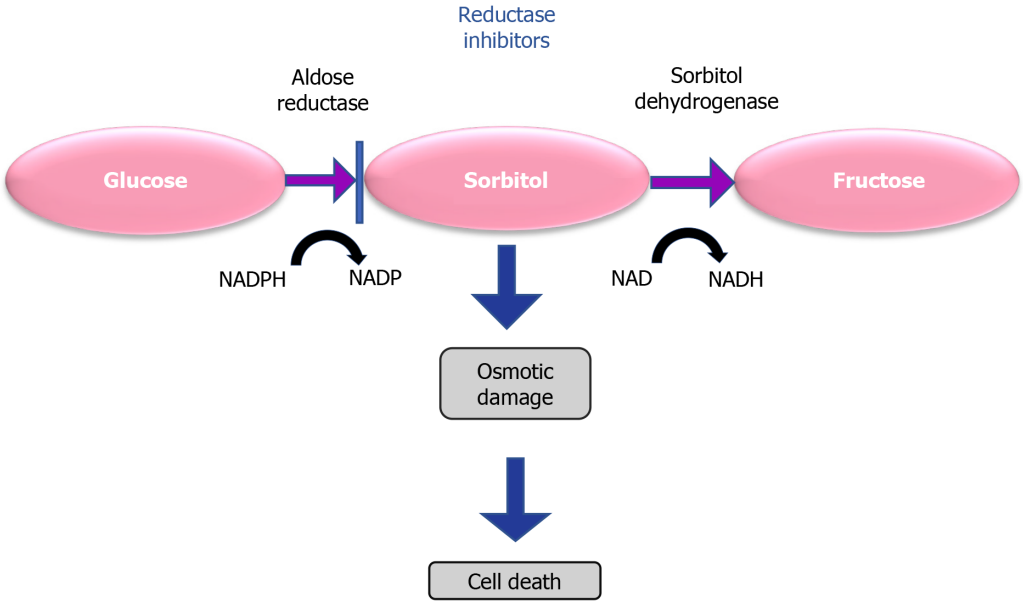

Figure 2 Sorbitol pathway. NADP: Nicotinamide adenine dinucleotide phosphate; NADPH: Nicotinamide adenine dinucleotide phosphate hydrogen.

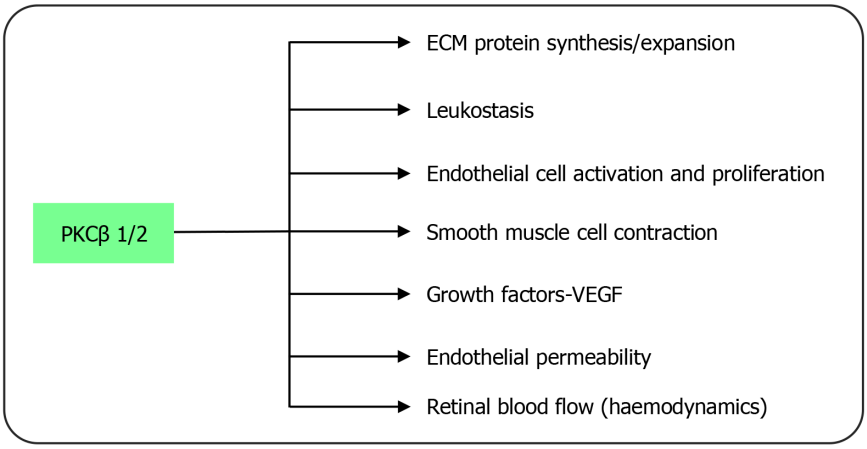

Figure 3 Pathway of oxidative stress on the development of diabetic complications. ECM: Extracellular matrix; PKCβ: Protein kinase C beta; VEGF: Vascular endothelial growth factor.

blood pressure and exhibits abnormalities in diabetic individuals[56]. In PDR, the expression of renin, angiotensin-converting enzymes I and II (ACEI and ACE II), angiotensin receptors, RAAS receptors and signaling molecules, has been observed to rise in DR[57]. There is evidence from experimental models that ACE inhibition reduces neovascularization, a defining characteristic of early DR.

Dyslipidemia and hypertension: Dyslipidemia and high blood pressure may also influence DR[58]. Blood pressure has been shown to have a substantial impact on the development of PDR by the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) and the United Kingdom Prospective Diabetes Study[59,60]. Furthermore, people with diabetes frequently experience hypertension. Additionally, an investigation by Patel *et al*[61] showed that blood flow to the retina was found to be reduced after effective photocoagulation, which was seen as a correction to hemodynamic autoregulation.

Through two different processes, hypertension is considered to speed up the development of DR. First, endothelial dysfunction is caused by mechanical strain and shear stress that elevate blood pressure, increase retinal perfusion, and increase blood viscosity placed on endothelial cells. Second, the pathophysiology of DR is separately linked to the endocrine system that regulates blood pressure[59].

Effective management of systemic risk factors is essential, but hyperglycemia (indicated by HbA1c levels) may contribute to approximately 10% of the risk for DR. Hypertension and dyslipidemia together may account for less than 10% of the risk, as seen in certain population-based studies[62,63]. This evidence implies that other, yet-to-be-identified factors, play a significant role in the initiation and progression of DR.

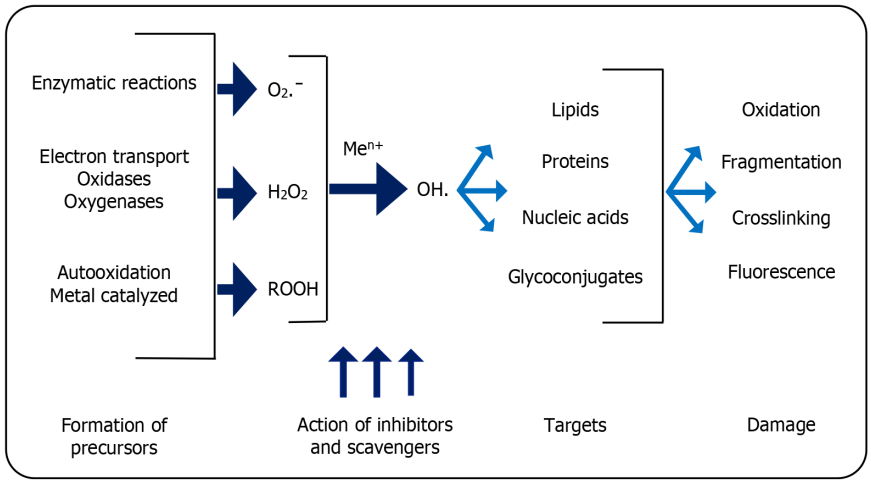

Figure 4 Regulation of pathophysiological processes in diabetic retinopathy by protein kinase C. H_2O_2: Hydrogen peroxide; Me^{n+}: Methyl Cation; O_2^-: Oxygen superoxide anion radical; OH.: Oxygen hydroxyl radical; ROOH: Hydroperoxides.

Subclinical inflammation and leukostasis: Many studies have documented that subclinical inflammation plays a key role in the development of DR[64]. While AGEs, oxidative stress, hypertension, and hyperglycemia are contributors to inflammation, further propagation of these pathways is caused by the inflammatory response itself, *via* various signaling responses involving VEGF, RAGE expression, nitric oxide, CRP, ICAM-1, and NF-B. Endothelial nitric oxide synthase (eNOS) causes the formation of new, fragile blood vessels and an increase in their permeability due to VEGF, which induces ICAM-1 and eNOS expression.

Leukostasis causes capillary blockage, ROS-mediated cell death, and an intense local inflammatory response in the retinal tissue. It is a significant event in the pathophysiology of DR. It is widely known that individuals with DR have significantly higher levels of soluble and cell surface adhesion molecule activation, systemic production of proinflammatory cytokines, and chemokine expression in the retina[64,65]. Numerous clinical investigations show a correlation between the development of DR and an increase in serum proinflammatory cytokines, adhesion molecules, and immune cell activation. The connection between leukocytes and endothelial cells is improved by endothelial dysfunction, elevated levels of proinflammatory cytokines, and adhesion molecules. This was further supported by research showing that leukocyte entrapment in retinal capillaries in experimental models was significantly decreased when adhesion molecules were knocked off.

Recent research has demonstrated that variations in the expression of carbohydrate chains on leukocyte surfaces trigger their activation, rolling and adherence to the vascular endothelial cells. In diabetic individuals, UDP-GlcNAc: Galβ1-3GalNAcβ-R-β-1-6-N-acetylglucosaminyltransferase (C2GNT) has increased activity. The enhanced O-glycosylation-type alterations on the leukocyte's surface carbohydrate chains caused by this hyperglycemia and the TNF-α induced enzyme result in increased leukocyte dysfunction and leukostasis. The severity and development of DR and neuropathy have both been linked to the enzyme activity[50].

The pathophysiology of DR is also hypothesized to involve inflammatory factors at a local level, such as the triggering of microglia, macrophages, and other immune cells. The pathophysiology of DR has been linked to higher levels of proinflammatory cytokines, ROS, growth factors, matrix metalloproteinases, and nitric oxide, produced more often when microglia are activated in the diabetic retina. The anti-inflammatory antibiotic minocycline stops microglial activation and halts DR progression.

Growth factors: VEGF, insulin-like growth factor-1 (IGF-1), PEDF, basic fibroblast growth factor, angiopoietin (Ang)-1 and -2, stromal-derived factor-1, epidermal growth factor, transforming growth factor-beta 2, platelet-derived growth factors, and erythropoietin, are some of the growth factors that have been attributed to the development and progression of DR[66].

Most human tissues manufacture insulin-like growth factors (IGFs), and elevated levels of IGF-1 are found in the vitreous and serum of individuals with diabetes. IGF's specific significance in the development of DR is not yet clear. IGFs appear to function both systemically and directly inside target tissues, according to mounting data. Additionally, much research points to vascular endothelial growth factor (VEGF) as the regulator of IGF action in neovascularization [67].

VEGF is the growth factor that has been the focus of most studies on DR. It increases vascular permeability in the ischemic retina, stimulates angiogenesis, breaks down the blood-retinal barrier, and causes endothelial cell proliferation and neovascularization. The activation of two membrane-bound tyrosine kinase receptors is the mechanism through which VEGF exerts its cellular effects. Two possible signaling routes, a calcium influx channel or a mitogen-activated protein kinase signaling pathway, may be activated by the binding of VEGF to the membrane-bound receptors. The blood-retinal barrier degradation and vascular leakage that VEGF has been linked to occur *via* both mechanisms. The angiogenic function of VEGF in the retina is assumed to be a result of an interaction with angiotensin II. Leukocyte adherence to retinal endothelial cells has been linked to VEGF, and this is thought to happen when nitric oxide synthase

and intracellular adhesion molecule-1 are induced[68].

Malfunction of insulin signaling in DR: Cellular absorption of fatty acids, carbohydrates, and proteins is heavily influenced by the presence of insulin. Insulin shows an inverse interaction with glucagon for the regulation of glucose, and these interactions are regulated by the signal transduction pathway[69]. In the presence of abnormalities in coagulation or insufficiency in insulin, this mechanism gets disrupted. Research that utilized exsanguinated animals proposed that there was a decrease in the rate of transport of insulin, along with alterations in the physiological functions of glial, neuronal, and vascular cells of the retina[69,70]. Current studies have discovered that insulin receptor activation in microvasculature shows a multitude of effects, such as an overlap of the insulin receptor, insulin receptor substrate-1, phosphatidylinositol3-kinase, and phosphotyrosine in neuronal cells of rats[69,71,72]. Different IR subsets signal differently[73]. Another study on hyperglycemic rats showed increased insulin receptor levels in retinal cells[74]. There is evidence of a link between insulin levels and retinopathy; however, more research is needed to understand the underlying mechanism fully.

Retinal neurodegeneration: The progression of DR begins with retinal neurodegeneration. Growing data suggests that retinal neurodegeneration may have a distinct pathogenesis apart from DR. Loss of ganglion cells and a decrease in retinal thickness were seen in a mouse model of diabetes before the development of microvascular changes. Patients with diabetes who had either no DR or early DR (microaneurysms) had inner retinal thinning. To develop possible therapeutic targets for DR early intervention, more research into the molecular pathways of retinal neurodegeneration is needed[75].

STRUCTURAL PATHOGENESIS MODEL OF DR - THE NEUROVASCULAR UNIT IN DR

Retinal neurovascular unit pathology, or DR, describes the interdependent interaction and functional linkage between neuroglia, neurons, and retinal vasculature that controls the retina's normal function[76]. Retinal capillaries consist of endothelial cells and pericytes and are closely linked with glial end feet, neural processes, and microglia. Retinal arterioles have smooth muscle cells in their vessel wall with marked pericyte coverage, depending on the order and size of the vessel. Pericytes respond dynamically to different vascular and neuronal (neural as well as glial) stimuli[77]. The responses can be visualized as "neurovascular coupling," which occurs in large and small vessels to adjust blood flow to attain the metabolic demands of the retina. Its dysregulation in DR is evidenced by abnormal retinal vascular response to diffuse illuminance flicker. This also occurs due to unusual endothelial-glia interactions, resulting in attenuated vascular dilatory responses that may have a prognostic value in early DR[77-79]. The concept of DR as a disorder involving both nerves and vessels together widens the potential therapeutic strategies for DR due to the multitude of cell-types that can be modulated by innovative therapies.

CLASSIFICATION SYSTEMS OF DR

Early treatment DR study

The details of the ETDRS classification are shown in Table 2.

Optical coherence tomography classification of diabetic macular edema

Optical coherence tomography (OCT) is a non-invasive, non-contact transpupillary imaging technique that has set the precedent for the onset of a new era in ophthalmic clinical practice in terms of ocular imaging, by producing histologically analogous images of the macula. OCT thereby allows objective evaluation of macular thickness and evaluation of the vitreomacular interface (Figures 5A-C). Various OCT patterns of structural macular changes linked with diabetic macular edema (DME) are shown in Table 3.

International clinical DR disease severity scale

To simplify the classification of DR, several faculties discussed and introduced the International Clinical Disease Severity Scale for DR[80]. This severity scale for the disease is founded on the interpretations presented by the WESDR and the ETDRS (Figures 6A and B). The details of the International Clinical Diabetic Retinopathy Disease Severity Scale classification are shown in Table 4.

Fluorescein angiographic classification

The ETDRS formulated that certain fundus changes in diabetes are discernible on fluorescein angiograms (FA) rather than colored fundus photographs. Hence, FA-based classification was also proposed, including stereoscopic FA of two 30° fields along the horizontal meridian, ranging from 25° nasal to the optic disc to 20° temporal to the macula. In the early-mid phase of the FA, the foveal avascular zone, loss of capillary flow, dilation of capillaries, arteriolar abnormalities, and RPE abnormalities were assessed. Fluorescein leakage, fluorescein leakage source, and cystoid changes were analyzed during the late FA phase[81]. This fluorescein angiographic classification scheme is time consuming, complex, and best-suited for the research setting, not for regular clinical use.

Table 2 Early treatment of diabetic retinopathy classification of diabetic retinopathy

Category	Features	Follow-up periods
No DR	No findings	12 months
Very mild NPDR	Microaneurysms only	Most of the patients in 12 months
Mild NPDR	Any or all of: Microaneurysms, retinal hemorrhages, exudates, cotton wool spots	6-12 months, depending on the severity of signs, stability, systemic factors, and patient's personal circumstances
Moderate NPDR	Severe retinal hemorrhages in 1-3 quadrants or mild IRMA; Significant venous beading in no more than one quadrant; Cotton wool spots	Approximately 6 months (PDR in up to 26%, high-risk PDR in up to 8% within a year)
Severe NPDR	The 4-2-1 rule; Severe retinal hemorrhages in all four quadrants; Significant venous beading in ≥ 2 quadrants; Moderate IRMA in > 1 quadrant	4 months (PDR in up to 50%, High-risk PDR in up to 15% within a year)
Very severe NPDR	≥ 2 of the criteria for severe	2-3 months (high-risk PDR in up to 45% within a year)
High-risk PDR	NVD > 1/3rd disc area; Any NVD with vitreous/Pre-retinal hemorrhage; NVE > 1/2 disc area with vitreous/pre-retinal hemorrhage	Laser photocoagulation Intravitreal Anti-VEGF agents Intravitreal Triamcinolone Pars Plana Vitrectomy; Lipid-lowering drugs
Advanced diabetic eye disease	Pre-retinal (retro hyaloid) and/or intragel hemorrhage; Tractional retinal detachment Tractional retinoschisis Rubeosis Iridis (Iris Neovascularization)	Pars plana vitrectomy

NPDR: Non-proliferative diabetic retinopathy; NVD: Neovascularization of the disc; NVE: Neovascularization elsewhere; PDR: Proliferative diabetic retinopathy.

Table 3 Optical coherence tomography classification of diabetic macular edema

Classification features
Large cystoid spaces
Serous detachment of the retina
Tractional detachment of the fovea or vitreomacular traction
Taut posterior hyaloid membrane
Diffuse retinal thickening
Cystoid macular edema with posterior hyaloidal traction serous retinal detachment Tractional retinal detachment

Modified Airlie House classification

In 1968, a group of faculties met in Airlie House, Virginia, to discuss the known factors about DR at that time. After the symposium, a standardized classification system for DR was developed. This system underwent modifications and was utilized in the Diabetic Retinopathy Study[82]; it was later adapted for use in the ETDRS. The modified Airlie House Classification of DR is based on the grading of stereo images across seven fields. It categorizes DR into 13 detailed levels, from level 10 (no retinopathy present) to level 85 (vitreous hemorrhage or retinal detachment involving macula)[83]. Although highly valuable for research purposes, its complexity makes it impractical for routine clinical use. As a result, most ophthalmologists do not employ this classification in their everyday practice.

TREATMENT PROTOCOLS IN DR AND OTHER ASSOCIATED SYSTEMIC DISEASES, AND THEIR LIMITATIONS

Ocular treatment protocols

Ocular treatment protocols for DR comprise of laser photocoagulation, intravitreal anti-VEGF and steroidal injections, and vitreoretinal surgery. Recent therapeutics emphasize treatment of advanced diseases such as PDR or DME.

For PDR, pan-retinal photocoagulation (PRP) is the first-line treatment (Figure 6C). Laser burns to the peripheral retina can induce recession of neovessels, and the ability of PRP to reduce occurrence of severe vision loss in cases of PDR was confirmed in a DR study[79]. Complications reported in post-PRP eyes include peripheral visual field loss, delayed dark adaptation, and atrophic creep over extended follow-up periods. To solve those issues, the pattern scan laser was used and the pain, time, expansion of the coagulation, nerve fiber layer loss, and inflammatory cytokines significantly reduced [84]. The ETDRS eventually told that less aggressive focal or grid laser treatment given to the macula decreases the rate of

Table 4 International clinical diabetic retinopathy disease severity scale classification of diabetic retinopathy

Disease	
Concerning diabetic retinopathy	
No apparent retinopathy	No findings
Mild NPDR	Only microaneurysms
Moderate NPDR	More microaneurysms and less than severe disease
Severe NPDR	No signs of PDR; Intraretinal hemorrhages in all four quadrants; Venous beading in ≥ 2 quadrants; Prominent IRMA ≥ 1 quadrant
PDR	Neovascularization; Vitreous or subhyaloid hemorrhage Figure 6 (Fundus picture showing PDR)
Concerning DME	
DME apparently absent	No retinal thickening and hard exudates at the posterior
DME apparently present	Apparent retinal thickening and hard exudates present at the posterior pole. Furthermore, it can be classified into three subtypes based on the area of thickening and hard exudates in the center of the Fovea
Mild DME	The retinal thickening or hard exudates are located farther away from the center of the fovea
Moderate DME	Retinal thickening or hard exudates are near the center of the macula but not involving the fovea
Severe DME	Hard exudate and thickening present in the center of the fovea

DME: Diabetic macular edema; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy.

moderate visual impairment in eyes with DME by 50% over 3 years[85]. Recently, sub-threshold diode laser micropulse photocoagulation, invisible retinal phototherapy, has been used to treat parafoveal edema mild macular edema, including that of the fovea, owing to its capacity to apply energy to the retinal pigment epithelium to stimulate it without triggering cell death[86].

In this modern era, three clinical sittings of intravitreal anti-VEGF injections enhance visual gains in eyes with DME[87-89]. A recent comparative efficacy study of the most advised anti-VEGF injections showed that aflibercept, bevacizumab, and ranibizumab were all effective in visual improvement[90,91]. However, treatment with aflibercept provided better visual gains as compared with bevacizumab and ranibizumab where initial visual acuity was poorer. Steroid intravitreal injections against VEGF are the first-line treatment for most eyes with centrally involved DME, and they can also be beneficial in treating DME[92,93]. However, intravitreal steroid usage is limited because of ocular side effects, such as cataracts and glaucoma.

In eyes with PDR, anti-VEGF medication has been strongly recommended as a means of regressing retinal neovascularization[94]. Recent studies have shown anti-VEGF to be an effective treatment option in eyes with PDR, especially with coexistent DME. Additionally, the advantages of anti-VEGF over PRP laser include reduced chances of peripheral visual field loss, DME, and vitrectomy over 2 years. Even with these positive outcomes, anti-VEGF therapy may not be optimal for patients who cannot present themselves for the near-monthly follow-up. Evidence on the efficacy and safety of anti-VEGF therapy and comparison with other treatment modalities is available from the Diabetic Retinopathy Clinical Research Network (drcr.net).

Steroid treatment is considered in the case of diffuse macular edema because of its anti-inflammatory effect downregulating the proinflammatory and pro-angiogenic mediators implicated in the progression of DME. Topical corticosteroids are preferable for DME rather than systemic administration as it has multiple side effects. The various routes of administration of corticosteroids include intravitreal injection, sub-Tenon injection, and dexamethasone intravitreal implant (Ozurdex; Abbvie, Chicago, IL, United States). Intravitreal triamcinolone acetonide (IVTA) has been used to treat DME for decades with substantial improvements in macular thickness and visual acuity[95]. Sub-Tenon triamcinolone acetonide injection (STTA) is also preferred to treat DME patients, though it has some controversial results[96]. The Ozurdex implant has become an alternative to IVTA and STTA because it provides a sustained-release formulation for dexamethasone required for adequate treatment and prevention of PDR recurrences[97].

Vitreoretinal surgery is used for non-clearing vitreous hemorrhage in PDR and tractional retinal bands[98]. In cases where there is an epiretinal membrane or some component of vitreoretinal traction causing retinal thickening, pars plana vitrectomy with or without peeling of the internal limiting membrane is done to treat associated DME. Though retinal thickening often improves after vitrectomy for DME, with results showing approximately a third of patients experiencing significant visual improvement, the visual outcomes may not be optimal, as evidenced by 20%–30% of patients who have significant loss of vision following this intervention.

Although current therapies are effective at preventing vision loss and often yield favorable visual outcomes for patients with both PDR and DME, there remain unmet treatment needs. Approximately 40%–50% of eyes with DME do not fully respond to anti-VEGF therapy, highlighting the need for new, advanced treatments. Moreover, for both PDR and DME, there is a need for non-invasive, non-destructive, and longer-lasting treatment options.

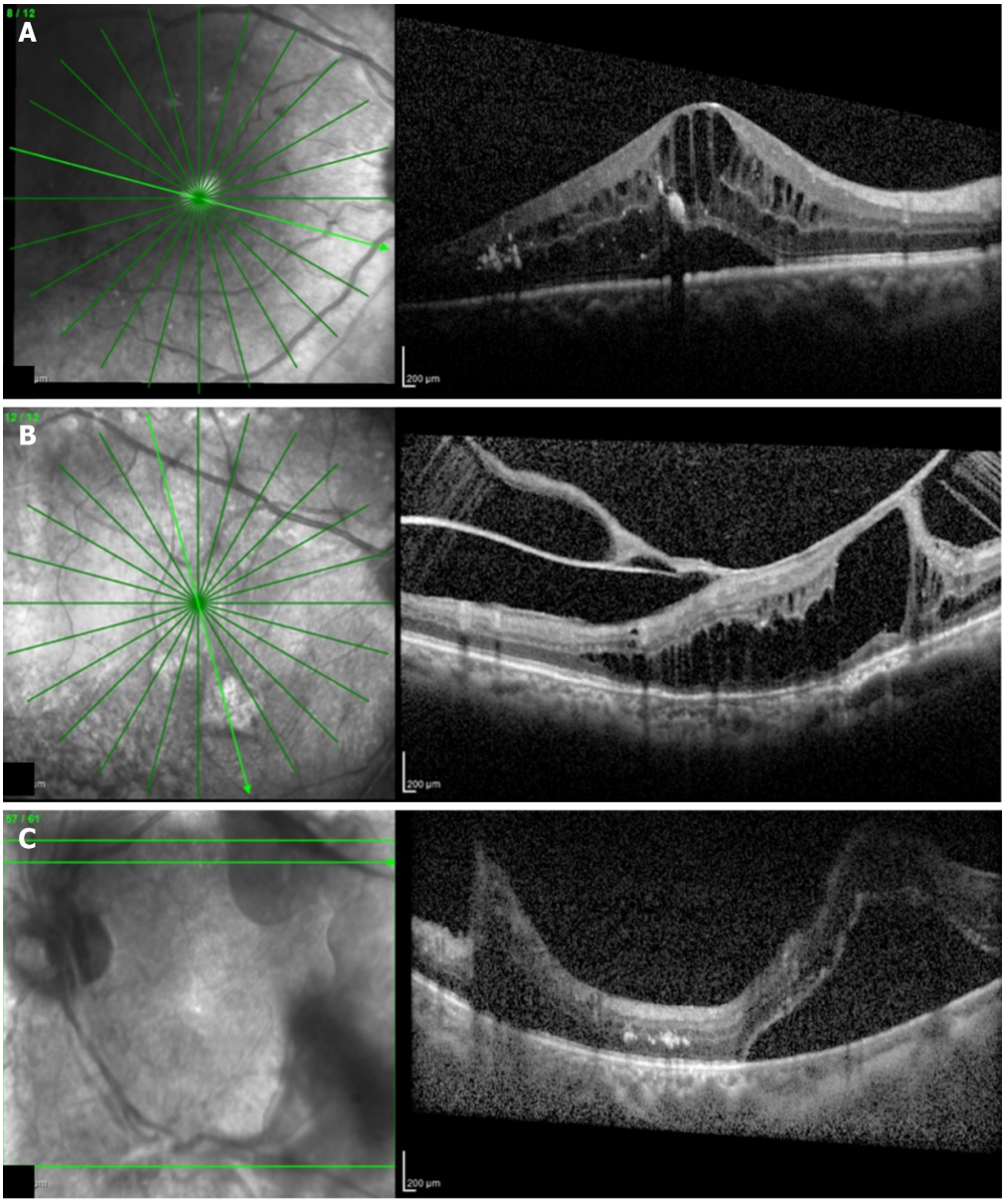

Figure 5 Optical coherence tomography images. A: Cystoid macular edema; B: Tractional retinal detachment; C: Tractional retinal detachment due to vitreous hemorrhage.

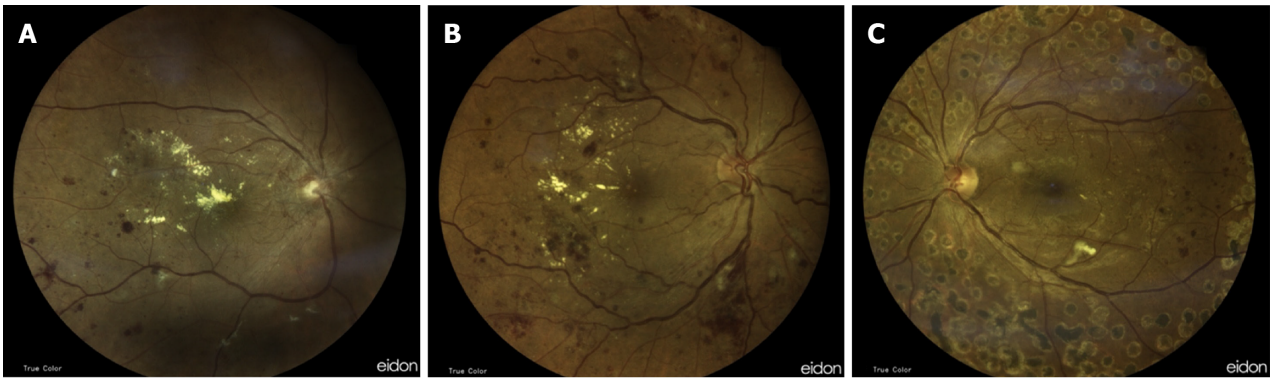

Figure 6 Fundus. A: All suggestive findings of severe non-proliferative diabetic retinopathy; B: Severe proliferative diabetic retinopathy; C: Pan-retinal photocoagulation laser marks.

Other supportive essential treatments for diabetes

Strict control of hyperglycemia and associated comorbidities are the first step. If macular edema worsens after PRP with moderate vision reduction, other modalities of treatment may be needed.

It is common to see raised intraocular pressure after intravitreal injections in the initial phase. This usually reduces within 3-6 h. One tablet of acetazolamide 250 mg stat may be used after the procedure. Follow-up is essential the next day, after which they are planned as needed. Further management is decided based on OCT done at every follow-up, whether repeat injections, and/or laser or surgery would be needed.

NEW THERAPEUTIC APPROACHES IN DR

While there have been substantial developments in management protocols for DR, additional approaches are warranted because recent therapies exclusively target advanced DR. Anti-VEGF injection is only partially effective against DME, and the identification of additional, VEGF-independent pathogenic molecules in this scenario is important, as it may lead to new treatments that aid better preservation of vision[99]. Broadening treatments beyond direct suppression of pathologic vascular changes may have more benefits. Recognizing DR as a disease of the neurovascular unit highlights the need to expand therapeutic targets. Broadening the focus beyond just vascular leakage and neovascularization to include neuroprotection and intraretinal revascularization would set ambitious goals for DR treatment. The idea that epigenetic modifications related to metabolic memory play a role in DR is another pathogenic process deserving of therapeutic focus [100]. Topical drug formulations capable of penetrating the retina could reduce systemic side effects and enable patients to self-administer treatments over extended periods. These novel therapeutic approaches demonstrate promising advancements. Future strategies hold the potential to significantly revolutionize the management of DR with even more innovative solutions.

FUTURE APPROACHES TO DR

Artificial intelligence in DR

Artificial intelligence (AI) is becoming popular in diagnosing fundus images using the basic convolutional neural network, as it is more sensitive and specific for the diagnosis of DR in comparison with human capabilities. Studies have also reported that AI systems can perform automated grading of DR.

IDxDR is the first United States Food and Drug Administration (FDA)-approved commercially available DR detection and referral system. This system uses lesion-based grading with a sensitivity of approximately 80%, but with a specificity of less than 90%[101]. Although it is an effective tool, it remains less popular because of the high cost and bulky size.

Morya *et al*[101] have shown that the first smartphone-based online annotation tool for DR and common retinal disorders is very effective for faster and more accurate image labeling, using AI-based deep learning (DL) for DR (Figure 7). The DL algorithm creates a binary classification system for diabetic retinopathy referrals based on whether a patient's retinal image indicates the presence of referable DR. A team of 32 retinal specialists, eight IIT engineers, and supporting staff used the tool for over 200,000 images. This tool was flexible and portable with accurate grader variability in concurrence with image annotation[101,102].

Sosale *et al*[102] created and investigated Remidio Medios, an offline AI. This algorithm was developed to operate offline due to restricted internet access and demands considerable computational capabilities, unlike cloud-based AI systems commonly used in developing nations. Fundus can be imaged using a handheld camera (Remidio Non-Mydriatic Fundus on Phone) and the image directly processed on a smartphone graphics processing unit, with 86% specificity and 98% sensitivity.

Retmarker can decrease the workload of humans grading pictures by 48%[103]. Rather than visiting specialized hospitals, these systems enable diabetic participants to obtain fundus pictures or OCT images at nearby basic healthcare clinics. These images can then be used for direct grading, providing recommendations for follow-up or referral. This approach enhances convenience and efficiency for diabetic patients undergoing fundus screening, substantially reducing the workload of ophthalmologists. As a result, it can greatly enhance compliance with fundus screening among diabetic patients[102].

Protective mechanisms

Significant research has been devoted to identifying the pathogenic pathways involved in the initiation and progression of DR. A notable emerging perspective highlights the paramount value of autogenous protective mechanisms against DR [104,105]. In a study, nearly 40% of participants with confirmed diabetes decades before strict glycemic control became standard of care, had no or only mild DR[106]. Additionally, in studies involving groups with shorter durations of diabetes, the severity of DR has not been correlated with either current or historical HbA1c levels. This suggests that some individuals possess endogenous protective factors that prevent the progression to advanced DR. Understanding these mechanisms could pave the way for innovative strategies to prevent the initiation and progression of diabetic ocular disease.

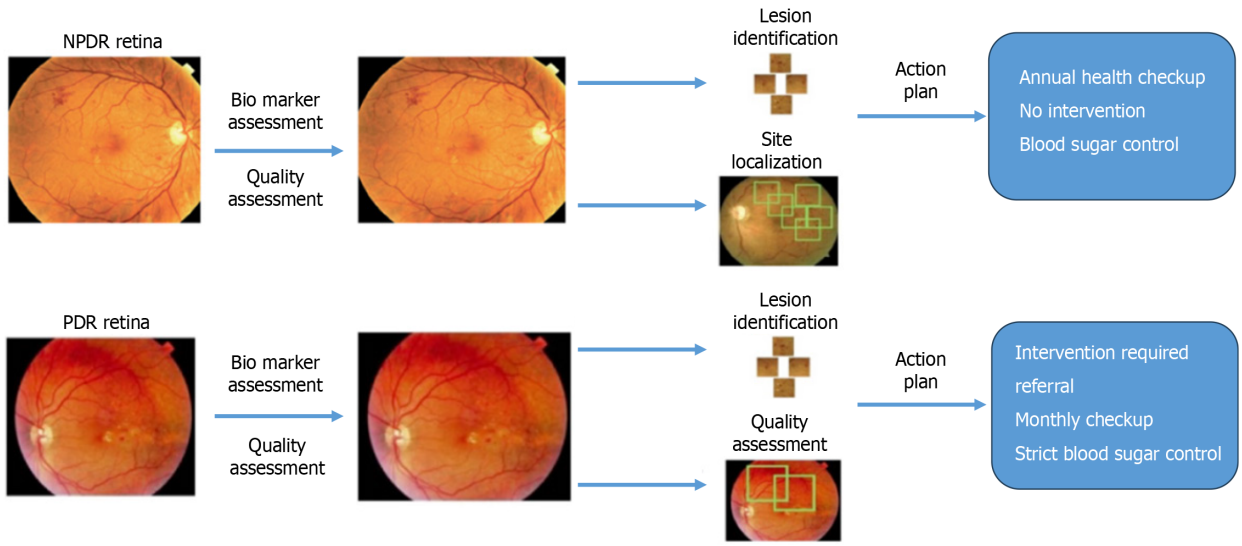

Figure 7 How artificial intelligence software assesses diabetic retinopathy into referable and non-referable interventions. NPDR; Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy.

CONCLUSION

Patients with DM show a domino-like cascade of development and progression of DR. As it is a microvascular disease, there are multiple variables involved with intricate correlation. According to several experimental and clinical findings, inflammation and retinal neurodegeneration may be regarded as separate pathogenic pathways in DR. Some individuals may develop DME, while others may progress toward PDR. The development of medications targeting molecules in those pathologic pathways may provide new therapeutic treatments. New approaches should embrace a comprehensive understanding of the impact of diabetes impact on the fundus, allowing for treatments tailored to distinct disease phenotypes. This holds promise for achieving successful clinical outcomes for all patients. A deeper insight into patient variability and its influence on clinical phenotypes will strengthen efforts toward more precise and effective management of DR.

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FOOTNOTES

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Country of origin: India

ORCID number: Arvind Kumar Morya 0000-0003-0462-119X; Prasanna Venkatesh Ramesh 0000-0002-6105-8666; Prateek Nishant 0000-0003-3438-0040; Bharat Gurnani 0000-0003-0848-5172; Aarti Heda 0000-0002-5252-6800.

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MINIREVIEWS

Biobanks and biomarkers: Their current and future role in biomedical research

Michael Colwill, Samantha Baillie, Richard Pollok, Andrew Poullis

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Michael Colwill, Samantha Baillie, Richard Pollok, Andrew Poullis, Department of Gastroenterology, St George's University Hospital NHS Foundation Trust, London SW17 0QT, United Kingdom

Corresponding author: Michael Colwill, BSc, MBBS, MRCP, Doctor, Research Fellow, Department of Gastroenterology, St George's University Hospital NHS Foundation Trust, Blackshaw Road, London SW17 0QT, United Kingdom. michael.colwill@nhs.net

Abstract

The importance and utility of biobanks has increased exponentially since their inception and creation. Initially used as part of translational research, they now contribute over 40% of data for all cancer research papers in the United States of America and play a crucial role in all aspects of healthcare. Multiple classification systems exist but a simplified approach is to either classify as population-based or disease-oriented entities. Whilst historically publicly funded institutions, there has been a significant increase in industry funded entities across the world which has changed the dynamic of biobanks offering new possibilities but also new challenges. Biobanks face legal questions over data sharing and intellectual property as well as ethical and sustainability questions particularly as the world attempts to move to a low-carbon economy. International collaboration is required to address some of these challenges but this in itself is fraught with complexity and difficulty. This review will examine the current utility of biobanks in the modern healthcare setting as well as the current and future challenges these vital institutions face.

Key Words: Biobanks; Biomarkers; Biomedical research; Research methodology; Research ethics

Core Tip: Biomarkers and the biobanks used to help discover them are growing in number, scope and importance. Our article reviews the different models of biobanks that exist globally as well as some of the biomarkers that have been discovered from these institutions. We review the challenges biobanks face and their future utility in biomedical research and personalised medicine.

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INTRODUCTION

Biomarkers are defined as a specific characteristic that is used as an indicator of a normal or pathological biological process or a response to a therapeutic intervention[1]. Their use has grown in recent decades and they are now crucial tools in healthcare and an area of heavy investment and research.

Alongside the development of biomarkers has been the growth of biobanks with the first description of their use in the literature in 1996[2] although the earliest similar facilities, known as biorepositories, were established at the end of the 19th Century[3]. One of the first biorepositories was a programme set up by the United States Department of Defence (DoD) and is now part of the Joint Pathology Centre(JPC)[4]. This collected samples from soldiers and veterans as early as 1862 with the initial aim of providing a second diagnostic pathology opinion and this continues to be the primary aim of the JPC today. Technological advances now mean that samples historically collected in these biorepositories for a single research question can now be utilised for a variety of different projects. An example of this was the application of modern techniques to samples stored in the DoD serum repository, a biorepository of over 50000 serum specimens initially set up in the 1980s to investigate the human immunodeficiency virus epidemic, to identify over 200 potential biomarkers of occupational exposure[5] demonstrating the potential benefits of applying modern technology to historical biorepositories.

Modern biobanks, as defined by the Organisation for Economic Co-operation and Development, are 'a collection of biological material and associated data and information stored in an organised system, for a population or a large subset of a population[6]'. Their role in improving our understanding of health and disease as well as their size and scope has massively increased since their inception and now represent an industry projected to be worth $50 billion by 2026[7]. Biobanks are either academic, which are usually research-driven with institutional or grant funding, or industry-funded which tend to focus on end products and be more business-driven. The difference in these models can be problematic which will be discussed later in this article.

Whilst biobanks were initially focused on cancer research they, and the biomarkers stored within them, are now key facets in the development of personalized medicine through the emerging fields of metabolomics, proteomics and epigenomics and are playing a more and more important role in cutting edge medicine. This article will discuss their current and future roles in healthcare as well as the challenges facing them.

CURRENT UTILITY

There are various classification systems for biobanks, but these can be cumbersome and confusing. A convenient and effective way to distinguish between them is whether they are population-based or disease-oriented entities.

Population-based biobanks

Population banks obtain samples primarily from volunteers without having an inclusion or exclusion criteria. Their goal is to use vast numbers of samples to give an accurate representation of either an entire population or specific sub-population and identify specific biomarkers of genetic susceptibility that, along with external factors, contribute to disease. An example of this is the United Kingdom Biobank, a stand-alone research entity, which has collected genetic and health information from over half a million individuals since 2006. This data is anonymised and made freely available to researchers around the globe and has been used to investigate biomarkers thought to be important in sepsis [8] and, through blood and urine sample analysis, to identify biomarkers for the risk of stroke[9]. These biomarkers have since been used to develop polygenic risk scores for certain diseases including chronic kidney disease, type 2 diabetes mellitus and gout[9].

The Danish National Biobank (DNB), whilst also academic in nature and funding, uses a different model through close integration into the Danish healthcare system and incorporates various projects, including the Danish Blood Donor Biobank, Danish Cancer Biobank and the Danish National Genome Centre, which allows a wider-array of biological samples from a greater donor pool to be collected. It also incorporates a large-scale sample collection programme from new-borns, *via* umbilical vein blood, as well as over 5 million adult individuals. Use of DNB data has led to the development of biomarkers for dementia with the identification of micro-RNA targets involved in vasculogenesis, lipoprotein transport and amyloid precursor protein which could offer new therapeutic options for Alzheimer's[10]. Further work using DNB data has also identified biomarkers in rheumatic disease[11], which can be used to facilitate earlier diagnosis, improve prognostication and monitor the efficacy of treatments, and the PREDICT study which aims to understand the underlying biological mechanisms in inflammatory bowel disease (IBD)[12].

As well as academic population-based biobanks, industry funded institutions are also growing in number and scope. An example is the Shanghai Zhangjiang biobank which is wholly owned and operated by Shanghai Outdo Biotech Co. Ltd and aims to collect 10 million human samples, including from the faecal microbiome, tissue and blood. Output from

this biobank has included an at-home-test for liver cancer using micro-RNA biomarkers developed by Roche diagnostics [13]. The complexity of grant funding and financial pressures on academic biobanks means that these industry-funded projects are likely to become more important in the future and provide a greater share of research output.

Disease-oriented biobanks

Whilst population-based biobanks have definite advantages, the range of research questions that they can address can be limited such as when investigating a specific sub-group of patients of a particular disease. This is where disease-oriented biobanks, which collect samples focused on either a specific tissue-type or disease, can be useful and they have certainly contributed significantly to healthcare in the past decades.

Earlier disease-oriented biobanks were primarily targeting cancer with the aim of identifying novel biomarkers to aid early detection as well as developing and testing novel therapeutics such as the impact of Programmed Cell Death-1 inhibitors[14] in immunotherapy for cancer. Biobanks continue to be crucial to cancer research across the entire spectrum of the disease. A more recent example is the VIVO biobank in the United Kingdom which has a focus on childhood cancer [15]. Research utilising this resource has been able to advance treatment of acute lymphoblastic leukaemia through genomic analysis and biomarker identification[16]. Genomic analysis using VIVO biobank studies has also been used to identify biomarkers which can help risk-stratify patients with medulloblastoma[17] and a whole host of other research projects are continuing to use this valuable resource.

The number of biobanks, both academic and industry-funded, investigating cancer continues to increase but disease-oriented biobanks are also playing a more substantial role in non-oncological disease. The National Institute for Health Research (NIHR) IBD Bioresource in the United Kingdom[18] was established to provide a genetic and clinical resource that would be available to researchers and allow the development of better treatments for patients with IBD. Work using this biobank to identify epigenetic biomarkers is ongoing[19] and, with the discovery of the IBD-hi and IBD-lo[20] biomarkers predictive of more aggressive disease, the NIHR IBD Bioresource will continue to produce important research well into the future with a large number of projects ongoing.

In Europe and the United States there has also been the establishment of disease-oriented biobank networks, such as the Brain Net Europe[21] or the NIH NeuroBioBank[22], which aim to co-ordinate collection of post-mortem brain tissue for study. This has yielded results in the form of, amongst others, the discovery of biomarkers for susceptibility to Alzheimer's disease[23] and identification of a differential regulation of tau exon 2 and exon 10 that could be useful biomarkers or possible therapeutic targets for Huntington's disease[24]. Given the financial pressures on biobanks and relative scarcity of some pathological specimens, it is likely that the importance of biobank networks will increase in the future.

It should also be noted that these disease-oriented biobanks, whilst more focused than their population-based equivalents, can also contribute to broader research questions such as the NIHR IBD Bioresource contributing it's stored genetic data to the 100000 genomes project using whole genome sequencing to increase the diagnostic yield of various rare diseases[25].

As can be seen, biobanks and biomarkers currently represent a key part of healthcare research and with the advent of artificial intelligence and an ever-growing understanding of metabolomics, proteomics and epigenomics it is likely their importance will only increase in the future.

THE FUTURE

The biobank industry has been growing in size, scope and complexity since it's creation and the pace of this growth has been increasing[7]. This is representative of the move, at least in terms of research even if it has not yet translated fully into clinical practice, from generalised to personalised and precision medicine. Whilst the reality of an individual and tailored treatment for each patient based upon their genetic and metabolic profile is still some way off, it is clear that biobanks and the biomarkers contained within them will be crucial to achieving this holy grail of medicine.

Personalised medicine aims to provide the right treatment to the right patient at the right time. An area where this has been successful is through the use of oncological biobanks to predict an individual's response to radiotherapy and chemotherapy in a wide variety of cancers. Biobank data has recently been instrumental in discovering patient-derived organoids[26] which could be used to developed targeted and personalised treatments for gastrointestinal cancers. As well as targeting treatments, biomarkers have also been used to understand a patient's risk profile thereby facilitating earlier diagnosis and treatment, such as in Alzheimer's[27], which can drastically impact upon prognosis. These examples highlight the potential uses of biomarkers and biobanks in personalised medicine, a field which will continue to grow into the future as technology continues to develop.

The advent of technologies such as artificial intelligence (AI) offers to bring a promising data analysis capability to the discovery and development of biomarkers. AI is able to analyze the vast volumes of data–be it proteomic, metabolomic or genomic–held in biobanks and help to identify novel biomarkers. Several have already been discovered across a variety of diseases using AI[28,29] and there have been cases where these AI-supported discoveries have outperformed current processes, such as Niu *et al*[30] who used plasma and liver proteomic datasets to identify circulating biomarkers that were able to diagnose the degree of fibrosis in alcohol related liver disease patients more accurately than current conventional biomarkers. As well as discovery, AI also has a role in translating these biomarkers into clinically useful tests and overcoming the logistical challenges this can pose[29] which should help to bring these discoveries from the research realm into real-world clinical use much more quickly than is currently possible.

Challenges

As discussed, the use of biomarkers and importance of biobanks will only increase in the coming decades and become a crucial part of cutting-edge healthcare. However, with this will come significant challenges, summarized in Figure 1, which will need to be overcome if we are to exploit their full potential.

Since the first biobanks appeared, the number of both academic and industry-funded biobanks has ballooned but has done so in a relatively hap-hazard manner often without national, let alone international, co-ordination. As a result, many biobanks are performing similar roles without pooling data sets which impacts upon the quantity and quality of output and wastes resources. Addressing this requires greater co-ordination between different institutions but this also comes with challenges, specifically around the logistics of data sharing and ethical considerations concerning data sharing and ownership. In response to these challenges international organizations have been established such as the International Society for Biological and Environmental Repositories (ISBER) and the Biobanking and Biomolecular Resource Research Infrastructure European Research Infrastructure Consortium (BBMRI-ERIC). These organizations aim to foster co-operation and data sharing between different biobanks to improve the output from biomedical research.

However, implementing this co-operation will be a challenge. Logistical barriers such as different languages spoken and computer software can be relatively easily overcome and there are multiple examples of international organisations which function well in spite of this such as the European Organisation for Nuclear Research[31]. However, a more significant challenge is sample standardisation. The protocols and standards for sample collection, cataloguing and storage can vary significantly between different biobanks even if collecting similar data. When attempting to combine data from multiple facilities, or even within the same facility but from different time periods or projects, this heterogeneity can impact upon the reproducibility and validity of the study in question. In order to foster collaborative work which produces scientifically valid results, developing and implementing standardised protocols for sample collection and storage is essential and organisations like the BBMRI-ERIC will play a crucial role.

Whilst greater collaboration will help to overcome some difficulties, it will also exacerbate some current legal conundrums. Intellectual property (IP) laws differ from country to country and prior to engaging in collaborative working there would need to be agreement amongst stakeholders about ownership of biobank facilities, the samples within them, any scientific or commercial output as well as access mechanisms to this IP for future research purposes. International agreements regarding the collective enforcement of IP legislation are needed to provide protection and security to biobanks although we do recognize this has not been possible in many other industries so may not be forthcoming in the immediate future. This will require collaboration amongst biobanks and with international organisations such as the World Trade Organisation.

One possible solution to the IP question is relinquishing the term ‘ownership’ entirely. The nature of biobanks and their various stakeholders–funding agencies, philanthropic individuals, participants, researchers–has led to the development of complex arrangements with regards to control and ownership. This negatively impacts on the access to the biobank data and research output. An alternative proposal has been to create biobanks as ‘custodianships’[32] where all those involved have a caretaking obligation from collection to distribution of any findings. It has been suggested these custodianships would then be able to endorse legal and ethical practices and share accountability amongst stakeholders [33] although this remains an area of debate.

Together with these legal challenges are ongoing ethical questions such as confidentiality, privacy and consent. The collection of large volumes of personal data and tissue requires stringent protocols and guidelines defining who has access to the data and what it is used for. Poor or inadequate implementation of these practices can result in breaking confidentiality and the invasion of participant’s privacy. The ISBER publishes guidance on best practices[34] with regards to these areas but there is no framework to ensure these are followed and this needs addressing at an international level.

Along with confidentiality and privacy, consent continues to be a challenging area and one of ongoing debate. There is variability in the consent process between different biobanks and different research projects with some obtaining fully informed consent related to one specific project. This can present challenges if investigators want to apply new tests or analyses to samples but do not have express consent and the process of re-contacting participants to obtain this consent may be considered too invasive. Other institutions use a looser or broad consent process but this has ethical implications. There is no ‘one-fits-all’ approach and this has led to debate over the optimal form of consent and whether so-called ‘open-consent’ is more appropriate for biobanks[35]. However, there is as of yet no international consensus on this and it will continue to be an area of debate in the near future.

A further challenge is with regards to the sustainability of these repositories. The collection and storage of biological samples is a costly undertaking, both financially and in terms of their environmental impact. Different funding models, as discussed earlier, create challenges such as value for money for publicly funded institutions or providing sufficient income to make privately funded institutions economically viable in the longer term. This can lead to publicly funding entities, such as public hospitals or the NIHR, not being willing to pay high maintenance costs and researchers not being able to afford high access fees charged by commercial facilities. Both of these outcomes impact upon the utility of biobanks and negatively affect the volume and quality of scientific output. These financial challenges will continue into the future[36] and co-ordination on research topics, sharing of expertise and pooling of resources will be key to maintaining a financially viable system. The environmental cost, given high energy and other resource requirements, is becoming more of a frontline issue and there has been work to try and reduce the impact of these facilities through renewable energy and minimising waste generation but there still remain significant challenges in adopting a zero-carbon and environmentally sustainable model[37].

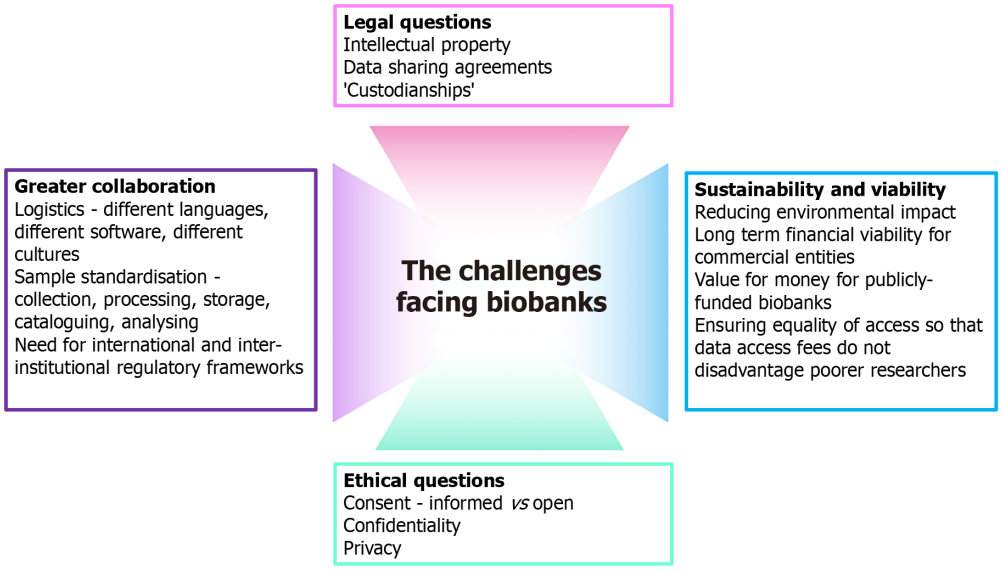

Figure 1 The current and future challenges facing biobanks.

CONCLUSION

With recent genuine advances towards that elusive goal of personalised and precision medicine, the importance of biomarkers has never been greater and the same is true of the biobanks that are essential to their development. The research output and practical, real-world applications are increasing at an almost exponential rate and with this comes questions about how to ensure the highest quality output is achieved without compromising on efficiency or legal and ethical standards. Improved international collaboration will be essential for the coming years and decades to achieve this and help us move towards truly personalised medicine.

FOOTNOTES

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Country of origin: United Kingdom

ORCID number: Michael Colwill 0000-0001-6925-8358; Samantha Baillie 0000-0003-3280-0347; Richard Pollok 0000-0001-6452-6763; Andrew Poullis 0000-0003-0703-0328.

Corresponding Author's Membership in Professional Societies: British Society of Gastroenterology, No. BSG60672.

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MINIREVIEWS

Pharmacological adjuvants for diabetic vitrectomy surgery

Ramesh Venkatesh, Chaitra Jayadev, Vishma Prabhu, Priyanka Gandhi, Rupal Kathare, Naresh K Yadav, Ayushi Choudhary, Jay Chhablani

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Ramesh Venkatesh, Department of Ophthalmology, Narayana Nethralaya, Bangalore 560010, India

Chaitra Jayadev, Vishma Prabhu, Priyanka Gandhi, Rupal Kathare, Ayushi Choudhary, Department of Retina, Narayana Nethralaya Eye Institute, Bangalore 560010, India

Naresh K Yadav, Department of Vitreo Retina, Narayana Nethralaya, Retina Serv, Super Specialty Eye Hospital and Post Graduate Institute of Ophthalmology, Bangalore 560010, India

Jay Chhablani, Department of Retina, University of Pittsburg School of Medicine, Pittsburg, PA 15213, United States

Corresponding author: Ramesh Venkatesh, MBBS, MD, MS, Doctor, Surgeon, Department of Ophthalmology, Narayana Nethralaya, 121/C. 1st R block, West of Chord Road, Rajaji Nagar, Bangalore 560010, India. vramesh80@yahoo.com

Abstract

Diabetic vitrectomy is a highly intricate surgical procedure performed during the advanced stages of diabetic retinopathy (DR). It is used to treat conditions such as tractional or combined retinal detachment, vitreous hemorrhage, and subhyaloid hemorrhage, which are all severe manifestations of proliferative DR. The results of the surgery are uncertain and variable. Vitreoretinal surgery has made significant progress since the early stages of vitrectomy. In the past ten years, advancements in intravitreal pharmacotherapy have emerged, offering new possibilities to improve the surgical results for our patients. Within the realm of medical terminology, an "adjunct" refers to a pharmaceutical or substance employed to aid or expedite the primary therapeutic intervention for a particular ailment. Their introduction has broadened the range of therapeutic choices that are accessible prior to, during, and following surgical procedures. This review article will specifically analyze the pharmacological adjuncts used in diabetic vitrectomy surgery, with a focus on their role in facilitating or aiding specific steps of the procedure. The implementation of this system of categorization offers benefits to the surgeon by allowing them to foresee potential difficulties that may occur during the surgical procedure and to choose the appropriate pharmacological agent to effectively tackle these challenges, thus enhancing surgical success rates.

Key Words: Diabetic retinopathy; Vitrectomy; Intravitreal injections; Anti-vascular endothelial growth factor; Adjuvants; Outcomes

Core Tip: For advanced diabetic retinopathy, diabetic vitrectomy is a complex procedure with unpredictable outcomes. In the last decade, intravitreal pharmacotherapy has advanced, providing new ways to improve surgical outcomes for our patients. In medicine, an "adjunct" refers to a drug or substance that supplements the main treatment. This review will look at the pharmacological adjuncts used in diabetic vitrectomy surgery and how they affect specific steps. The categorization system enables surgeons to anticipate surgical issues and select the appropriate pharmacological agent to address them, thereby increasing surgical success rates.

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INTRODUCTION

The treatment approach for diabetic retinopathy (DR), which poses a risk to vision, typically involves medical management using intravitreal pharmacological agents and/or laser therapy or in some cases, surgical management in the form of pars plana vitrectomy[1,2]. The primary goals of vitrectomy in the context of DR encompass several key objectives. These include reducing the presence of vascular endothelial growth factor (VEGF) within the vitreous cavity, enhancing oxygen supply to the retinal tissue, eliminating any media opacities, alleviating any antero-posterior or tangential forces exerted on the retinal surface, and impeding the advancement of angiogenesis and the subsequent emergence of end-stage neovascular glaucoma[3–5]. Therefore, the primary indications for vitrectomy in DR are as follows: Severe non-clearing vitreous hemorrhage (VH), significant dense premacular blood, taut posterior hyaloid with macular traction with or without associated macular tractional retinal detachment, combined retinal detachment, diabetic macular edema (DME) associated with overlying tractional epiretinal membrane (ERM), and early stages of neovascular glaucoma secondary to DR[3,6–11]. In recent years, advancements in vitrectomy instrumentation have led to better surgical success and improved patient recovery times. This has prompted a desire amongst the clinicians to decrease treatment costs and complications associated with repeated laser photocoagulation and intravitreal pharmacological therapies. As a result, the criteria for primary vitrectomy in cases of DR have expanded. This now also includes eyes with non-tractional DME, including both treatment-naïve and persistent cases[12–14]. Additionally, eyes with early proliferative DR, with or without minimal preretinal hemorrhage, are now considered eligible for primary vitrectomy[15,16]. The decision to perform repeat vitrectomy in cases of DR is typically based on several factors, including the recurrence of VH, the presence of residual premacular blood, the development of rhegmatogenous retinal detachment, the formation of an ERM with increased macular traction, as well as progression to neovascular glaucoma[17–19].

The main challenges frequently encountered during vitrectomy in the management of DR involve insufficient removal of posterior cortical vitreous and dissection of tractional membranes, massive intraoperative hemorrhage and the occurrence of iatrogenic retinal breaks[3,10,20,21]. In medical terminology, an "adjunct" is a drug or substance used to "assist or facilitate" the primary treatment of a disease. The use of pharmacological adjuncts to vitrectomy surgery is beneficial for achieving surgical success and improved anatomical and functional outcomes. Their introduction has expanded the therapeutic options available before, during, and after surgical procedures[22,23].

In this review article, we will focus on the pharmacological adjuncts utilized in diabetic vitrectomy surgery, specifically examining their role in facilitating or aiding specific steps of the surgical procedure for DR. The utilization of this categorization system provides advantages to the surgeon by enabling them to anticipate potential challenges that may arise during the surgical procedure. This allows the surgeon to select the appropriate pharmacological agent to effectively address these challenges, thereby improving surgical success rates and enhancing patient outcomes.

CHALLENGES FACED BEFORE, DURING AND AFTER DIABETIC VITRECTOMY

Pre-operative decision-making for planning vitrectomy in eyes suspected with co-existent tractional and non-tractional components of DME

Multiple mechanisms have been ascribed to the etiology of the diffuse form of DME. The conditions encompassed in this category consist of vitreomacular traction, extrafoveal vitreopapillary and/or vitreoretinal traction, contraction resulting from the overlying ERM, as well as the presence of vasoactive factors such as VEGF, protein kinase C, nitrous oxide, erythropoietin, and various others[8,24–27]. In contemporary clinical practice, it is not uncommon to encounter instances of DME that exhibit multifactorial etiology. There exist scenarios in which both the tractional and non-tractional components of DME are present concurrently, leading to a quandary regarding the appropriate course of action, namely whether to pursue treatment through vitrectomy or intravitreal pharmacological agents in such circumstances[28]. In

cases like these, it may be prudent to initially consider the use of intravitreal pharmacological agents, such as anti-VEGF drugs or triamcinolone acetonide (TA). The reduction of macular edema can be accomplished through the reduction of vasoactive factors as previously mentioned, either with or without the release of posterior vitreous traction from the retinal surface. The absence of any change in the DME's condition suggests a prevailing tractional element in the DME, thereby favoring the consideration of vitrectomy as a potential treatment approach. Therefore, the utilization of intravitreal pharmacological agents for the initial treatment of DME may aid clinicians in comprehending the precise pathogenesis underlying its development and selecting the appropriate course of treatment.

Facilitation of intraoperative posterior cortical vitreous separation

Bleeding within the eye in cases of proliferative DR is observed in three distinct spaces: The intravitreal space, sub hyaloid space, and sub internal limiting membrane (ILM) space. These occurrences are clinically characterized as VH, sub hyaloid hemorrhage, and sub ILM hemorrhage, respectively[29]. This can arise from either the antero-posterior force exerted by the posterior cortical vitreous or the tangential force exerted by the ERM or ILM on the angiogenetic vessels [30]. The removal of the posterior cortical vitreous is considered a crucial determinant for the success of diabetic vitrectomy surgery[5]. In cases where there is severe sub hyaloid hemorrhage, either with or without accompanying VH, there is a notable degree of posterior cortical vitreous separation. This separation greatly facilitates surgical intervention and is associated with favorable outcomes. Nevertheless, in cases where there is a boat-shaped sub hyaloid premacular hemorrhage with limited separation of the posterior cortical vitreous, it is imperative to actively induce posterior vitreous detachment. The utilization of enzymatic vitrectomy or pharmacological vitreolysis through intravitreal injection of autologous plasmin enzyme has been suggested as a viable neoadjuvant therapy for vitreous surgery[31–33]. This approach aims to enhance the surgical separation of the posterior hyaloid and vitreoretinal membranes. Diaz-Llopis *et al* [34] conducted a study to investigate the impact of enzymatic vitrectomy on individuals with DR and DME[34]. The study observed that a full posterior vitreous detachment occurred in 38% of cases (24 eyes) following a single injection of plasmin. Subsequently, after the administration of a second injection, separated by a minimum of one month, the overall occurrence of complete PVD increased to 51% (32 eyes). In all instances, there was a notable improvement of the central macular thickness, with a 100% success rate. Additionally, there was an improvement in best-corrected visual acuity in 89% of cases. Ultimately, it was observed that a significant reduction in the regression of new vessels occurred in 50% of eyes affected by proliferative DR. In their study, Rizzo and Bacherini[35] investigated the impact of ocriplasmin on eyes afflicted with DR and vitreomacular traction syndrome[35]. To administer the drug, a dosage of 125 μg in 0.1 mL was injected intravitreally. In these eyes, the authors successfully demonstrated the enzymatic release of the posterior cortical vitreous. Hence, the utilization of enzymatic vitreolysis involving the intravitreal administration of autologous plasmin enzyme may be regarded as a viable therapeutic option and can be employed as a neo-adjuvant treatment approach in individuals with proliferative DR and DME.

The visualization of the vitreous, preretinal membranes, and retinal surface is a crucial necessity in the context of vitrectomy surgery. TA is currently predominantly employed as an additional treatment to vitrectomy for this specific purpose[36–39]. The utilization of TA during pars plana vitrectomy for DR enables the visualization of the posterior hyaloid, preretinal membrane, and ILM within the intraoperative setting. This application of TA contributes to the enhancement of safety and efficacy in the procedure. TA-assisted vitrectomy is commonly utilized in the surgical treatment of DR, as well as other vitreoretinal procedures such as macular hole repair, rhegmatogenous retinal detachment, proliferative vitreoretinopathy, uveitis, and various other conditions. Furthermore, this methodology has the capability to reveal the remaining hyaloid cortex pattern subsequent to surgical posterior vitreous detachment. The presence of diffuse posterior hyaloid cortex is a common occurrence in individuals with DR and high myopia. In such cases, it is not uncommon for a residual island-like cortex to remain on the macula. This residual cortex has the potential to serve as a structural framework for the development of future macular pucker.

Intraoperative assistance for peeling the ERM and ILM during diabetic vitrectomy surgery

DR has been identified as a risk factor associated with the proliferation of ERMs. The incidence of ERM in individuals with DME is significant affecting approximately 27-35% of individuals diagnosed with diabetes[24]. There exist notable distinctions in the optical coherence tomography characteristics between an idiopathic ERM and a secondary ERM caused by DR. The expression of glial fibrillary acidic protein, a known indicator of Muller cell activity, is observed to be higher in the eyes affected by diabetic ERMs[40]. This elucidates the rationale behind the increased difficulty in peeling diabetic ERMs as opposed to idiopathic ERMs. The study conducted by Rabina *et al*[41] examined the effects of ERM peeling, both with and without ILM peeling, on visual acuity gain, central macular thickness reduction, and the frequency of intravitreal injections per year[41]. Additionally, the presence of residual ERM resulting from incomplete removal, presence of ILM and development of retinal breaks intraoperatively has the potential to serve as a framework for the recurrence of proliferative growths[42–44]. Therefore, it is imperative to perform thorough staining and ensure the complete removal of the ERM, as well as the peeling of the ILM in the majority of cases involving DR, regardless of its severity in the presence of DME. The application of various pharmacological agents, such as dyes, enables the staining of both the ERM and the ILM. TA consists of suspended particles that, upon intravitreal injection, exhibit the ability to stain the boundaries of the ERM[45]. There is no established association between retinal toxicity and the use of TA. However, it is important to exercise caution when using this medication in individuals who are responsive to steroids or who have glaucoma, as retained triamcinolone may lead to increased intraocular pressure. Additionally, the use of TA may potentially contribute to the progression of cataracts. Trypan Blue is employed as a visualization agent for the purpose of selectively staining ERM[46]. Additionally, the utilization of this technique aids in distinguishing the ERM from any remaining posterior cortical vitreous, thereby ensuring the thorough extraction of the ERM. The brilliant blue G (BBG) dye exhibits selective staining of the ILM, albeit with varying intensities[47]. When employing BBG, the ILM is stained, while the ERM does not

exhibit staining. Consequently, negative staining can be utilized to identify the ERM[47].

Intraoperative assistance during membrane dissection

The primary goal of conducting a diabetic vitrectomy in cases of proliferative DR is to effectively eliminate all membranes that exert traction on the surface of the retina[5]. Achieving an accurate visualization of the primary and secondary membranes, as well as establishing the appropriate dissection plane, would be necessary for this task. The visualization of preretinal membranes and the ILM can be accomplished through the administration of pharmacological agents, including trypan blue, TA, and BBG[48]. During diabetic vitrectomy, it is necessary to have an open tissue plane situated between the retinal surface and the membranes in order to facilitate the dissection of the membranes. In many instances, this goal can be accomplished through the utilization of the blunt dissection technique, wherein the vitrectomy cutter probe is carefully inserted between the membrane and the surface of the retina[7]. In situations where the appropriate plane is not achieved through blunt dissection, it is possible to inject dispersive viscoelastic agents, either in their plain form or when combined with BBG, using small gauge cannulas positioned between the membranes and retina[49]. This technique allows for the attainment of the desired dissection plane.

Minimizing the intraoperative bleeding during diabetic vitrectomy

The dissection of extensive angio-fibrotic membranes has the potential to result in significant intraoperative bleeding, incomplete removal of the membranes, and consequently, unfavorable anatomical and visual outcomes. This may necessitate additional surgical interventions and impede the recovery process. The administration of anti-VEGF agents *via* intraocular injection prior to surgery, typically within a timeframe of 3-5 days, has been suggested as a potential strategy for mitigating the occurrence of these complications[50]. The utilization of anti-VEGF agents has been shown to effectively decrease the quantity and vascularity of abnormal neovascularization linked to proliferative DR. This reduction in abnormal vessels can aid in their dissection during surgical procedures, leading to a decrease in bleeding both during and after surgery. Consequently, the implementation of anti-VEGF agents holds the potential to enhance surgical outcomes in patients with proliferative DR. In a prospective study conducted by Li *et al*[51] a comparison was made between the utilization of pre-operative and intraoperative intravitreal ranibizumab[51]. The findings of the study revealed that the administration of preoperative anti-VEGF injection resulted in notable reductions in surgery duration, as well as a decrease in the occurrence of intraoperative bleeding, utilization of intraocular electrocoagulation, iatrogenic retinal breaks, relaxing retinotomy, and the need for silicone oil tamponade during surgery. The term "anti-VEGF crunch syndrome" refers to the development of tractional retinal detachment in the context of intravitreal anti-VEGF therapy in a patient with proliferative DR[52]. In cases where anti-VEGF treatment is administered prior to a scheduled vitrectomy procedure, it is advisable to closely observe patients for the manifestation of crunch warning signs. If there is any indication of new or advancing tractional retinal detachment, it is recommended to promptly proceed with the surgical intervention. In cases where individuals with minimal preexisting traction in their eyes experience the development of crunch following anti-VEGF treatment, it is recommended that surgeons proceed with vitrectomy within a period of seven days[52]. The utilization of perfluorocarbon liquid intraoperatively, for a brief period or to perform fluid-gas exchange during surgical procedures, can effectively induce a tamponade on the bleeding vessels, thereby facilitating hemostasis. In some cases of persistent intraoperative bleeding, fibrin glue can be used to achieve intraoperative hemostasis[53].

Preventing post-operative vitreous cavity hemorrhage

The occurrence of post-operative vitreous cavity hemorrhage subsequent to diabetic vitrectomy has a significant impact on visual outcomes, leading to a higher incidence of resurgery and hampering patient recovery. According to a review conducted by Smith and Steel and published in the Cochrane database, the utilization of pre- or intraoperative anti-VEGF has been found to reduce the occurrence of early post-operative vitreous cavity hemorrhage[54]. Moreover, the incidence of complications associated with the administration of these anti-VEGF agents appears to be minimal. Furthermore, the utilization of intraoperative gas tamponade has demonstrated a decrease in the occurrence of post-operative vitreous cavity hemorrhage[55].

Table 1 summarises the roles of various pharmacological adjuvants used at different stages of diabetic vitrectomy.

CONCLUSION

In summary, despite the utilization of state-of-the-art vitrectomy equipment, retinal surgeons face a multitude of challenges when performing diabetic vitrectomy surgery. At present, there exists a wide range of pharmacotherapies that can be employed prior to, during, and subsequent to surgical procedures with the aim of optimizing the surgical outcome for our patients. The utilization of individualized medical interventions before, during, and after vitrectomy is expected to rise due to the emergence of additional evidence that supports the advantages of pharmacotherapy as a supplementary treatment alongside vitrectomy.

Table 1 Summary of pharmacological adjuvants used in patients with advanced diabetic eye disease requiring vitrectomy

Stage of vitrectomy	Objective	Adjuvants used
Before vitrectomy	To differentiate between tractional and non-tractional DME	Intravitreal anti VEGF agents
		Intravitreal TA
During vitrectomy	Facilitation of intraoperative posterior cortical vitreous separation	Use of autologous plasmin enzyme
		Use of intravitreal TA
	Dissection of ERM and ILM	Use of intravitreal pharmacological agents such as TA, Tryphan blue and Brilliant blue G
	Dissection of proliferative membranes	Use of intravitreal pharmacological agents such as TA, Tryphan blue and Brilliant blue G
		Blunt dissection with the use of intravitreal viscoelastic
	Minimizing the intraoperative bleed	Use of pre-operative intravitreal anti VEGF agents
		Use of intraoperative perfluorocarbon liquid or performing fluid air-exchange
		Intraoperative fibrin glue
After vitrectomy	Treatment of recurrent vitreous hemorrhage	Intravitreal anti VEGF agent
		Repeat fluid air exchange and gas endotamponade

DME: Diabetic macular edema; VEGF: Vascular endothelial growth factor; TA: Triamcinolone acetonide; ERM: Epiretinal membrane; ILM: Internal limiting membrane.

FOOTNOTES

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Country of origin: India

ORCID number: Ramesh Venkatesh 0000-0002-4479-9390; Chaitra Jayadev 0000-0001-8392-7159; Vishma Prabhu 0000-0001-6845-0209.

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MINIREVIEWS

Research surveys and their evolution: Past, current and future uses in healthcare

Michael Colwill, Richard Pollok, Andrew Poullis

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Michael Colwill, Richard Pollok, Andrew Poullis, Department of Gastroenterology, St George's University Hospital NHS Foundation Trust, London SW17 0QT, United Kingdom

Corresponding author: Michael Colwill, BSc, MBBS, MRCP, Doctor, Researcher, Department of Gastroenterology, St George's University Hospital NHS Foundation Trust, Blackshaw Road, London SW17 0QT, United Kingdom. michael.colwill@nhs.net

Abstract

Research surveys are believed to have originated in antiquity with evidence of them being performed in ancient Egypt and Greece. In the past century, their use has grown significantly and they are now one of the most frequently employed research methods including in the field of healthcare. Modern validation techniques and processes have allowed researchers to broaden the scope of qualitative data they can gather through these surveys such as an individual's views on service quality to nationwide surveys that are undertaken regularly to follow healthcare trends. This article focuses on the evolution and current utility of research surveys, different methodologies employed in their creation, the advantages and disadvantages of different forms and their future use in healthcare research. We also review the role artificial intelligence and the importance of increased patient participation in the development of these surveys in order to obtain more accurate and clinically relevant data.

Key Words: Research surveys; Methodology; Sampling; Artificial intelligence

Core Tip: Research surveys have been utilised for centuries and have grown in scope and use with regards to healthcare in the past century. Whilst undoubted strengths there are also weaknesses associated with this methodology. This article looks at past and current use, their strengths and weaknesses and likely use in the future.

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INTRODUCTION

Research surveys are believed to have originated in antiquity with evidence of census surveys being performed by governments in ancient Egypt and Greece in order to better understand their respective populations. The modern incarnation of the national population census started in the United States (USA) in 1790[1] and since then the type and scope of surveys has increased exponentially. In the 19th century surveys utilised for social research became a key part of guiding public policy, such as that performed by Joseph Rowntree to investigate poverty in the 1890s in the United Kingdom (UK)[2]. It was in the early 20th century that the use of surveys in healthcare research became a common methodology with one of the first being performed in the USA in the form of the National Health Interview Survey (NHIS) in 1957 which provided an insight into the healthcare problems faced by the nation[3].

Today, research surveys remain a widely practiced and important methodology in healthcare. This article will examine their methodology, current uses and how these have evolved, their strengths and weaknesses and their future utility in healthcare research.

SURVEY METHODOLOGY

The methodology employed in producing healthcare surveys can vary significantly but choosing the appropriate protocol is crucial to produce accurate research.

Sampling

Clearly, getting information from every single person affected by a condition is impractical and therefore sampling, where a proportion of the target population provides the survey responses, is utilised. The choice of sampling method is decided by the researching team and is broadly divided into probability sampling or non-probability sampling. Probability sampling includes simple random, stratified random, systematic (or interval) and clustered random compared to non-probability which incorporates convenience, judgmental and snowball sampling. Non-probability sampling methods are in general quicker, easier and more cost-effective however they can introduce bias as they do not guarantee equal chances of each subject in the target population being involved. An example is snowball sampling where one interviewee essentially provides the researcher with the name of at least one more potential participant and, whilst this can be useful for rare pathologies or very small populations, it introduces sample bias and can reduce the diversity of the sample population so that the results are indicative of a sub-population rather than the true target population[4].

Sample size

Together with an appropriate sampling method, accurate calculation of the required sample size is also required to generate accurate data and various statistical techniques and software programmes are available to perform this. The sample size calculation is also dependent upon the methodology chosen by the researching team and with regards to non-probability sampling, the commonest method used for surveys in healthcare research, sample size calculations are largely irrelevant as it is likely to produce non-generalisable results[5]. In this case, researchers should instead include as many subjects as possible from different demographics and sub-groups or consider using sample matching to minimise selection bias.

Research design

As well as accurately sampling populations as discussed, the type of research design is also important in producing scientifically valid data and testing the hypothesis. Cross-sectional surveys, which provide a snapshot of data at one specific time, can assess several variables at once but cannot demonstrate cause and effect. However, for example comparing obesity levels to physical activity levels, these surveys can demonstrate potential correlation signals which may require further research. Longitudinal surveys employ continuous or repeated measures to provide data over different time periods. This allows researchers to identify changes or trends in real time and provide insight into cause and effect. However, these studies take longer to complete, are more costly financially and temporally and results can be negatively impacted by incomplete or interrupted follow-up.

Validity

Further challenges that researchers face when utilising any form of survey is the need to ensure that the data they are collecting will provide accurate answers to the questions being addressed which is referred to as validity. There are various methods to assess validity, either through content validity, construct validity or criterion validity and these have previously been discussed in detail[6]. The process of validation, using whichever of these three metrics is felt to be most appropriate, can be challenging and cumbersome and often requires the involvement of experienced researchers to be done correctly.

Advantages and disadvantages of research survey forms

As discussed, the choice of methodology employed in research surveys is crucial but the technique used to collect data is equally important to produce accurate results. This data can be collected using multiple different formats and each of these have their own strengths and weaknesses. The most common method is through online surveys where participants are sent a link to a pre-configured survey which they can complete without the need for a separate interview. Multiple

companies have developed software to facilitate this to optimise participant recruitment and completion. This method is relatively cheap and can be performed quickly particularly if the survey in question is already validated. The anonymous nature of the process may also mean that patients are more willing to provide truthful answers and not be biased, consciously or unconsciously, by an interviewer. However, online research surveys also have problems with low response rates, inability to be performed by low literacy audiences and there is no scope for answers to be probed further by an interviewer.

The advantages and disadvantages of other, less frequently used, research survey methodologies are summarised in Table 1; this is adapted from the Food and Agriculture Organisation of the United Nations[7].

Another disadvantage, particularly with regards to patient satisfaction surveys, is that they can have a negative impact upon the very practice they are being used to assess and improve. Patient satisfaction is poorly defined and developing surveys that can be utilised to improve services based upon this is extremely difficult[8]. Consequently, by lacking a clearly defined objective, incorrect data can be corrected leading to false conclusions being drawn. There is also evidence that patient satisfaction surveys often focus on outdated metrics which do not accurately reflect the quality of care provided and can cause practices to focus solely on elements that will score highly on feedback surveys[9]. For effective use as a quality improvement tool, patient feedback surveys need to have accurately defined criteria and be regularly updated to ensure they are assessing the correct criteria and these surveys are further discussed below.

CURRENT UTILITY OF SURVEYS IN HEALTHCARE RESEARCH

National surveys

National healthcare surveys are used across the world by thousands of agencies and researchers each year. The relatively low cost of performing them means that they can be performed on a regular basis and collect different tranches of data which allow trends to be studied which can then influence healthcare policy and resource allocation. One of the longest running examples of this is the NHIS in the USA[3]. Since 1957 it has, through interviews performed by trained personnel, conducted surveys to get an accurate idea of illness in the non-institutionalised population of the USA. The survey collects data on a wide range of areas such as demographics, insurance coverage, smoking rates, mental health burden and access to, and utilisation of, preventative services. This data is used to monitor health objectives set by the department of health and human services as well as by epidemiological researchers. Crucially, the survey design is reviewed after every decennial census to ensure accurate and pertinent data is collected. Similar programmes exist in multiple other countries such as India in the form of the National Family Health Survey which started to collect data in 1992[10].

As well as interviews, national surveys can also be performed through direct mail campaigns, such as the general practitioner (GP) patient survey performed in the UK by IPSOS on behalf of the National Health Service (NHS)[11]. This long-running survey is sent through the mail to approximately 2 million patients each year to provide representative feedback on the performance of GPs across the country, highlight any concerns patients may have and, through feedback to the practices and the NHS management, can help to improve services.

Along with untargeted surveys, such as the GP patient survey, national surveys can also be targeted at specific groups. An example from the UK is the national inflammatory bowel disease (IBD) survey, performed periodically by a charity called IBD UK. Through surveys sent out to IBD care teams across the country they collect data on the services that each trust provides and compares it to the agreed national standards to help trusts identify deficiencies in their service such as understaffing.

Individual surveys

Whilst some surveys are distributed nationally, charities such as IBD UK also send surveys out to individual patients to provide personalised feedback in order to improve their local services. These surveys are usually conducted using direct mail or e-mail recruitment and data is collected *via* a web portal or by returning a completed paper form. As discussed earlier, these feedback surveys have been shown in a previously published review[12] to be a validated quality improvement tool and do provide data specific to local services which can be used to improve care. However, they suffer from a high non-response rate, response bias and sample bias[13]. Correcting for this bias can be challenging and labour intensive but is necessary to generate accurate data which will then guide changes to actually improve services. There are also concerns about the overinterpretation of these surveys and the performing institutions subsequently focusing too much on measurable outcomes, rather than actual patient concerns.

Individualised research surveys are also used to collect patient reported outcomes (PROs) which have become a key part of clinical trials[14] where patients are provided with surveys to complete on a regular, sometimes daily, basis documenting their symptoms and well-being. This data is then fed back anonymously to the investigating team and conglomerated for central analysis helping to demonstrate the efficacy of the treatment being investigated. Whilst this offers researchers the opportunity to identify trends over time, it can be skewed by day-to-day complications, for example a patient developing temporary symptoms due to gastroenteritis whilst being part of a study examining a new IBD treatment, and researchers must allow and correct for this on a case-by-case basis.

Together with the growing use of PROs and patient feedback surveys, there has also been greater patient involvement in the developing and authoring of these surveys. Many organisations have developed patient involvement initiatives such as The Royal Marsden NHS Foundation Trust[15], Crohn's and Colitis UK[16] and the Health Regulation Authority [17]. These are designed to ensure that patients are involved in the process of developing research surveys so that the data collected better represents the concerns of those impacted. With regards to clinical trials, this patient involvement

Table 1 Advantages and disadvantages of research survey methodologies

Survey methodology	Advantages	Disadvantages
Mail	Low cost; Lack of interviewer means participants may be more likely to give honest, unbiased answers	Low response rates; Unable to probe answers because of lack of interviewer
Interview	Good response rates; Allows probing of answers; Allows observation of attitudes	Expensive; Time consuming; Requires interviewer training; Risk of interviewer introducing bias
Phone	Easy accessibility in most countries; Anonymity; Flexible for participants; Computer aided techniques allow for rapid data collection	Lack of visual materials; Limitations in nature of questions that can be asked and answered (non-open ended); Call screening can limit response rate

also helps to recruit and retain participants. A review published in 2020 by the National Institute for Health and Care research also found that there is an active desire amongst patients to provide constructive feedback but that the NHS often does not use this feedback, collected from surveys, effectively to generate long-term improvements in services[18]. This suggests that whilst there may have been improvement in the methodology of collecting patient feedback, implementation of change has not yet caught up in the NHS.

Future

The use of artificial intelligence (AI) is already changing the research survey landscape and will be a powerful ally in the field of research surveys including in healthcare. Tools such as Amazon's Mechanical Turk already exist to help generate populations that produce more reliable and accurate data[19] and applying this and similar tools to healthcare surveys offers significant potential. As discussed previously, one of the commonest ways for surveys to be performed is through an online portal. AI can change the functionality of these portals so that the survey data is collected in a conversational manner, rather than simple question and answer, which will improve the depth and quality of data collected particularly with regards to qualitative data. Along with improved data collection, AI also has potential to improve analysis and interpretation. AI is already used for this purpose in healthcare settings[20] and with regards to research surveys it offers the capability to improve the efficiency and speed of survey response interpretation and analysis[21].

Whilst there has been some concern regarding the use of AI in healthcare research, particularly with regards to ethical considerations[20], data has shown that patients are broadly in favour of increasing the role of AI in healthcare[22] and provided that there is sufficient regulation and transparent practices in place then these concerns can be adequately addressed. Further questions remain over ownership, for example if an AI programme develops, distributes and collects data who has the intellectual property rights to this data and who bears responsibility for this data? It should also be noted that AI is still very much in it's infancy and that whilst it has utility to augment human performance as described above, it does not replace experienced and competent researchers and this is unlikely to change in the foreseeable future.

Along with AI, the level of patient and public involvement in the development of research surveys is increasing[23] and, given the benefits discussed earlier, this trend will likely continue in the future in order to ensure the most accurate and appropriate data is collected.

CONCLUSION

Research surveys have been an important part of healthcare research for close to a century. Given their various advantages, particularly their inexpensive nature and speed at which they can be performed, their widespread use will continue in the future and with the careful and appropriate implementation of modern technologies and evolving methodology, their value will likely increase in the future.

FOOTNOTES

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Country of origin: United Kingdom

ORCID number: Michael Colwill 0000-0001-6925-8358; Richard Pollok 0000-0001-6452-6763; Andrew Poullis 0000-0003-0703-0328.

Corresponding Author's Membership in Professional Societies: British Society of Gastroenterology, BSG60672.

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Remission of type 2 diabetes mellitus: Emerging concepts and proposed diagnostic criteria

Arkiath Veettil Raveendran

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Arkiath Veettil Raveendran, Department of Internal Medicine, Former Assistant Professor of Medicine, Govt. Medical College, Kozhikode 673010, Kerala, India

Corresponding author: Arkiath Veettil Raveendran, FRCP, MBBS, MD, Doctor, Department of Internal Medicine, Former Assistant Professor of Medicine, Govt. Medical College, Specialist in Internal Medicine, Badr Al Samaa, Barka, Sultanate of Oman, Kozhikode 673010, Kerala, India. raveendranav@yahoo.co.in

Abstract

The remission of type 2 diabetes mellitus (T2DM) is a topic that has been widely discussed recently, and it gives new hope for people with T2DM. Achievement of normal blood glucose levels or levels below the diagnostic threshold for T2DM without pharmacotherapy among people with T2DM after metabolic surgery and carbohydrate or calorie-restricted diet paved the way for more enthusiastic research in this area. There is a lot of confusion regarding the appropriate terminology and definition of remission of T2DM. In this short review, we briefly analyzed the emerging concepts and proposed criteria for diagnosing remission of T2DM, which will be helpful for healthcare providers and people with T2DM.

Key Words: Remission; Reversal; Diabetes; Mitigation; Type 2 diabetes mellitus

Core Tip: There is a lot of confusion regarding the criteria for remission of type 2 diabetes mellitus (T2DM), as it is described differently by various professional bodies. Therefore, we proposed criteria that will be useful for healthcare professionals worldwide for diagnosing remission. Five components should be satisfied to diagnose remission of T2DM: Previous diagnosis of T2DM; blood sugar normalization or level below the diagnostic threshold for T2DM; withdrawal of pharmacotherapy or intervention and after its washout period; improvement in the pathophysiological mechanism; and the absence of any complications, comorbidities, or disease leading to a reduction of blood sugar or its normalization.

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INTRODUCTION

The remission of type 2 diabetes mellitus (T2DM) is a topic that is widely discussed not only among healthcare professionals but also among the public[1]. Present reports of achievement of normal glucose levels without pharmacotherapy among people with T2DM after metabolic surgery and carbohydrate or calorie-restricted diet paved the way to more enthusiastic research in this area. There is a lot of confusion regarding the appropriate terminology. Various professional bodies define remission of T2DM differently, again adding to the confusion among healthcare providers and the public [2].

Various terminologies

Various terminologies used in this aspect include reversal, resolution, cure and remission. T2DM resolution implies that an entirely normal state has been established permanently. Cure of T2DM gives the impression that the pathophysiological aspect is normalized, and further follow-up or management is not required. T2DM reversal indicates the return of blood glucose levels below those used to diagnose T2DM, but it does not imply that further support is needed to prevent an increase in blood glucose level. T2DM remission indicates returning blood glucose levels to normal or below the threshold used to diagnose T2DM and the need for continued support[3-5]. Hence remission is the term widely used to denote those who achieved blood glucose levels below those used to diagnose T2DM as they require continued support and regular follow-up to maintain the blood sugar value below the threshold level, identify relapse at the earliest if it occurs, and monitor for complications (Table 1).

Remission of T2DM-pathophysiological basis

In people with T2DM, insulin resistance, hyperinsulinemia, and subsequent hyperglycemia are the predominant pathophysiology in the early stages followed by deterioration of beta cell function and insulinopenia in the later part of the disease. Any measures reducing insulin resistance like weight reduction will result in improvement in hyperglycemia and even normalization of blood sugar value. Similarly, any measures that improve insulin secretion also improve hyperglycemia in people with T2DM. In addition, reduction in the insulin requirement will also help to control blood glucose value even at the stage of insulinopenia.

As per the twin cycle hypothesis, chronic calorie excess leads to the accumulation of fat in the liver and subsequently in the pancreas[6] (Figure 1). Accumulation of fat in the liver leads to hepatic insulin resistance and in the pancreas leads to impaired insulin secretion. When fat deposition exceeds the "personal fat threshold" of that person, they develop T2DM [7].

Based on the twin cycle hypothesis, weight reduction is associated with improvement in fatty infiltration of the liver and pancreas, thereby improving insulin resistance and insulin secretion, which is responsible for remission of T2DM as per the current concepts[8]. Significant weight loss (about 15 kg) is an important factor in predicting the chance of remission.

The remission of T2DM is not just the normalization of glycemic status in the absence of active therapeutic intervention. Improvement in glycemic status is the reflection of improvement in the pathophysiological aspect of T2DM, *i.e.* improvement in insulin secretion and insulin resistance. Therefore, the extent and duration of normalization of blood sugar depends upon the extent of improvement of insulin resistance and improvement in insulin secretion. Hence people with T2DM who achieved remission require regular monitoring to identify the re-emergence or relapse of T2DM.

The extent of normalization of glycemic status remission can either be partial remission or complete remission[9] (Figure 1). Depending upon the duration of remission achieved we classify it into transient remission, short-term remission, long-term remission, and prolonged remission. Those without established T2DM, *i.e.* pre-diabetes, can also achieve normalization of glycemic status, usually as complete remission.

Euglycemia achieved because of continuous carbohydrate restriction only lasts as long as carbohydrate restriction is maintained. This is called 'state of mitigation' and has to be differentiated from remission[10].

In people with T2DM, normalization of the blood sugar value can persist for variable periods after temporary use of pharmacotherapy because of improvement in the deleterious effect of poor metabolic control on insulin secretion and action (*e.g.*, glucotoxicity and lipotoxicity) without altering the basic pathophysiology of T2DM. This should not be confused with remission, as there is no improvement in the pathophysiologic mechanism. Remission of T2DM has to be differentiated from mere normalization of blood glucose levels.

Challenges in the diagnosis of remission

To define remission, people with previously diagnosed T2DM should have sustained normal blood glucose values (complete remission) or below the diagnostic threshold for T2DM (partial remission) by any means like blood glucose testing [fasting blood sugar (FBS), post prandial blood sugar (PPBS), random blood sugar, oral glucose tolerance test], glycated hemoglobin (HbA1c), continuous glucose monitoring (CGM) values, estimated A1c (eA1c level), or glucose management indicator (GMI). Each method has its advantages and limitations.

Table 1 Various terminologies used

Terminology	Word meaning	Blood sugar target for remission	Pathophysiological status	Follow-up
Resolution	The subsidence of a pathological state	Attained	Permanent normalization	No
Cure	A complete or permanent solution	Attained	Permanent normalization	No
Reversal	A change from one state to the opposite state	Attained	Permanent normalization	No
Remission	An abatement or reduction in intensity or degree (as in the manifestations of a disease)	Attained	Improvement	Yes

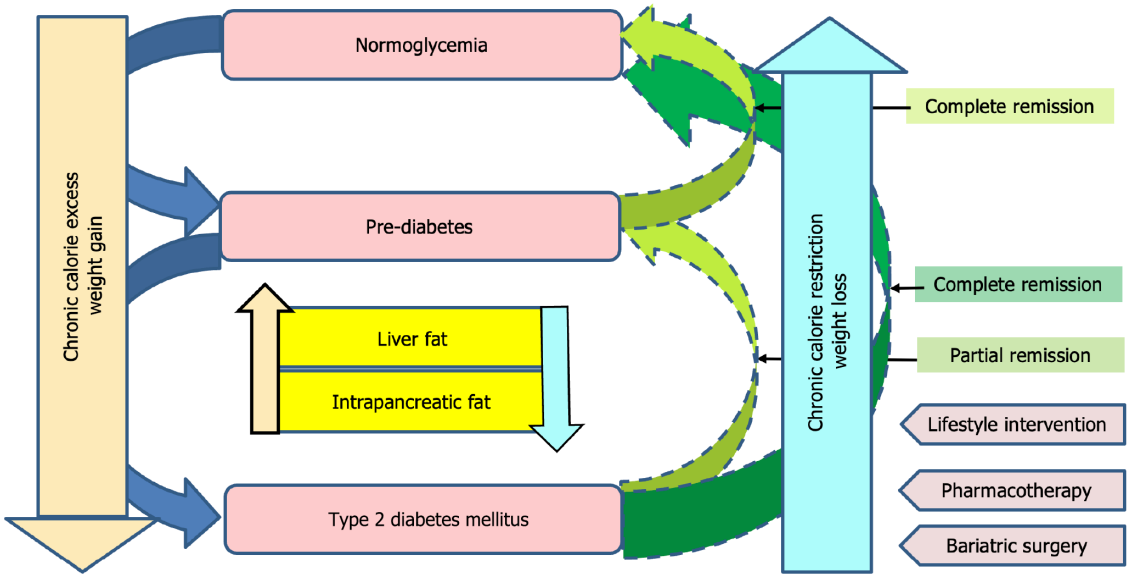

Figure 1 Types of remission of type 2 diabetes mellitus and pathophysiological basis of remission.

Blood sugar values (*e.g.*, FBS, PPBS, random blood sugar) undergo wide fluctuation and show significant variation between repeated measurements. Similarly, 2-h post-glucose after 75 g oral glucose load is also associated with high variability between repeated measurements[11]. FBS and CGM values are more variable, and some experts recommend repeated testing to confirm remission. In those with post-bariatric surgery, there is early hyperglycemia followed by later hypoglycemia making interpretation of 2-h post-glucose value difficult[5].

HbA1c is an inaccurate indicator of glycemic status in certain conditions like anemia, with abnormalities of red blood cell survival, those with hemoglobin variants, splenomegaly, asplenia, uremia, severe hypertriglyceridemia, *etc*[12,13].

CGM values can be used to diagnose remission. eA1c or GMI can be calculated from it and used to establish remission. HbA1c of < 48 mmol/mol (< 6.5%) calculated from 24-h CGM values can be used to denote remission[5].

Ideally, HbA1c, FPG, 2-h PPBS, CGM, eA1c, and GMI all should be within normal limits or below the level for the diagnosis of T2DM to diagnose remission. However, it is practically very difficult and time-consuming to measure all these parameters to establish remission. There is a subset of people with T2DM having normal FBS and high 2-h PPBS. If we measure only FBS in such individuals and diagnose remission, it will be a false diagnosis of remission. A similar situation can happen in people with high FBS and normal 2-h PPBS levels. Even though it is not practical to do all these measurements, it is always better to select the test that has the maximum chance to detect any blood sugar value above the cutoff in that particular patient. If there is any probability of getting a false value with any of the above methods, another alternative modality has to be used to confirm remission.

While selecting a particular test to demonstrate normoglycemia, one should consider the inherent property of the test, like the duration of the glycemic status that particular test represents (Figure 2). For example, HbA1c reflects the glycemic status of the last 3-4 mo. Therefore, if we do HbA1c before 3 mo of stopping anti-diabetic treatment, we will get a false low HbA1c, indicating remission even when it is actually not present. HbA1c has to be done after a minimum of 3 mo after the washout period of a particular intervention.

Similarly, tests to assess normoglycemia should not be performed before completing the washout period of a pharmacotherapy or intervention (Figure 2). For almost complete elimination of any medication, it usually takes four to five half-life periods (t ½). For example, the t ½ of metformin is 17.6 h, and usually it will take five t ½ (5 × 17.6 h = 98.6 h) for the medicine to be almost completely eliminated from the body[14]. So FBS, PPBS, and CGM should not be done to demonstrate normoglycemia after stopping therapy before 98.6 h in people who stopped metformin.

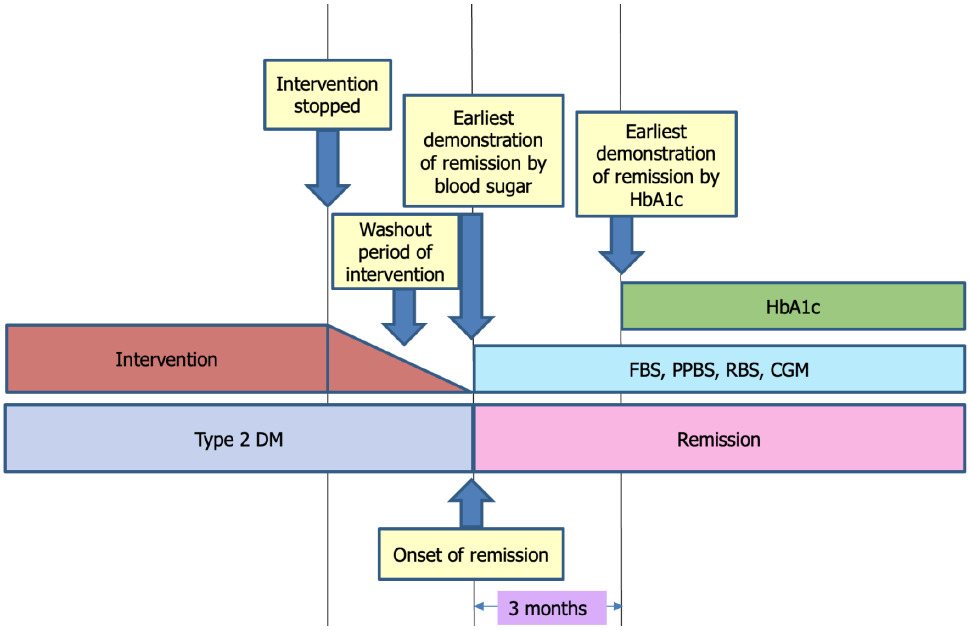

Figure 2 Selecting the ideal time to test for remission of type 2 diabetes mellitus. CGM: Continuous glucose monitoring; DM: Diabetes mellitus; FBS: Fasting blood sugar; HbA1c: Glycated hemoglobin; PPBS: Post prandial blood sugar; RBS: Random blood sugar.

Once remission is achieved, it is difficult to predict how long it will persist. But there are a lot of factors like duration of T2DM, body weight, β cell function, *etc* that help to assess the feasibility of remission. The duration of remission is a retrospective assessment. Those who maintain 5 years of remission are said to have achieved prolonged remission[9].

The durability of remission varies with the interventions, and bariatric surgery usually gives long-lasting remission compared to other modalities[15]. It is better to mention the intervention adopted to achieve remission than simply mentioning remission of T2DM (*e.g.*, remission of T2DM achieved by bariatric surgery).

Diet control and exercise are integral parts of treatment of T2DM. Hence it is called non-pharmacological therapy, medical nutrition therapy, *etc.* Another important concern while defining criteria for remission of T2DM is whether one can continue non-pharmacological therapy like dietary intervention and exercise.

In an ideal condition, remission of T2DM requires persistent normalization of blood sugar values even after withdrawal of all the interventions (pharmacological and non-pharmacological), so that its direct blood sugar-lowering action will be washed out. However, all the current definitions do not require the withdrawal of non-pharmacological interventions like diet control and exercise to define remission[1,2]. In our opinion, it is better to add maintained with diet control and/or exercise to the diagnosis of T2DM remission to understand the ongoing interventions and to emphasize the need for continuing diet control and exercise to maintain remission.

Another important concern is about the withdrawal of interventions or pharmacotherapy. Some guideline says that the patient should be off all anti-diabetic medication, while others say it is ok to continue medication like metformin if it was started for a non-glycemic indication[1,2]. Examples of such medications, started for a non-glycemic indication that have beneficial effects on blood sugar levels include liraglutide for obesity, SGLT-2 inhibitors for heart failure and renal protection, and metformin for polycystic ovary syndrome.

Even if the drugs that reduce blood sugar are started for non-glycemic indications, it is not advisable to stop these drugs just to confirm remission, which would increase the risk of complications of the underlying problem for which the medication was started. But for those who are on these medications, even if the blood glucose parameters are within normal limits, we cannot ideally consider it as remission and is better categorized as incomplete remission.

The effect of pharmacotherapy or bariatric surgery is evident quickly. However, lifestyle intervention is slow (requires more time), and it may require up to 6 mo to stabilize the effect[5]. Again, 3 mo is required for the HbA1c to reflect these changes[5]. Follow-up HbA1c monitoring should not be done more frequently than every 3 mo and not less than every year. Compared to HbA1c, FBS or eA1c derived from CGM stabilizes early and can be used to monitor early. However, as these values are more variable, it should be confirmed by repeated measurement. Even though we need a 3-mo period to diagnose remission, tests that reflect glycemic control early can be used to document remission after the washout period of pharmacotherapy/intervention, even before completing the 3-mo period.

Follow-up after remission

For those with poorly controlled T2DM, rapid reduction in blood sugar and HbA1c may result in worsening of microvascular complications like retinopathy[5]. Hence rapid reduction of HbA1c in people with retinal changes beyond microaneurysms (more than background retinopathy) is not advised. However, this risk is less after metabolic surgery [17].

Weight gain, stress, poor sleep, and inability to maintain a healthy lifestyle and diet may result in relapse of T2DM in those who already achieved remission. Metabolic memory-like phenomena can occur even after remission, resulting in

the development of classical complications of T2DM after remission. Those who achieved remission need regular medical supervision not only to monitor glycemic status but also complications like retinopathy, neuropathy, nephropathy, and cardiovascular complications[5,16].

PROPOSED DIAGNOSTIC CRITERIA FOR REMISSION OF T2DM

Methodology

We reviewed the literature on remission of T2DM and found that there are no clear-cut criteria to diagnose remission, though partial and complete remission is already described. To diagnose remission, first we have to confirm T2DM, for which we adopted the American Diabetes Association diagnostic criteria to define T2DM and pre-diabetes[18]. Those achieving blood sugar below the cutoff for T2DM and pre-diabetes are defined as partial and complete remission, respectively. Since there is no clear consensus about the duration of normalization of blood sugar, the interventions adapted to achieve remission, any ongoing interventions, and improvement in pathophysiological mechanisms, we tried to define these parameters. Any conditions resulting in transient hyperglycemia can be misdiagnosed as remission of T2DM. To avoid this, we defined exclusion criteria for the diagnosis of remission. We expect that the proposed criteria will be helpful for healthcare providers and people with T2DM worldwide.

Proposed diagnostic criteria

Our diagnostic criteria contain five components, and all five components should be satisfied to make a diagnosis of remission of T2DM (Table 2).

Establishing the diagnosis of T2DM/ pre-diabetes: As per the criteria, a clear diagnosis of T2DM is a prerequisite for the diagnosis of remission. We use the American Diabetes Association diagnostic criteria to define T2DM[18]. Any transient hyperglycemia misdiagnosed as T2DM results in an erroneous diagnosis of remission.

Evidence of maintenance of normal blood sugar or blood sugar below the threshold for T2DM: Biochemical remission in people with established T2DM in the absence of any active intervention. Demonstration of normal glycemic parameters or blood sugar below the threshold for T2DM is an essential component of the diagnosis of remission. Various parameters like FBS, PPBS, HbA1c, eA1c, CGM, GMI, *etc* can be used to document remission. All these tests are associated with their own merits and limitations. If there is any chance for a false result of a particular test in the patient (*e.g.*, HbA1c in people with anemia), an alternative test has to be done to demonstrate remission. A single type of test (*e.g.*, PPBS) may not reflect glycemic status in some patients. In such a situation, multiple types of tests are required (*e.g.*, PPBS may be low in people who underwent metabolic surgery, and FBS or CGM may sometimes pick up abnormal blood sugar values).

Duration criteria: For the intervention and for the test. Persistence of normoglycemia even after the withdrawal of glucose-lowering intervention (pharmacotherapy/active intervention) is documented after a reasonable period to wash out the direct effect of medication or intervention. The glucose-lowering intervention can be non-pharmacological (medical nutrition therapy or physical activity) or pharmacological intervention (medication or surgical intervention). There should not be any ongoing pharmacological or surgical procedures (ongoing procedures like repeated placement of endoluminal devices or intragastric balloons). However, non-pharmacological (medical nutrition therapy or physical activity) interventions are continued in most of the reports of remission. Should non-pharmacological interventions (medical nutrition therapy or physical activity) be discontinued to diagnose remission? Ideally, the answer is yes. But for all practical purposes, the answer is no. In our opinion in people who achieved remission and continue non-pharmacological interventions, it is better to mention that remission is maintained with diet control and/or exercise.

The testing should be scheduled in such a way that the value must reflect the glycemic status after the washout period of the intervention (*e.g.*, HbA1c after 3 mo of washout period of intervention). Similarly, the washout period of the intervention also has to be considered while scheduling the test. Usually after pharmacological therapy washout period is after five t ½ of that particular drug.

Duration of remission is a retrospective assessment. A minimum of 3 mo of maintenance of blood sugar below the specified level is required to categorize it as remission. Remission for more than 5 years is called prolonged remission. We classify remission as transient, short-term, long-term, and prolonged if it lasts less than 6 mo, 6 mo to 1 year, 1-5 years, and more than 5 years, respectively.

Evidence of improvement of the pathophysiological mechanism: Normalization of the blood sugar value as a result of improvement in insulin secretion and insulin resistance helps to differentiate remission from mitigation. Significant weight loss is considered as indirect evidence of loss of fat from the liver and pancreas resulting in improvement in insulin secretion and insulin resistance. Therefore, weight loss is considered as evidence of improvement of the pathophysiological mechanism.

Satisfy exclusion criteria: Exclusion of transient hyperglycemia and improvement after removal of precipitating event or drugs (*e.g.*, stress hyperglycemia, drug-induced hyperglycemia), normalization of blood sugar due to complications (*e.g.*, diabetic kidney disease), and comorbidities or concomitant illness (like malignancy, sepsis, or endocrine disorders) are important to avoid false categorization as remission of T2DM.

Table 2 Diagnostic criteria for remission of type 2 diabetes mellitus

A: Establishing the diagnosis of T2DM/pre-diabetes			
Documented evidence of T2DM based on established criteria like ADA criteria			
Diagnosis	HbA1c	FPG	2-h PG
T2DM	≥ 6.5%; ≥ 48 mmol/mol	≥ 126 mg/dL; ≥ 7 mmol/L	≥ 200 mg/dL; ≥ 11.1 mmol/L
Pre-diabetes	5.7% to 6.4%; 39 to 47 mmol/mol	100 to 125 mg/dL; 5.6 to 6.9 mmol/L	140 to 199 mg/dL; 7.8 to 11.0 mmol/L
B: Evidence of maintenance of blood sugar below the threshold for T2DM or normal range (biochemical remission) in people with established T2DM even after the withdrawal of pharmacotherapy/active intervention			
Remission	HbA1c	FPG	2-h PG
Partial	5.7% to 6.4%; 39 to 47 mmol/mol	100 to 125 mg/dL; 5.6 to 6.9 mmol/L	140 to 199 mg/dL; 7.8 to 11.0 mmol/L
Complete	< 5.7%; < 39 mmol/mol	< 100 mg/dL; < 5.6 mmol/L	< 140 mg/dL; < 7.8 mmol/L
One or more components needed to establish remission			
C: Duration criteria for the intervention and for the test			
Normoglycemia persists even after the withdrawal of glucose-lowering intervention (pharmacotherapy/active intervention), which is documented after a reasonable washout period			
	Glucose-lowering intervention can be non-pharmacological (medical nutrition therapy or physical activity) or pharmacological intervention (medication or surgical intervention)		
	No ongoing pharmacological or surgical procedure (ongoing procedures like repeated placement of endoluminal devices or intragastric balloon)		
	If any medication that can reduce blood sugar is continued for non-glycemic indication, it is considered incomplete remission		
Duration criteria for the intervention			
	Drugs after washout period (after five t ½ of the drug)		
	Lifestyle modification takes 3-6 mo to stabilize its effect		
Duration criteria for the tests			
	HbA1c after 3 mo of washout period of intervention		
	FBS/PPBS/RBS/CGM after 24 h of washout period of intervention		
Duration of remission is a retrospective assessment. Depending upon the duration of remission			
Normoglycemia persisting			
	3-6 mo: Transient remission		
	6 mo-1 yr: Short-term remission		
	1-5 yr: Long-term remission		
More than 5 yr: Prolonged remission			
D: Evidence of improvement of the pathophysiological mechanism			
Improvement in insulin resistance and β cell function			
Indirect evidence of this is significant weight loss, about 15 kg			
E: Satisfy exclusion criteria			
Normalization of blood sugar value in people with T2DM is not due to any complications (*e.g.*, nephropathy or hepatic dysfunction) or comorbid disease that causes reduced appetite, weight loss, or hypoglycemia (*e.g.*, sepsis, adrenal or pituitary disease, malignancy)			
Exclusion of stress hyperglycemia, gestational diabetes, or transient hyperglycemia			
Exclusion of hyperglycemia due to any medications: Drug-induced diabetes (*e.g.*, steroid, anti-malarial drugs, atypical antipsychotics, protease inhibitors)			

ADA: American Diabetes Association; CGM: Continuous glucose monitoring; FBS: Fasting blood sugar; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; PG: Post glucose; PPBS: Post prandial blood sugar; RBS: Random blood sugar; T2DM: Type 2 diabetes mellitus; t ½: Half-life.

Table 3 Interpretation of proposed criteria for remission of type 2 diabetes mellitus

Diagnosis of T2DM/pre-diabetes	Evidence of biochemical remission	Antidiabetic treatment/ongoing intervention	Duration criteria	Reversal of pathophysiologic mechanism	Exclusion criteria	Interpretation
Yes	Complete	No	+	+	+	Complete remission
	Partial					Partial remission
Yes	Complete	Yes, but for non-glycemic indication	+	+	+	Incomplete remission
	Partial					Incomplete partial remission
No	Complete/partial	No	+/-	+/-	+/-	Transient hyperglycemia. No remission. Improvement in risk factors
Yes	Complete/partial	No	+	-	+	State of mitigation/T2DM mitigation

T2DM: Type 2 diabetes mellitus.

Interpretation of criteria

In a person with established T2DM, if there is an achievement of glycemic status below the pre-diabetes range (partial remission) or within the normal limit (complete remission) and satisfying duration, pathophysiological improvement, and exclusion criteria, we can categorize it as remission (Table 3). Those not satisfying pathophysiological improvement criteria have to be categorized as T2DM mitigation. Those satisfying all these criteria but medications that can reduce blood sugar are continued for the non-glycemic indication are categorized as incomplete remission (incomplete partial remission if blood sugar is in the pre-diabetes range and incomplete remission if blood sugar is in the normal range).

CONCLUSION

Achievement of normal glucose levels or levels below the threshold for the diagnosis of pre-diabetes without pharmacotherapy among people with T2DM after metabolic surgery and carbohydrate or calorie-restricted diet can result in remission. The twin cycle hypothesis helps to understand the pathophysiological mechanism leading to remission. The lack of clear-cut criteria for diagnosing remission is a challenge healthcare professionals are facing now. As per our proposed criteria, five components should be satisfied to diagnose remission of T2DM. Our proposed criteria will be useful for healthcare professionals worldwide for diagnosing remission.

FOOTNOTES

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Country of origin: India

ORCID number: Arkiath Veettil Raveendran 0000-0003-3051-7505.

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MINIREVIEWS

Relation between dysbiosis and inborn errors of immunity

Öner Özdemir

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Öner Özdemir, Department of Pediatric Allergy and Immunology, Sakarya University, Medical Faculty, Adapazarı 54100, Sakarya, Türkiye

Corresponding author: Öner Özdemir, MD, Full Professor, Department of Pediatric Allergy and Immunology, Sakarya University Research and Training Hospital, Adnan Menderes Cad, Adapazarı 54100, Sakarya, Türkiye. ozdemir_oner@hotmail.com

Abstract

Inborn errors of immunity (IEI) disorders, formerly primary immune deficiency diseases, are a heterogeneous group of disorders with variable hereditary transitions, clinical manifestations, complications and varying disease severity. Many of the clinical symptoms, signs and complications in IEI patients can be attributed to inflammatory and immune dysregulatory processes due to loss of microbial diversity (dysbiosis). For example, in common variable immunodeficiency patients, the diversity of bacteria, but not fungi, in the gut microbiota has been found to be reduced and significantly altered. Again, this was associated with a more severe disease phenotype. Compromise of the STAT3/Th17 pathway in hyper-IgE syndrome may lead to dysbiosis of the oral microbiota in these patients, causing *Candida albicans* to switch from commensal to pathogenic. Modification of the microbiota can be used as a therapeutic approach in patients with IEI. Prebiotics, probiotics, postbiotics and fecal microbiota transplantation can be used to restore the balance of the gut microbiota and reduce pathogenicity in IEI patients. Clinical trials are currently underway to understand the impact of this dysbiosis on the phenotype of IEI diseases and its role in their treatment.

Key Words: Immunodeficiency; Microbiome; Microbiota; Fecal microbiota transplantation; Immunoglobulin

Core Tip: Inborn errors of immunity (IEI) disease is associated with microbial dysbiosis and systemic inflammation, especially in the presence of immune dysregulation. Fecal microbiota transplantation in particular, besides not being used as a stand-alone treatment strategy, could be a potential therapeutic tool for dysbiosis in IEI, considering the complications and the complexity of IEI.

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INTRODUCTION

Inborn errors of immunity (IEI, formerly primary immunodeficiency) diseases are a heterogeneous group of disorders with variable genetic transmissions, clinical manifestations, complications, and varying disease severity[1]. Many of the clinical symptoms, signs, and complications in IEI patients can be ascribed to inflammatory and immune dysregulation processes due to loss of microbial diversity (dysbiosis) and imbalances in the diet-microbiome-host-immune system axis [2]. The microbiome in IEI patients is reported to have a key role in serving the host immune system preserve homeostasis in the gut. In particular, the intestinal microbiome is a favorable area of study and interest in these aspects in IEI patients. Although the association between the microbiome and humoral immunodeficiency is better known, the relationship between combined immunodeficiency and the microbiome and its possible therapeutic benefits are still under investigation[2,3]. Additional studies investigating the efficacy of microbiota-based approaches and treatments in IEI-related dysbiosis in these patients are needed[2-4].

The contemporary understanding of the microbiome concerning the clinical symptoms and complications found in IEI patients and its potential as a therapeutic approach in IEI forms are the main basis of the aim of this minireview article.

Evaluation tools of microbiome/microbiota in studies

When carrying out microbiome studies, it is important to assess alpha diversity in the sample (single ecosystem) to be studied and beta diversity among individuals. It indicates the quantity and their prevalence of diverse taxa detected in each sample. Beta diversity is an indicator of the variety of the microbial population among different subjects or samples. It is also a marker for the number of different taxa and their prevalence in an environment. In brief, the average species variety of a place at the local measure is called alpha diversity[2,4]. Beta diversity reflects the diversity ratio between regional and local species[2,4].

Microbiome in most common IEI diseases

Here, microbiome and microbiota studies in more common and better-known IEI diseases will be presented in the light of current literature data (Table 1).

Common variable immunodeficiency

The foremost gastrointestinal tract symptom of common variable immunodeficiency (CVID), which is one of the most common immunodeficiencies, is temporary or persistent diarrhea seen in 21%-57% of cases[5]. Detectable pathogens include *Cytomegalovirus*, *Salmonella species*, *Clostridium difficile*, *Giardia lamblia*, *Cryptosporidium parvum,* and *Campylobacter jejuni*[6]. In some studies, *Hungatella hathewayi* from normal gut microbiota has been related to CVID, like some chronic inflammatory diseases (such as cystic fibrosis and IgA nephropathy)[7]. CVID patients with chronic diarrhea were found to have lower alpha diversity compared to healthy housemates or CVID patients without diarrhea[8]. New research indicates that the immune dysregulation yielding difficulties in CVID patients might be the result of a changed microbiome arrangement and augmented microbial translocation[2].

Decreased bacterial alpha diversity was also found in the more severe CVID phenotype with undetectable low serum IgA levels[2]. IgA production against commensal microbes occurs in Peyer's patches (PP) where live bacteria are presented by dendritic cell (DC) to B and T cells. Furthermore, secretory IgA selectively adheres to M cells in the gut PP and contributes to exciting the acceptance of IgA-bound pathogen antigens for distribution to DCs, ensuring a positive feedback loop. IgA thus has an essential role in controlling the pro-inflammatory reaction to the bacteria it covers, in establishing and maintaining the integrity of the gut mucosal barrier, and in determining the content of the gut microbiota. IgA-deprived mice were found to have meaningfully lesser gut microbial diversity than wild-type offspring [9].

IgA deficiency detected in CVID patients is highly associated with augmented morbidity from inflammation. Intestinal epithelial damage occurring in CVID cases may be caused by IgA deficiency leading to mucus invasion and epithelial infection. The alpha diversity index of cases with severe IgA deficiency was meaningfully decreased compared with CVID patients with low/normal IgA levels. The 3 bacterial taxa that were more copious in CVID patients than in healthy donors were Clostridia (*genera Lachnospiraceae Roseburia* and *Lachnospiraceae Dorea*), *Bacilli* and *Gammaproteobacteria*. In contrast, *Firmicutes* (*genus Blautia* of *Lachnospiraceae* and *family Christensenellaceae*), Actinobacteria (*e.g., family Bifidobacteriaceae*), and *Deltaproteobacteria* (*genus Desulfovibrionales*) were detected to be greatly reduced in CVID[10].

One of the groundbreaking types of research on the microbiome in CVID cases showed low levels of alpha diversity and *Bifidobacterium* species. However, increased *Bacilli*, *Clostridia*, and *Gammaproteobacteria* species were detected in these cases[10,11]. Among the 3 diverse bacterial taxa, *Geobacillus, Acinetobacter baumannii* and the *otu 15570* bacterium are among those that may contribute to CVID enteropathy[12].

The presence of dysbiosis and reduced alpha diversity is well known, especially in diseases such as CVID. There is no significant difference in beta diversity between adults and children, but alpha diversity is lesser in children than in adults. When compared to adults, the microbiota configuration in children shows a greater diversity of *Ruminococcaceae*, *Bacilli*, *Actinobacteria*, and *Bacteroidetes phyla* and a lesser diversity of *Methanobacteriales phyla*[13].

Table 1 Microbial dysbiosis on the clinical implications in various inborn errors of immunity

Inborn errors of immunity/diseases	Microbiota	Clinical findings	Ref.
Hyper-IgE syndrome	Predominance of *Candida albicans*, decreased abundance of *C. parapsilosis*, *Boletus*, and *Penicillium*	STAT3/Th17 axis play an important role in maintaining *C. albicans* as a commensal organism	[28]
Wiskott–Aldrich syndrome	Increased abundance of potentially, pathogenic *Proteobacteria* and *Roteobacteria*. Decreased levels of protective commensals, *e.g., Faecalibacterium prausnitzii, Bacteroidetes* and *Verrucomicrobia*	It may lead to periodontal lesions	[18]
Severe combined immunodeficiency	Increased abundances of *Escherichia*, *Staphylococcus*, *Enterococcus*, *Veillonella*, *Enterobacteriaceae*, *Adenovirus*, and *Bocavirus*	Increase in disease severity	[16, 18]
Selective IgA deficiency	Higher abundance of *Firmicutes*, *Bacteroidetes*, *Gammaproteobacteria* and *Prevotella*	Increase in systemic inflammation	[1,6, 24]
Common variable immunodeficiency	Decreased abundance of beneficial bacteria, *e.g., Bifidobacterium* and *Lactobacillus*, *Bacteroides* and *Firmicutes*. Increased abundance of *Clostridia*, *Bacilli*, *Prevotella*, and *Gammaproteobacteria*	Increase in systemic inflammation	[10, 14]

CVID patients have shown a less diverse and significantly altered bacterial, but not fungal, gut microbiota. Again, this has been associated with a more severe disease phenotype[14].

Selective IgA deficiency

Using a metagenomic approach, the researchers compared the intestinal microbial groups in the feces of 21 IgA-deficient cases with 34 age- and sex-matched healthy controls. Seventeen microbial species in the phyla Firmicutes, Bacteroidetes, and Proteobacteria (*Gammaproteobacteria* only, comprising *E. coli*) were greater in IgA-deficient patients. Moreover, 3 oral commensal bacteria (*Haemophilus parainfluenza*, *Streptococcus sanguinis* and *Veillonella parvula*) and two *Prevotella* species were also found at high rates in the selective IgA deficiency cohort. Most of the bacteria lost in IgA-deficient patients (13 of 14) belonged to the phylum *Firmicutes* (*genus Faecalibacterium* and *family Lachnospiraceae*), while one belonged to the phylum Bacteroides. In short, IgA deficiency caused a loss of some typical favorable symbionts and an increase in pathobionts[15].

Faecalibacterium, a genus with anti-inflammatory effects for the intestinal mucosa, was markedly reduced in patients with inflammatory bowel disease (IBD). However, the pro-inflammatory species, *Gammaproteobacteria* and *Prevotella*, are increased in patients with selective IgA deficiency. Analysis of the gut microbiota in these cases shows that the oral microbiota is ectopically localized in the lower digestive tract[6].

Severe combined immunodeficiency

A study showed that the bacterial taxonomy of the intestinal microbiota in severe combined immunodeficiency patients changes in long periods of time, resulting in altered microbiome spectrum before and after hematopoietic stem-cell transplantation (HSCT)[6]. Graft-*vs*-host disease, which can also be seen after HSCT, is affected by different factors, plus the intestinal microbiota. Decreased microbial miscellany after HSCT causes the predominance of *Staphylococcus*, *Escherichia*, and *Enterococcus* species[16,17].

Wiskott–Aldrich syndrome

Bacteroidetes and *Verrucomicrobia* were less abundant in patients with Wiskott–Aldrich syndrome (WAS), whereas *Proteobacteria* were significantly more abundant compared to healthy controls[18,19]. Roughly 10% of WAS patients live with dysbiosis causing severe, sporadic, and recurrent gastrointestinal inflammation. Therefore, WAS cases are inclined to develop an acute and early IBD that phenotypically resembles polygenetic IBD[4].

Hyper-IgE syndrome

Candida albicans are more common in autosomal dominant (AD)- Hyper-IgE syndrome (HIES) patients than others (*e.g., C. parapsilosis*, *Boletus*, and *Penicillium*) compared to healthy patients. AD-HIES patients have severe dysbiosis with *Candida albicans* predominating during active fungal infection. In uninfected patients, the genus *Malassezia* was predominant. A modification of the skin microbiota towards gram-negative colonization (especially *Acinetobacter spp.*) is linked with a weak *in vitro* immune reaction to *C. albicans* and *S. aureus*[18].

Immunodeficient cases with defects in the Th17/IL-17 pathway are more inclined to propagate oral fungal infections. Patients with HIES due to STAT3 deficiency have been reported to have low salivary antifungal activity as a result of the reduction of specific antimicrobial effectors containing human β-defensin 2 and multiple histatins. In these patients, the STAT3-Th17 axis is important for *C. albicans* commensalism and the formation of oral bacterial groups. In these cases, *C. albicans* forms a symbiotic life with orally present *Streptococcus mutans* and *Streptococcus oralis*[18]. A compromised STAT3/Th17 pathway may lead to dysbiosis of the oral microbiota in these patients, causing *C. albicans* to shift from commensal to pathogenic[4,20]. *Selected oral streptococci* can increase the virulence of *C. albicans* by invading oral tissue and causing mucosal lesions[6]. Another study reported a decrease in abundant gram-negative bacteria (such as

Fusobacteria and *Prevotella*) in oral swabs of HIES patients.

In a study, the oral microbiome of a large cohort of 36 patients with AD-HIES (STAT3 deficiency) was analyzed. Oral bacterial groups were also found to be dysbiotic in AD-HIES, especially when active *Candida* infection was present. Many prevalent oral commensal bacteria, comprising *Porphyromonas*, *Neisseria*, and *Haemophilus*, had lesser comparative copiousness in autosomal dominat-HIES patients, even though the genus *Capnocytophaga* was unequally represented[19,20].

Management

Modification of the microbiota can be used as a therapeutic approach in IEI patients[4]. Prebiotics, probiotics, postbiotics, and fecal microbiota transplantation (FMT) have been established to renovate the equilibrium of intestinal microbiota and reduce pathogenicity in IEI patients[4,21,22].

Dysbiosis can be treated by oral intake of live, natural probiotic bacteria. Metabolites from prebiotic fibers serve as a material for probiotic commensal bacteria. The ability of prebiotics to modify immunity has been utilized to produce complementary immunomodulatory therapies for a range of IEIs. Probiotics increase the manufacture of bioactive peptides by enabling the interaction of gut epithelial and mucosal immune cells and intestinal microbiota and help protect intestinal epithelial barriers[4].

Secretory IgA and systemic IgG are known to act synergistically in defense against gut microbiota. High serum levels of IgG directed against gut microbiota have been detected in animal models of IEI diseases. Furthermore, IgG antibodies to *E. coli* have been detected in IBD cases and secretory IgA-deficient mice[23]. Fadlallah *et al*[24] have also shown that serum anti-microbiota IgG is increased in cases with selective IgA deficiency compared to controls[24]. These circulating IgGs are formed against preserved antigenic motifs and protect against commensal bacteria. It is thought that intravenous immunoglobulin products consisting of selective IgA-deficient individuals in the pool may increase protection against dysbiosis and microbial displacement in CVID patients[4,16,24].

FMT involves the administration of healthy donor feces to the patient to restore spoiled intestinal microbiota and provide therapeutic profits. FMT, which is the standard for the treatment of recurrent *Clostridium difficile* infections, may not be used as a single treatment modality but as likely management of immune dysregulation in IEI, considering its side effects and the complexity of IEI[2]. A case with immune dysregulation, polyendocrinopathy, enteropathy, X-linked disease, severe enteropathy, and chronic diarrhea was reported to be efficaciously treated with FMT[16,25]. The disadvantage of this type of therapeutic management includes procedure-related risks, such as insufficient prior screening of FMT for multidrug-resistant microorganisms, especially for immunocompromised recipients[2,26]. Gut dysbiosis has been observed in germ-free mice transplanted with feces from CVID cases with non-infectious problems. No dysbiosis was observed with FMT using only feces from CVID cases with an infectious phenotype or from household contacts. Intestinal dysbiosis in non-infectious CVID cases is seen with augmented richness of *Dysgonomonas mossii* and *Bacillus massiliensis*[2,27,28].

CONCLUSION

The presence of dysbiosis in different types of IEI patients has been demonstrated in different clinical studies. Studies are ongoing to understand the role of this dysbiosis on the phenotype of the IEI diseases and in their treatment.

FOOTNOTES

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Country of origin: Türkiye

ORCID number: Öner Özdemir 0000-0002-5338-9561.

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ORIGINAL ARTICLE

Retrospective Study

Hepatocellular carcinoma national burden across different geographical regions in the United States between 2001 and 2020

Yazan Abboud, Raj Malhotra, Muhammad Hassaan Arif Maan, Anna Mathew, Ibrahim Abboud, Chun-Wei Pan, Saqr Alsakarneh, Fouad Jaber, Islam Mohamed, David Kim, Nikolaos T Pyrsopoulos

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Yazan Abboud, Raj Malhotra, Muhammad Hassaan Arif Maan, Anna Mathew, David Kim, Department of Internal Medicine, Rutgers New Jersey Medical School, Newark, NJ 07103, United States

Ibrahim Abboud, University of California Riverside School of Medicine, Riverside, CA 92521, United States

Chun-Wei Pan, Department of Internal Medicine, John H Stroger Hospital of Cook County, Chicago, IL 60612, United States

Saqr Alsakarneh, Fouad Jaber, Islam Mohamed, Department of Internal Medicine, University of Missouri-Kansas City, Kansas, MO 64108, United States

Nikolaos T Pyrsopoulos, Division of Gastroenterology and Hepatology, Rutgers New Jersey Medical School, Newark, NJ 07101, United States

Co-corresponding authors: Yazan Abboud and Nikolaos T Pyrsopoulos.

Corresponding author: Yazan Abboud, MD, Doctor, Department of Internal Medicine, Rutgers New Jersey Medical School, 150 Bergen Street, Newark, NJ 07103, United States.
yazanabboud.md@gmail.com

Abstract

BACKGROUND

While prior data showed an increasing incidence of hepatocellular carcinoma (HCC) in the United States, there are limited comprehensive and comparative data on the geographical variations of HCC trends in different demographic-specific populations.

AIM

To evaluate sex and age-specific incidence rates and time trends in different geographical regions in the United States.

METHODS

Age-adjusted HCC incidence rates were collected from the United States Cancer Statistics (USCS) database which covers approximately 98% of the population in the United States. HCC rates were stratified by sex, age, and geographical region.

annual percentage change (APC) and average APC (AAPC) were estimated using Joinpoint Regression. A pairwise comparison was conducted between sex-specific trends.

RESULTS

There were 467344 patients diagnosed with HCC in the United States in the USCS database between 2001 and 2020. The rates and trends varied by geographical region. When looking at the West region (115336 patients), incidence rates of HCC were overall increasing and also increasing in older adults. However, when evaluating younger adults, HCC incidence rates decreased in men but not in women with a sex-specific absolute AAPC-difference of 2.15 (P = 0.005). When evaluating the Midwest region (84612 patients), similar results were seen. While incidence rates were increasing in the overall population and in older adults as well, they were decreasing in younger men but not in women with a sex-specific absolute AAPC-difference of 1.61 (P < 0.001). For the Northeast region (87259 patients), the analysis showed similar results with decreasing HCC incidence rates in younger men but not counterpart women (Sex-specific AAPC-difference = 3.26, P < 0.001). Lastly, when evaluating the south (180137 patients), the results were also decreasing in younger men but not in women (Sex-specific AAPC-difference = 2.55, P < 0.001).

CONCLUSION

Nationwide analysis covering around 98% of the United States population shows an increasing incidence of HCC across all geographical regions, most notably in the South. While younger men experienced decreasing HCC incidence, younger women had a stable trend and this was noted across all regions as well. Our study offers insight into the epidemiology of HCC in different demographic groups across various United States geographical regions. While the reasons contributing to our findings are unclear, they can be related to sex and regional disparities in healthcare access and utilization. Future research is warranted to characterize the temporal change in HCC risk factors across different United States regions.

Key Words: Hepatocellular carcinoma; Incidence; Epidemiology; Health disparity; Geography

Core Tip: In this retrospective study of the United States Cancer Statistics database (which covers approximately 98% of the United States population), we analyzed sex and age-specific hepatocellular carcinoma (HCC) incidence across different United States regions between 2001-2020. HCC incidence rates were significantly increasing in the West, Midwest, Northeast, and South of the United States, most notably in the South. While younger men experienced decreasing HCC incidence, younger women had non-decreasing incidence, and this was noted across all regions. While this can be due to regional disparities in healthcare access/utilization, future research is needed to investigate regional HCC risk factors, especially in younger adults.

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INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for around 80% of liver cancers and its incidence has tripled since 1980[1]. Although HCC can occur sporadically, almost 90% of cases can be attributed to underlying liver diseases such as hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol-associated liver disease, and metabolic dysfunction associated steatotic liver disease (MASLD). With the routine vaccination against HBV and an increase in the proportion of HCV patients with sustained virologic response, coupled with increased prevalence of MASLD, epidemiological changes in HCC risk factors are expected in the coming years[2].

HCC burden is unequally distributed with disparities occurring at various steps of the cancer care continuum including implementation of screening programs, access to specialist care, timely diagnosis, and treatment. HCC is usually rare under the age of 40 years, and its incidence increases with age before plateauing around the age of 70 years [3]. The incidence of HCC is disproportionately greater in males, with associated mortality reported to be three times higher than in women[4]. These differences are attributed to a variation in the prevalence of risk factors such as alcohol use, smoking, viral hepatitis, and MASLD which disproportionally affect men and women. The evolving trends in sex- and age-specific HCC incidence rates call for further exploration and analysis of data at a national level to guide future interventions.

American Cancer Society projects cancer deaths in 2024 from liver and bile duct cancer to be the highest in California (3580), followed by Texas (2960) and Florida (2180)[1]. Limited data comparing regional variation in HCC incidence show rates are highest in Texas, followed by Hawaii, New Mexico, and California; argued to be in part due to their racial/ethnic diversity[5]. While recent data showed an increasing overall incidence of HCC with variations based on age and sex[4], literature is scarce on demographic-specific trends across geographic regions. Understanding the epidemiological differences at a national level is imperative to identify regional variabilities in epidemiology and study their impact on HCC-associated morbidity and mortality. Therefore, we aimed to perform a comprehensive analysis of HCC incidence rates and time trends stratified by sex and age in different geographical regions in the United States using the United States Cancer Statistics (USCS) database.

MATERIALS AND METHODS

We report a time trend comprehensive analysis of national incidence rates of HCC in the United States between 2001 and 2020 across various regions in the United States using publicly available and de-identified data from the USCS database which covers nearly 98% of the United States population[6]. HCC incidence rates were age-adjusted to the standard 2000 United States population using SEER Stat software [version 8.4.2, National Cancer Institute (NCI)]. The rates were categorized by sex and age into younger and older adults (defined with an age cutoff 55 years)[4]. HCC incidence rates were also stratified by geographical region in the United States into West, Midwest, Northeast, and South. Time-trends were reported as annual percentage change (APC) and average APC (AAPC) and were generated using Joinpoint Regression Software (version 5.0.2, NCI) *via* the weighted Bayesian Information Criteria (BIC) method (which is a data-driven analytical method used to estimate trends over time that is recommended to be used in large databases)[7-9]. A pairwise comparison was done between the sex-specific trends using the tests of parallelism and coincidence with a two-sided *P*-value cutoff at 0.05[10].

RESULTS

During the study period of 2001-2020, there were 467344 patients diagnosed with HCC in the United States. The majority of the patients were men (74.0%) and were diagnosed in the South (38.5%). HCC incidence rates and time trends varied between the cohorts across different geographical regions.

In the West regions (115336 patients; 26.9% women), HCC incidence rate per 100000 population significantly increased in the overall population from 5.57 to 6.48 between 2001 and 2020, and also in older adults (95152 patients; 28.2% women) from 19.66 to 26.31 between 2001 and 2020 (Figure 1). However, in younger adults (19160 patients; 19.8% women), while HCC incidence rates decreased in men from 3.77 to 1.97 between 2001 and 2020 (AAPC = -2.92, $P < 0.001$), the rates did not decrease in women (AAPC = -0.78, $P = 0.10$) with a significant difference between the sexes (Sex-specific absolute AAPC-difference = 2.15, $P < 0.005$) (Table 1 and Figure 2).

When evaluating the Midwest (84612 patients; 26.8% women), similar results were seen where HCC incidence rates per 100000 population were significantly increasing in the overall population from 3.84 to 5.16 between 2001 and 2020, and also in older adults (70631 patients; 27.5% women) from 13.65 to 20.83 between 2001 and 2020 (Figure 1). However, in younger adults (13169 patients; 22.3% women), while HCC incidence rates were decreasing in men from 2.40 to 1.61 between 2001 and 2020 (AAPC = -1.95, $P = 0.002$), the rates did not decrease in women (AAPC = -0.35, $P = 0.65$) with an absolute sex-specific AAPC -difference of 1.61, $P = 0.1$ (Table 1 and Figure 2).

In the Northeast (87259 patients; 24.9% women), similar results were also seen where HCC incidence rates per 100000 population were increasing in the overall population from 5.01 to 5.74, and in older adults (72391 patients; 225.8% women) from 17.36 to 23.41, between 2001 and 2020 (Figure 1). However, in younger adults (14225 patients; 19.4% women), HCC rates were decreasing in men from 3.70 to 1.73 between 2001 and 2020 (AAPC= -3.38, $P < 0.001$), and this was not seen in women who experienced a stable trend (AAPC= -0.13, $P = 0.87$) with an absolute sex-specific AAPC-difference of 3.26, $P < 0.001$ (Table 1 and Figure 2).

Lastly, in the south (180137 patients; 25.5% women), similar results were also seen with increasing HCC rates per 100000 population in the overall population from 4.31 to 6.81 between 2001 and 2020, and also in older adults from 14.69 to 27.68 between 2001 and 2020 (Figure 1). However, younger adults (467344 patients; 20.8% women) experienced decreasing HCC incidence rates in men from 3.28 in 2001 to 2.14 in 2020 (AAPC = -2.05, $P < 0.001$), but not in women who had a stable trend (AAPC = -0.05, $P = 0.95$) with an absolute sex-specific AAPC-difference of 2.55, $P < 0.001$ (Table 1 and Figure 2).

DISCUSSION

Our nationwide analysis of data covering nearly all HCC patients in the United States shows increasing overall incidence of HCC in older adults across all geographical United States regions, most notably in the South. However, in younger adults, HCC incidence was decreasing in men but not in counterpart women, and that sex-specific difference was seen across all geographical regions in the United States.

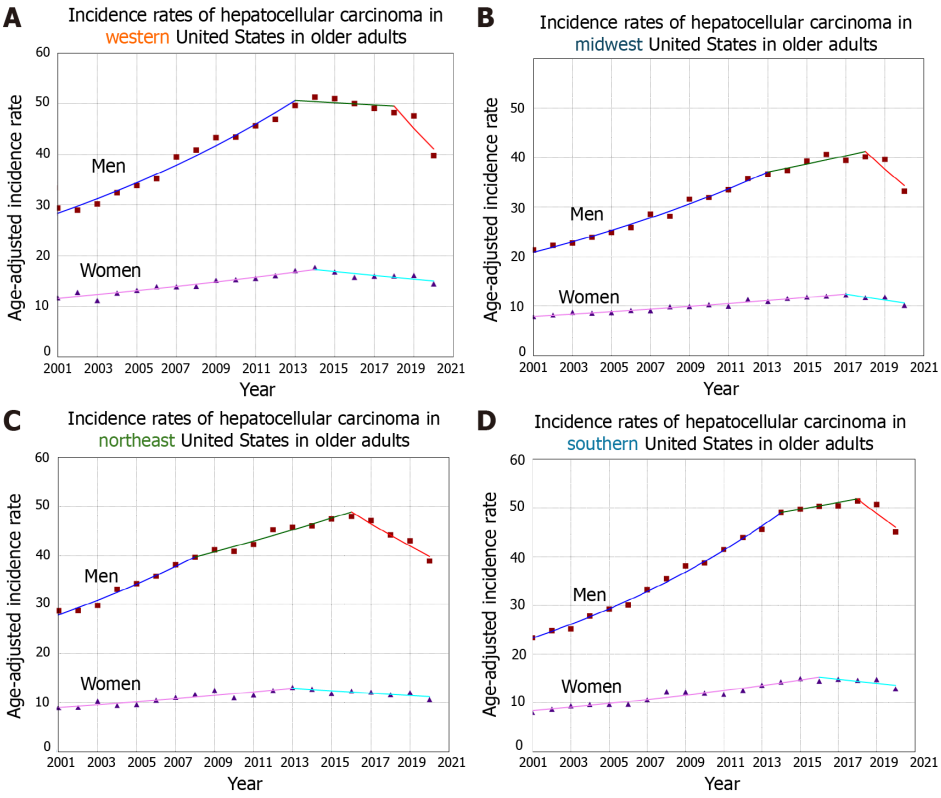

Figure 1 Sex-specific time-trends and age-adjusted incidence rates per 100000 population for hepatocellular carcinoma in older adults aged < 55 years categorized by United States geographical region. A: Western United States; B: Midwest United States; C: Northeast United States; D: Southern United States.

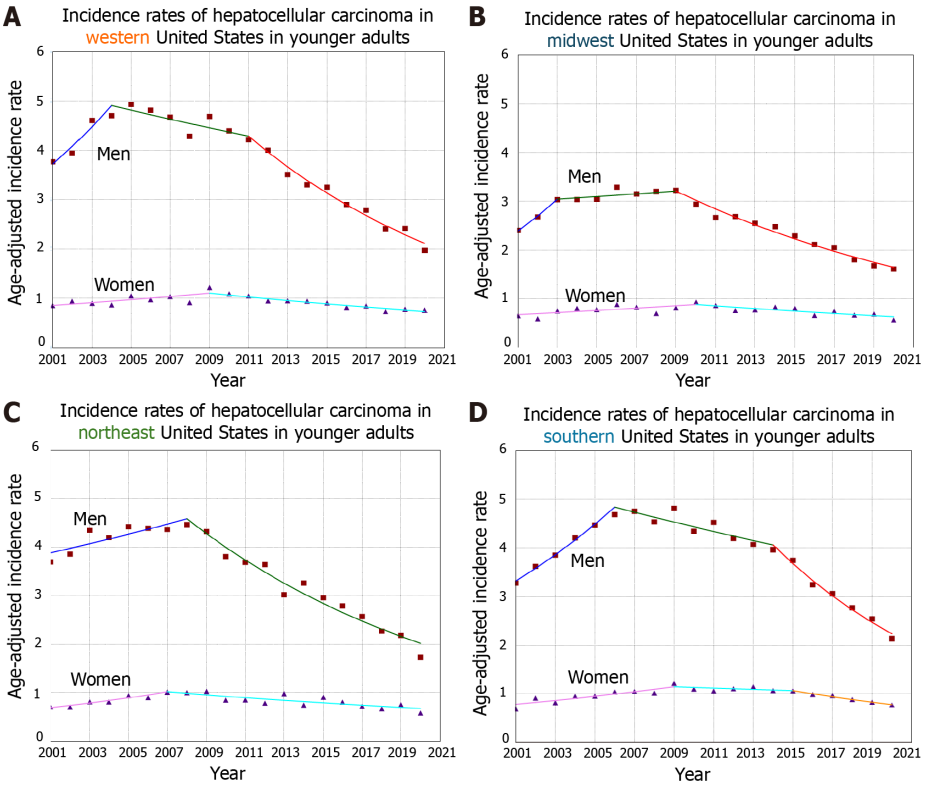

Figure 2 Sex-specific time-trends and age-adjusted incidence rates per 100000 population for hepatocellular carcinoma in younger adults aged < 55 years (15-54 years) categorized by United States geographical region. A: Western United States; B: Midwest United States; C: Northeast United States; D: Southern United States.

Table 1 Hepatocellular carcinoma incidence trends in different age and sex-specific groups across United States geographical regions

Age group, year	Cases (*n* = 467344)[1], (%)	Trends[2]			Sex-specific AAPC difference (95%CI)[3]	Pairwise comparison *P* values		
		Time period	APC	AAPC		Sex-specific AAPC difference	Coincidence[4]	Parallelism[5]
West								
All ages								
Women	31008 (6.64)	2001-2014	2.66[a]	0.96[a]	-0.02 (-0.86 to 0.82)	0.95	< 0.001	0.008
		2014-2020	-2.61[a]					
Men	84328 (18.04)	2001-2009	4.42[a]	0.94[a]				
		2009-2014	1.66[a]					
		2014-2018	-1.72					
		2018-2020	-8.68[a]					
Aged ≥ 55 years								
Women	26804 (5.74)	2001-2014	3.10[a]	1.36[a]	0.61 (-0.42 to 1.65)	0.24	< 0.001	0.002
		2014-2020	-2.30[a]					
Men	68348 (14.62)	2001-2013	4.95[a]	1.97[a]				
		2013-2018	-0.44					
		2018-2020	-8.91[a]					
Aged < 55 years								
Women	3786 (0.81)	2001-2009	3.26[a]	-0.78	-2.15[a] (-3.65 to -0.64)	0.005	< 0.001	< 0.001
		2009-2020	-3.61[a]					
Men	15383 (3.29)	2001-2004	9.67[a]	-2.92[a]				
		2004-2011	-1.91[a]					
		2011-2020	-7.54[a]					
All ages								
Women	3786 (0.810)	2001-2009	3.26[a]	-0.78	-2.15[a] (-3.65 to -0.64)	0.005	< 0.001	< 0.001
		2009-2020	-3.61[a]					
Men	15383 (3.291)	2001-2004	9.67[a]	-2.92[a]				
		2004-2011	-1.92[a]					

		2011-2020	-7.54[a]					
Midwest								
All ages								
Women	22675 (4.851)	2001-2017	2.42[a]	1.12[a]	0.50 (-0.54 to 1.55)	0.34	< 0.001	0.02
		2017-2020	-5.56[a]					
Men	61937 (13.252)	2001-2012	3.90[a]	1.62[a]				
		2012-2018	0.99					
		2018-2020	-8.38[a]					
Aged ≥ 55 years								
Women	19403 (4.151)	2001-2017	2.82[a]	1.53[a]	1.12[a] (0.04 to 2.19)	0.04	< 0.001	< 0.001
		2017-2020	-5.08[a]					
Men	51228 (10.961)	2001-2013	4.89[a]	2.65[a]				
		2013-2018	2.15[a]					
		2018-2020	-8.72[a]					
Aged < 55 years								
Women	2942 (0.629)	2001-2010	3.02[a]	-0.35	-1.61 (-3.57 to 0.36)	0.10	< 0.001	< 0.001
		2010-2020	-3.28[a]					
Men	10227 (2.188)	2001-2003	12.75[a]	-1.95[a]				
		2003-2009	0.88					
		2009-2020	-5.89[a]					
Northeast								
All ages								
Women	21729 (4.645)	2001-2013	2.67[a]	0.74	0.14 (-0.90 to 1.17)	0.79	< 0.001	0.2
		2013-2020	-2.48[a]					
Men	65530 (14.021)	2001-2007	4.77[a]	0.88[a]				
		2007-2016	1.25[a]					
		2016-2020	-5.49[a]					
Aged ≥ 55 years								

Women	18703 (4.001)	2001-2013	3.01[a]	1.13[a]	0.76 (-0.26 to 1.78)	0.14	< 0.001	< 0.001
		2013-2020	-2.00[a]					
Men	53688 (11.487)	2001-2008	5.17[a]	1.89[a]				
		2008-2016	2.62[a]					
		2016-2020	-4.97[a]					
Aged < 55 years								
Women	2763 (0.591)	2001-2007	6.63[a]	-0.13	-3.26[a] (-5.08 to -1.43)	< 0.001	< 0.001	<0.001
		2007-2020	-3.10[a]					
Men	11462 (2.452)	2001-2008	2.39[a]	-3.38[a]				
		2008-2020	-6.60[a]					
South								
All ages								
Women	45975 (9.837)	2001-2015	3.74[a]	2.08[a]	0.46 (-0.53 to 1.45)	0.36	< 0.001	0.01
		2015-2020	-2.42					
Men	134162 (28.707)	2001-2007	6.14[a]	2.54[a]				
		2007-2014	3.66[a]					
		2014-2018	0.05					
		2018-2020	-6.50[a]					
Aged ≥ 55 years								
Women	38809 (8.304)	2001-2016	3.99[a]	2.53[a]	1.12[a] (0.10 to 2.13)	0.03	< 0.001	< 0.001
		2016-2020	-2.77					
Men	108315 (23.176)	2001-2014	5.89[a]	3.65[a]				
		2014-2018	1.4					
		2018-2020	-5.74[a]					
Aged < 55 years								
Women	6576 (1.407)	2001-2009	4.77[a]	0.5	-2.01[a] (-3.77 to -0.24)	0.02	< 0.001	< 0.001
		2009-2015	-1.2					
		2015-2020	-6.00[a]					

Men	25030 (5.355)	2001-2006	7.81[a]	-2.05[a]
		2006-2014	-2.16[a]	
		2014-2020	-9.46[a]	

[1]Data are presented as count numbers followed by percentages of the count numbers from the total cases of hepatocellular carcinoma in the database.
[2]Time-trends were computed using Joinpoint Regression Program (version 5.0.2, National Cancer Institute) with 3 maximum joinpoints allowed (4-line segments).
[3]A negative value indicates a greater average annual percentage change in women compared to men.
[4]Tests whether incidence trends were identical. A significant *P*-value indicates that the trends were not identical (*i.e.*, they had different incidence rates and coincidence was rejected).
[5]Tests whether incidence trends were parallel. A significant *P*-value indicates that the trends were not parallel (*i.e.*, parallelism was rejected).
[a]$P < 0.05$.
APC: Annual percentage change; AAPC: Average annual percentage change.

As of 2020, primary liver cancer is the fifth most common cancer in men worldwide, the ninth most common cancer in women worldwide, and the sixth most common cancer diagnosed overall[11]. According to the NCI, in 2023, there were about 41000 diagnoses and about 29000 deaths related to primary liver cancer in the United States. A recent analysis using the USCS database showed increasing overall HCC incidence, and decreasing rates in younger men but not women [4]. Recent data also suggests that HCC incidence is trending away from male predominance in younger adults, with a decreasing male-to-female incidence ratio[5]. We add to prior literature showing that the greatest increase in overall HCC was in the South and the greatest decrease in HCC incidence in younger men was in the Northeast. We also show that the stable trend in younger women was noted across all United States regions. These differences are multifactorial, in large part due to the racial and geographical disparities in access to and quality of care. The findings of non-decreasing HCC incidence rate in younger females may be attributable to the changing prevalence of risk factors over recent years across all regions of the United States[4].

A prior analysis of the SEER database of 43868 patients between 2000-2012 evaluating the most at-risk group in the United States (Southern region) compared to other regions, showed that blacks comprised a larger proportion of HCC patients in the South compared to other areas (32.4% *vs* 10.1%) and were diagnosed at a younger age, with more advanced stage at diagnosis and more metastases[12]. Furthermore, black patients were 58% less likely to receive liver transplant and 36% less likely to receive surgical therapy for HCC compared to patients of white race[13]. Of interest, this study also saw similar radial disparities in HCC outcomes in geographical regions outside the Southern United States. Another analysis of the SEER database from 1975-2017 showed that HCC mortality rates were highest in the South, followed by the West, Northeast, and Midwest[14]. These differences are multifactorial, in large part due to the racial and geographical disparities in access to and quality of care[15]. Our study builds on these prior studies, using a significantly larger sample size over a more recent period and stratifying the analysis by sex and age, demonstrating that the greatest increase in HCC incidence was in the South.

The introduction of direct-acting-antiviral treatment for HBV and HCV along with the increasing obesity epidemic in the United States has shifted the leading causes of HCC from viral hepatitis toward MASLD[16,17]. However, access to treatment has been a subject of public health concern, as fewer Medicaid and Medicare recipients with HCV receive timely treatment compared to those privately insured[18]. Furthermore, black Medicaid recipients are less likely to receive direct-acting antiviral therapy than white counterparts[18,19]. Viral hepatitis also disproportionately affects the black population. A prior study using the National Health and Nutrition Examination Survey database found that African Americans had a two to three-fold higher prevalence of chronic HBV than the general population between 1999

and 2008[20]. According to the United States Census Bureau in 2021, nine of the ten poorest states are in the South. These factors could explain the greater increase in HCC incidence in the South. These findings demonstrate a need for targeted public health intervention and multidisciplinary care in this high-risk, underserved, largely uninsured population.

MASLD is a leading cause of HCC in Western countries[21]. Sex differences in metabolic risk factors for HCC may explain the trends we observed. In the more recent years of our study period, in all regions but the Midwest, the HCC incidence rate in women older than 55 years of age has decreased less than that of men over 55 years of age. This could be explained in part by decreased estrogen levels in postmenopausal women. Estrogen may have protective effects on hepatic fibrinogenesis, causing later onset of HCC in the female population[22,23]. A single-center study reported significantly higher rates of MASLD in older women compared to younger women and older men[24]. Patients without screenable etiologies to cirrhosis are disproportionately identified later in the disease course; postmenopausal women may be part of this population[25,26]. Having said that, it is hard to blame a single risk factor for the observed findings, especially with the variation in environmental exposures, biologics, and socioeconomic status between different cohorts in the United States in different regions.

Our study has several strengths which include the stratified analysis by age and sex across different geographical regions, in addition to the large sample size (467344 patients), recent period (2001-2020), and the use of joinpoint regression with the BIC method and comparative analysis. With that in mind, our study is limited in the lack of clinical variables to assess for HCC risk factors. However, our manuscript is observational, and its epidemiological retrospective design is hypothesis-generating and aims to guide future efforts toward further investigations of the contributions leading to increasing HCC incidence across different United States populations and geographical locations. Our study suffer from other limitations inherent in large databases such as loss of records and coding reliability[27]. However, all the data used in our analysis were obtained from the USCS database which is the official source of cancer incidence data in the United States and undergoes many processes to ensure high-quality standardization and coding per the standards of the North American Association of Central Cancer Registries.

CONCLUSION

Our study offers insight into the epidemiology of HCC in different demographic groups across various United States geographical regions. While overall HCC incidence was increasing across all geographical regions, Southern states experienced the steepest increase. The non-decreasing trend in younger women was noted across different regions, compared to counterpart younger men who experienced a decreasing trend. The reasons contributing to our findings are unclear and can be related to sex and regional disparities in healthcare access and utilization. Future research is warranted to characterize the temporal change in HCC risk factors across different United States regions.

FOOTNOTES

Author contributions: Abboud Y designed the study, conducted the acquisition, analysis, and interpretation of data for the study; and drafted the manuscript; Malhotra R, Maan MHA, Mathew A, Abboud I drafted parts of the manuscript and revised the manuscript critically for important intellectual content; Pan CW, Alsakarneh S, Jaber F, Mohamed I, and Kim D revised the manuscript critically for important intellectual content; Pyrsopoulos NT supervised the work; contributed to the design of the study, and revised the manuscript critically for important intellectual content. All Authors have read and approved the manuscript. Abboud Y and Pyrsopoulos NT are co-corresponding authors because both authors contributed equally to the study conception, design, and methodology. While Abboud Y was responsible for data access, and conducting the statistical analysis, Pyrsopoulos NT supervised the work and reviewed the methods and results critically for important intellectual input. Abboud Y drafted the original version of the manuscript, and Pyrsopoulos NT edited the manuscript and reviewed it critically for important intellectual input. Abboud Y has access to the data used in the study and he is the lead author and will be able to reply to any correspondence or question raised, if any, in the future. Pyrsopoulos NT is the article senior author and is the most experienced author among the author list with extensive experience in the topic of the manuscript and can help in any future correspondence as well.

Institutional review board statement: Data used in this study were all publicly available and de-identified and therefore were exempted from review by the institutional review board, based on the National Human Research Protections Advisory Committee Policy.

Informed consent statement: Data used in this study were all publicly available and de-identified and therefore were exempted from review by the institutional review board, based on the National Human Research Protections Advisory Committee Policy.

Conflict-of-interest statement: The findings of this study were accepted to be presented at the Digestive Diseases Week 2024 conference at the "Liver and Biliary Tract Carcinoma (Hepatobiliary Neoplasia)" session on May 20th, 2024 (12:30 PM to 1:30 PM), in Washington, D.C.

Data sharing statement: Data used in this study were all publicly available and can be obtained from the United States Cancer Statistics Database.

Country of origin: United States

ORCID number: Yazan Abboud 0000-0003-0181-7744; Nikolaos T Pyrsopoulos 0000-0002-6950-8174.

Corresponding Author's Membership in Professional Societies: American College of Gastroenterology.

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ORIGINAL ARTICLE

Observational Study

Comparative evaluation of artificial intelligence systems' accuracy in providing medical drug dosages: A methodological study

Swaminathan Ramasubramanian, Sangeetha Balaji, Tejashri Kannan, Naveen Jeyaraman, Shilpa Sharma, Filippo Migliorini, Suhasini Balasubramaniam, Madhan Jeyaraman

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Swaminathan Ramasubramanian, Sangeetha Balaji, Tejashri Kannan, Department of Orthopaedics, Government Medical College, Omandurar Government Estate, Chennai 600002, Tamil Nadu, India

Naveen Jeyaraman, Madhan Jeyaraman, Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Chennai 600077, Tamil Nadu, India

Shilpa Sharma, Department of Paediatric Surgery, All India Institute of Medical Sciences, New Delhi 110029, India

Filippo Migliorini, Department of Life Sciences, Health, Link Campus University, Rome 00165, Italy

Filippo Migliorini, Department of Orthopaedic and Trauma Surgery, Academic Hospital of Bolzano (SABES-ASDAA), Teaching Hospital of the Paracelsus Medical University, Bolzano 39100, Italy

Suhasini Balasubramaniam, Department of Radio-Diagnosis, Government Stanley Medical College and Hospital, Chennai 600001, Tamil Nadu, India

Corresponding author: Madhan Jeyaraman, MS, PhD, Assistant Professor, Research Associate, Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Velappanchavadi, Chennai 600077, Tamil Nadu, India.
madhanjeyaraman@gmail.com

Abstract

BACKGROUND

Medication errors, especially in dosage calculation, pose risks in healthcare. Artificial intelligence (AI) systems like ChatGPT and Google Bard may help reduce errors, but their accuracy in providing medication information remains to be evaluated.

AIM

To evaluate the accuracy of AI systems (ChatGPT 3.5, ChatGPT 4, Google Bard) in providing drug dosage information per Harrison's Principles of Internal Medicine.

METHODS
A set of natural language queries mimicking real-world medical dosage inquiries was presented to the AI systems. Responses were analyzed using a 3-point Likert scale. The analysis, conducted with Python and its libraries, focused on basic statistics, overall system accuracy, and disease-specific and organ system accuracies.

RESULTS
ChatGPT 4 outperformed the other systems, showing the highest rate of correct responses (83.77%) and the best overall weighted accuracy (0.6775). Disease-specific accuracy varied notably across systems, with some diseases being accurately recognized, while others demonstrated significant discrepancies. Organ system accuracy also showed variable results, underscoring system-specific strengths and weaknesses.

CONCLUSION
ChatGPT 4 demonstrates superior reliability in medical dosage information, yet variations across diseases emphasize the need for ongoing improvements. These results highlight AI's potential in aiding healthcare professionals, urging continuous development for dependable accuracy in critical medical situations.

Key Words: Dosage calculation; Artificial intelligence; ChatGPT; Drug dosage; Healthcare; Large language models

Core Tip: This study reveals ChatGPT 4's superior accuracy in providing medical drug dosage information, highlighting the potential of artificial intelligence (AI) to aid healthcare professionals in minimizing medication errors. The analysis, based on Harrison's Principles of Internal Medicine, underscores the need for ongoing AI development to ensure reliability in critical medical situations. Variations in disease-specific and organ system accuracies suggest areas for improvement and continuous refinement of AI systems in medicine.

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INTRODUCTION

ChatGPT is a Large Language Model (LLM) developed by open artificial intelligence (AI). The GPT (Generative Pre-trained Transformer) architecture, more precisely GPT-3.5, is the foundation of this system[1]. This model is trained on a massive quantity of text data to comprehend and produce responses to user inputs that are human-like. It has potential uses in medical practice, research, and teaching[2]. Through curriculum development, simulated training, and language translation, ChatGPT could contribute to medical education. It could aid with information retrieval in research, and it could potentially enhance the accuracy and efficiency of medical recording in clinical settings[3]. The most sophisticated algorithm in Open AI, GPT-4, generates safer and more insightful responses[4]. Because of its superior general knowledge and problem-solving skills, it can more accurately tackle complex problems. It is more collaborative and innovative than ever. On activities involving creative and technical writing, it can produce, edit, and revise alongside users[5]. Google Bard is a similar experimental conversation AI service that is powered by Language Model for Dialogue Applications. It draws on information from the Web to provide fresh, high-quality responses to queries[6].

Errors in medication administration pose a serious risk to patients, especially in the emergency room. In this situation, over-dosage has been recognized as the most frequent drug mistake. Approximately 20% of IV medication orders differed by more than 10% from the suggested dose according to research done with emergency medicine residents[7]. One-third of pharmaceutical errors in hospitals involved patients under the age of 18, with newborns accounting for half of the occurrences according to a different study on numeracy errors in hospitals. Overdoses were the most common mistake type, mostly occurring *via* parenteral (IV) (77%) or oral (20%) routes[8]. Research also examined critical-care nurses' knowledge and its relationship to medication errors, identifying risk areas such as antibiotic administration intervals, high-risk medication dilution, concentration, infusion-rate errors, and administration of medications *via* nasogastric tubes [9,10]. In the context of pediatric residents, a study demonstrated that a substantial number of trainees made drug dose calculation errors, including life-threatening mistakes. Interestingly, there was no correlation between training length and the likelihood of errors[11].

LLMs, like ChatGPT and Bard, have the potential to help medical professionals minimize dosage errors by acting as knowledgeable resources that improve healthcare providers' understanding of dosage calculations and reduce errors from misinterpretation or insufficient knowledge. In this context, our study evaluates the reliability of LLMs, namely ChatGPT 3.5, ChatGPT 4, and Google's Bard, in providing accurate drug dosage information per Harrison's Principles of

Internal Medicine. The goal is to determine the credibility of these AI systems in minimizing dosage errors in clinical practice. Ultimately, the study aims to evaluate their ability to enhance patient safety and treatment efficacy by reducing dosage errors.

MATERIALS AND METHODS

To conduct a thorough and comparative evaluation of the reliability of AI systems in supplying medical drug dosages, a comprehensive methodology was followed. Initially, data regarding the use of drugs, their dosages, and routes of administration for various medical conditions were meticulously gathered from the 21st edition of Harrison's Principles of Internal Medicine[12]. This established a robust foundation for accuracy comparison. The next step involved the construction of queries in a natural language format. These queries were designed to closely mimic how medical professionals might inquire about drug dosages and administration in real-world scenarios. This approach ensured the relevance and applicability of the AI systems' responses to practical medical situations.

For the actual interaction with the AI systems, three platforms were selected: ChatGPT 3.5, ChatGPT 4, and Google's Bard. Each system was presented with an identical set of questions. The responses were then collected systematically for subsequent analysis. The evaluation of these responses was based on a 3-point Likert scale. Responses were scored as +1 for correct responses that aligned accurately with the information in Harrison's Textbook, 0 for neutral responses that were neither fully correct nor incorrect, and -1 for incorrect responses that contained misinformation or significant inaccuracies.

For data analysis, Python, along with its associated libraries such as SciPy, NumPy, and Matplotlib, was utilized. The analysis focused on several aspects. Basic statistics involved counting and categorizing the responses from each system and calculating the percentage of affirmative ('Yes') responses. The overall system accuracy was assessed by calculating weighted accuracies using the Likert scale scores. Additionally, disease-specific accuracy and body system accuracy were also analyzed and compared among the systems, providing insights into each system's strengths and weaknesses in various medical domains. The results were then presented in a user-friendly format, employing bar charts and tables for a clear visual representation of the data. This approach allowed for an effective comparative analysis of the performance of the three AI systems across different categories, thus providing a comprehensive understanding of their reliability in medical settings.

RESULTS

When examining the count of each type of response ('Neutral', 'No', 'Yes', which correspond to a score of +1, 0, and -1 respectively) for each system, the total responses for each system were consistent at 462. Among the three systems, GPT 4 demonstrated the highest percentage of 'Yes' responses with a staggering 83.77%. GPT 3.5 trailed closely behind with 77.06% 'Yes' responses, while Bard registered the lowest with 54.76%. Table 1 displays the distribution of 'Yes' responses demarcating the superior performance of GPT 4 relative to its counterparts. Table 2 succinctly represents the comparative performance of each model, indicating that ChatGPT 4 achieved the highest weighted accuracy at 0.6775, followed by ChatGPT 3.5 with 0.5519, and Bard with 0.3745. Figures 1 and 2 depict a bar chart representation of the same.

Upon analyzing the accuracy of different diseases, as illustrated in Table 3 and Figure 3, notable variations were observed. For instance, while all systems exhibited complete accuracy (1.0) in recognizing diseases like 'Acromegaly', 'Myoclonus', and 'Nephrolithiasis', they faltered on others. Notably, 'Myotonic dystrophy' saw a drastic drop in ChatGPT 3.5's accuracy to -1.0, in stark contrast to ChatGPT 4 and Bard, both of which maintained a 1.0 score. At the bottom of the performance spectrum, diseases such as 'Multiple sclerosis' and 'Hypothyroidism' registered -1.0 across both ChatGPT versions, with Bard following suit for 'Multiple sclerosis'.

Table 4 and Figure 4 depict the weighted accuracy evaluation for each organ system. Intriguing results surfaced with 'Cardiovascular system', 'Respiratory system', and 'Hematology' securing full scores across all systems. 'Infectious Diseases' and 'Immune system' showcased noticeable differences across the systems, with Bard especially lagging in the former with a score of 0.2059. The 'Gastrointestinal tract' presented consistent challenges across all systems, with no system surpassing a score of 0.5385.

DISCUSSION

The integration of LLMs like ChatGPT into medical information provision and clinical decision-making has been the focus of recent research. These studies, ranging from benchmarking LLMs against each other to comparing them with physicians and textbooks, provide insights into their potential utility and limitations in healthcare. Our study evaluated the accuracy of ChatGPT 3.5, ChatGPT 4, and Google Bard in providing drug dosage information. ChatGPT 4 achieved the highest correct response rate (83.77%) and weighted accuracy (0.6775), outperforming ChatGPT 3.5 (77.06% correct, 0.5519 accuracy) and Bard (54.76% correct, 0.3745 accuracy). Disease-specific analysis showed perfect scores for 'Acromegaly', 'Myoclonus', and 'Nephrolithiasis' across all systems, but significant variability for others like 'Myotonic dystrophy' and 'Multiple sclerosis'. Organ system analysis indicated high performance in 'Cardiovascular system, respiratory system', and 'Hematology', but lower and variable accuracy in 'Infectious Diseases' and 'Gastrointestinal tract'.

Table 1 Total count and percentage of 'Yes' responses for each Large Language Model

System	Neutral	No	Yes	Total
GPT 4	1	74	387 (83.77)	462
GPT 3.5	5	101	356 (77.06)	462
Bard	129	80	253 (54.76)	462

Data are *n* (%).

Table 2 Weighted accuracy comparison across the Large Language Model

Model	Weighted accuracy
ChatGPT 4	0.6775
ChatGPT 3.5	0.5519
Bard	0.3745

Table 3 Disease accuracy comparison

Name of disease	ChatGPT 4	ChatGPT 3.5	Bard
Acromegaly	1.0	1.0	1.0
Orthostatic hypotension	1.0	1.0	0.0
Myasthenia gravis	1.0	1.0	0.5
Myoclonus	1.0	1.0	1.0
Myotonic dystrophy	1.0	-1.0	1.0
Neonatal onset multisystem inflammatory disease	1.0	1.0	1.0
Neoplastic spinal cord compression	1.0	1.0	1.0
Nephrolithiasis	1.0	1.0	1.0
Neurological infections	1.0	1.0	0.0
Neuromyelitis optica	1.0	0.0	1.0
Thiamine deficiency	-1.0	1.0	1.0
Anaphylactic reaction	-1.0	-1.0	0.0
Reactive arthritis	-1.0	-1.0	0.0
Fibrous dysplasia	-1.0	-1.0	1.0
Hypothyroidism	-1.0	-1.0	-1.0
Multiple sclerosis	-1.0	-1.0	-1.0
Hypophosphatemia	-1.0	-1.0	1.0
Hypomagnesemia	-1.0	-1.0	0.0
Alcohol intoxication	-1.0	-1.0	0.0
Post-concussive state	-1.0	-1.0	0.0

Benchmarking studies

Lim *et al*[13] observed that ChatGPT-4.0 demonstrated superior accuracy (80.6% 'good' responses) in providing information on myopia care, outperforming both its predecessor, ChatGPT-3.5, and Google Bard. Particularly notable was its performance in 'treatment and prevention', along with its self-correction capabilities[13]. Similarly, O'Hagan *et al*[14] found that ChatGPT's responses to queries about Alopecia areata had a mean accuracy score of 4.41 out of 5, with ChatGPT 4.0 performing slightly better than 3.5. This study highlighted the variability of inappropriateness and accuracy based on the nature of the questions. Our study showed similar results, confirming ChatGPT-4.0's superior accuracy and reliability in medical information provision.

Table 4 Detailed accuracy values for each organ system across the three Large Language Model

Organ system	ChatGPT 4	ChatGPT 3.5	Bard
Cardio vascular system, respiratory system	1.0000	0.6667	0.6667
Hematology	1.0000	1.0000	-1.0000
Respiratory	1.0000	0.3333	0.3333
Respiratory system	1.0000	1.0000	0.5000
Infectious diseases	0.8039	0.7451	0.2059
Immune system	0.6752	0.4188	0.2650
Central nervous system	0.6585	0.6220	0.5610
Hematological malignancies	0.6429	0.5714	0.4286
Cardio vascular system	0.6000	0.6667	0.3333
Endocrine system	0.5556	0.4444	0.5714
Renal	0.5556	0.3704	0.5185
Gastrointestinal tract	0.5385	0.2308	0.2308

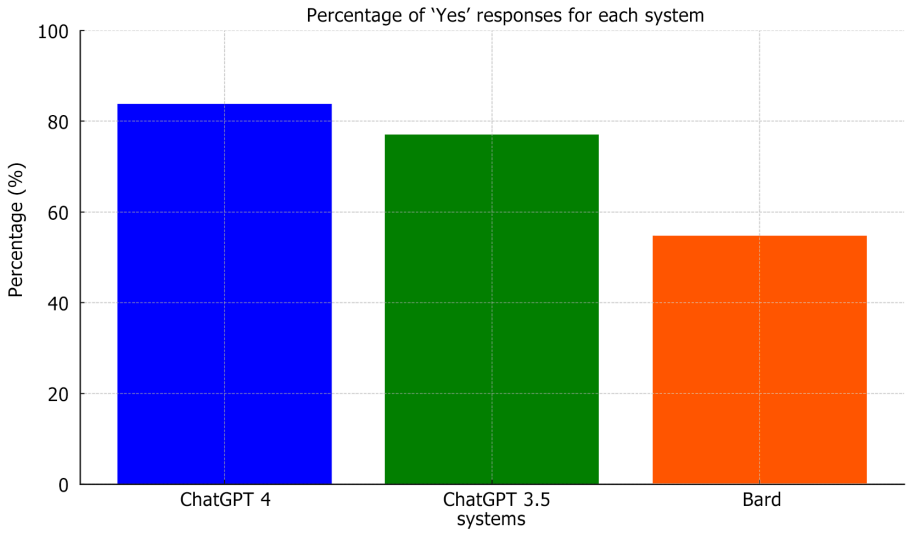

Figure 1 Percentage of 'Yes' responses for each Large Language Model.

Comparative efficacy of ChatGPT and physicians

Contrasting the responses generated by ChatGPT with those provided by medical professionals reveals favorable outcomes. However, the importance of verification with trusted sources and the need for further refinement of these models for clinical use are consistently emphasized across these studies.

Johnson *et al*[15] reported that the responses of ChatGPT to a wide range of medical questions had a median accuracy score of 5.5 on a six-point Likert scale, indicating a high level of correctness. However, they emphasized the need for ongoing research and development for clinical applications[15]. The article by Ramasubramanian S, focused on the application of ChatGPT for enhancing patient safety and operational efficiency in medical settings. The study found that a customized version of the model, text-davinci-003, had 80% accuracy compared to textbook medical knowledge, underscoring its potential as a tool for medical professionals[16].

In the field of endodontics, Mayo-Wilson *et al*[17] assessed the reliability of ChatGPT, finding an overall consistency of 85.44% in responses. The study revealed no significant variations based on question difficulty, although the accuracy rate for simpler queries was lower[17]. Hirosawa *et al*[18] evaluated the diagnostic accuracy of ChatGPT-3, noting an impressive 93.3% accuracy in differential-diagnosis lists for clinical vignettes, albeit slightly lower than the performance of physicians[18]. Hsu *et al*[19] conducted a prospective cross-sectional analysis to assess ChatGPT's accuracy and suitability in medication consultation responses. The study distinguished between real-world medication inquiries and questions regarding the interaction between traditional Chinese and Western medicines. ChatGPT showed a higher appropriateness rate for public medication consultation questions compared to those from healthcare providers in a hospital setting[19]. Finally, Rao *et al*[20] evaluated ChatGPT's effectiveness in clinical decision support, finding an overall accuracy of 71.7% across various clinical vignettes. This study highlighted the model's higher accuracy in making final

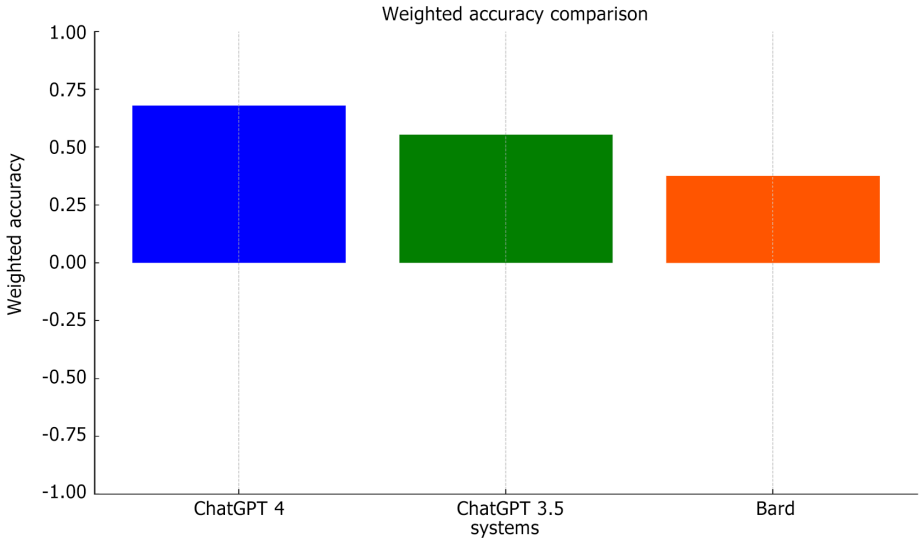

Figure 2 Weighted accuracy comparison across the Large Language Model.

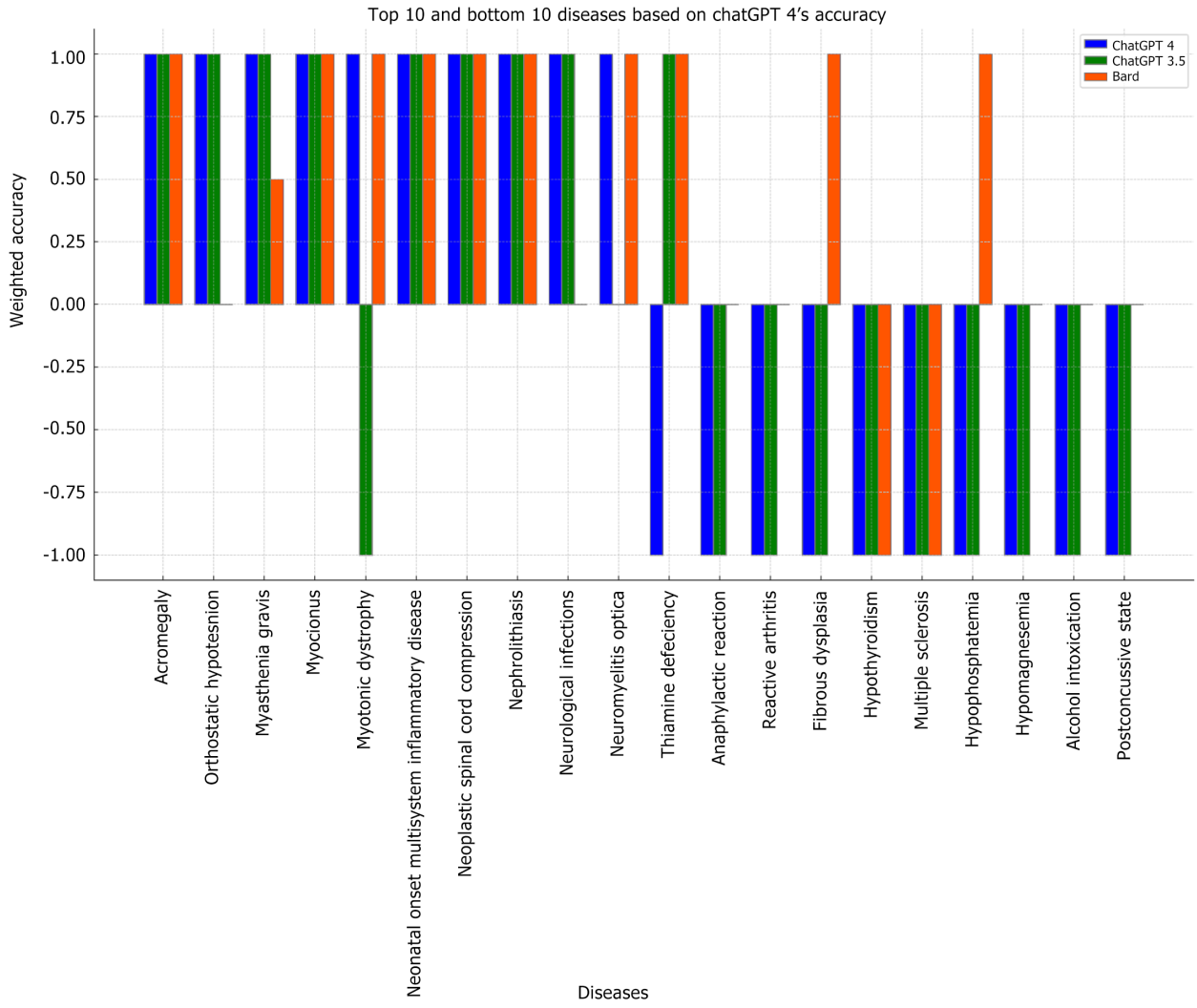

Figure 3 Weighted accuracy for each disease across the three systems (top 10 and bottom 10 based on ChatGPT 4's accuracy).

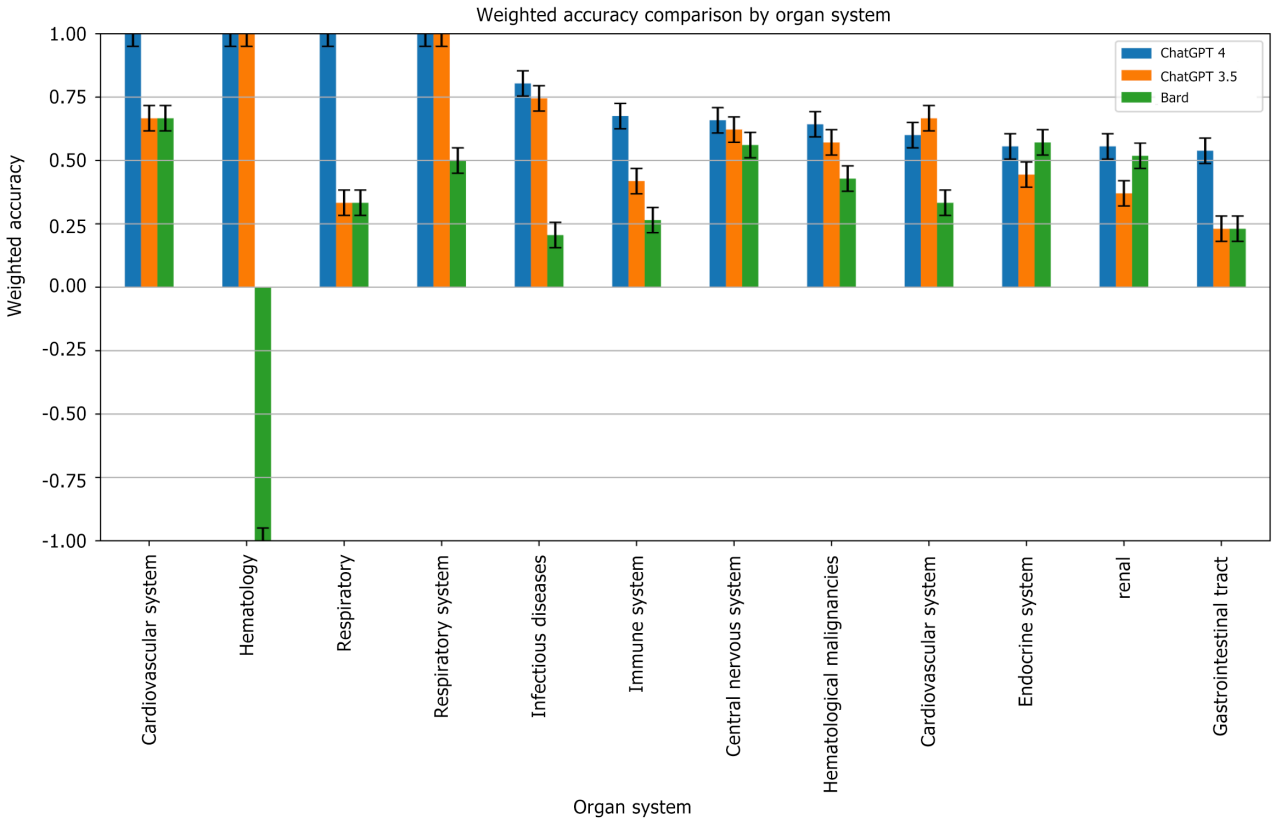

Figure 4 Weighted accuracy for each organ system across the three Large Language Model.

diagnoses compared to initial differential diagnoses and clinical management[20].

These studies collectively indicate a trend towards improved accuracy and appropriateness of responses with newer iterations of ChatGPT. They also highlight the potential of LLMs in supplementing medical professionals, especially in information provision and decision-making processes. Our study aligns with the current discourse on accuracy, showing that ChatGPT 4 achieved the highest rate of correct responses at 83.77% and demonstrated the best overall weighted accuracy of 0.6775 among other LLMs.

ChatGPT exhibits several limitations that warrant consideration (Figure 5). First, continuous improvement and ongoing evaluation are crucial for maintaining and enhancing the accuracy of LLMs, emphasizing the need for further research and model development[13,15,18,21]. Second, not all responses generated by ChatGPT are guaranteed to be accurate, underscoring the recommendation to use the model within the context of a comprehensive evaluation by a licensed healthcare professional and the importance of verifying information with trusted sources[14-16,21-23]. Third, the model may experience hallucinations, and its training data composition remains unclear, leading to errors in its outputs [19,20,24,25]. Lastly, reservations regarding ethics, legality, privacy, data accuracy, learning, and bias risks pose additional concerns, highlighting the need for vigilant consideration and responsible use of ChatGPT in various applications[24,26].

Several studies have explored the perception and application of ChatGPT in pharmacy practice, addressing pharmacists' opinions, its performance in clinical pharmacy, and its consistency in managing pharmacotherapy cases[22,24,27]. Abu Hammour *et al*[24] found mixed responses among Jordanian pharmacists, with concerns about accuracy, biases, and ethical, legal, and privacy issues[24]. Huang *et al*[27] demonstrated ChatGPT's strong performance in drug counseling but identified limitations in prescription review, patient education, adverse drug reaction recognition, and causality assessment[27]. Al-Dujaili *et al*[22] reported varying accuracy and consistency over time, suggesting potential in generating clinically relevant information but emphasizing the need for ongoing development and evaluation in pharmacy practice[22]. Despite the promise, pharmacists' concerns highlight the importance of cautious integration of AI technologies in healthcare. Wang *et al*[28] examined ChatGPT's potential in public health initiatives in low- and middle-income countries, highlighting its accessibility and benefits for health literacy and training. The study raised concerns about variable performance, accuracy, safety, and regulatory needs, emphasizing domain-specific pre-training, privacy, data protection, and ethical considerations, advocating for a cautious, expert-supported approach[28].

Recent studies highlight the potential of AI models in identifying and predicting drug-drug interactions (DDIs) and comparing their performance to human healthcare professionals. Al-Ashwal *et al*[21] found that ChatGPT-3.5 had the lowest accuracy (0.469), with slight improvements in ChatGPT-4, while Microsoft Bing AI was the most accurate, outperforming ChatGPT-3.5, ChatGPT-4, and Bard. ChatGPT models identified more potential interactions but had higher false positives, negatively affecting accuracy and specificity[21]. Juhi *et al*[29] reported that ChatGPT accurately identified 39 out of 40 DDI pairs consistently across question types but noted that responses were above the recommended reading level, suggesting a need for simplification for better patient comprehension[29].

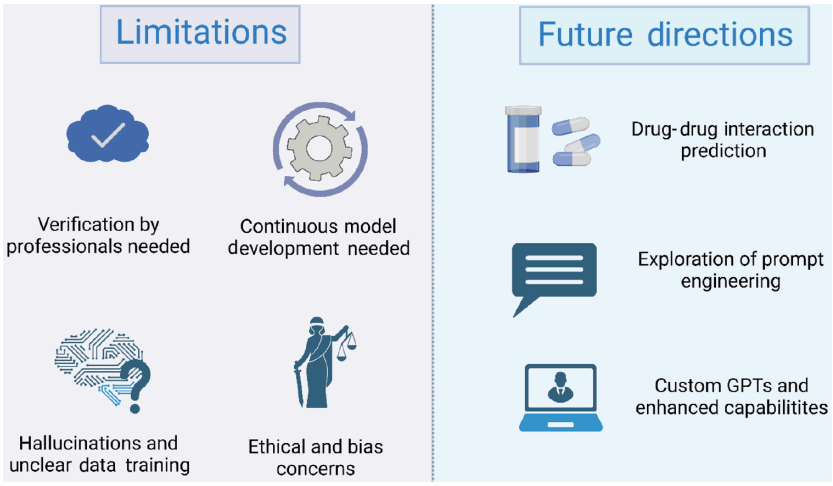

Figure 5 Limitations and future avenues of research of Large Language Model.

Shin's study systematically explores the use of appropriate prompt engineering while evaluating ChatGPT's performance in tasks related to pharmacokinetic data analysis, including report writing, code generation, and problem-solving. While ChatGPT displayed satisfactory proficiency in generating reports and code related to pharmacokinetics, it exhibited notable errors in numerical calculations involving exponential functions. The model's outputs were characterized by variability and lacked reproducibility for the same prompt. Although prompt engineering strategies were effective in reducing errors, they did not eliminate them[25].

Open AI has recently introduced a feature enabling users to create customized versions of ChatGPT by blending specific instructions, additional knowledge, and a combination of desired skills. Additionally, they have unveiled the GPT-4 Turbo model, which boasts enhanced capabilities, cost-effectiveness, and support for a 128K context window[30,31]. Google recently introduced a novel AI model named 'Gemini,' exhibiting capabilities comparable to GPT-4. Distinguished by its multimodal functionality, Gemini possesses the capacity to adeptly generalize and seamlessly comprehend, manipulate, and integrate diverse forms of information encompassing text, code, audio, images, and video [32,33].

As depicted in Figure 5, the advancing field of AI models in DDI prediction and the exploration of prompt engineering and custom GPTs represent promising avenues for further research and development. Continued investigations into these areas hold the potential to enhance the accuracy, specificity, and overall capabilities of AI tools in healthcare settings, contributing to improved patient care and safety.

CONCLUSION

Our research offers insights into the accuracy of AI systems (ChatGPT 3.5, ChatGPT 4, and Google Bard) in providing drug dosage information aligned with Harrison's Principles of Internal Medicine. ChatGPT 4 surpassed the other systems, demonstrating the highest rate of accurate responses and achieving the highest overall weighted accuracy. Nonetheless, the variability observed in disease-specific and organ system accuracies across different AI platforms highlights the ongoing need for refinement and development. While ChatGPT 4 demonstrates superior reliability, continuous improvement is essential to ensure consistent accuracy in diverse medical scenarios. These findings affirm the promising role of AI in supporting healthcare professionals, emphasizing the critical importance of enhancing AI systems' accuracy for optimal assistance in crucial medical contexts.

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FOOTNOTES

Author contributions: Ramasubramanian S, Balaji S conceived and designed the study and drafted the manuscript (original and revision); Jeyaraman M and Migliorini F supervised the study and drafted the manuscript (revision); Jeyaraman M, Migliorini F, and Sharma S drafted the manuscript (revision); Ramasubramanian S, Balaji S, Kannan T contributed to drafting (original); Ramasubramanian S, Migliorini F, Balasubramaniam S, Jeyaraman N conducted visualizations and data analysis; All authors have agreed to the final version to be published and agree to be accountable for all aspects of the work.

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Country of origin: India

ORCID number: Swaminathan Ramasubramanian 0000-0001-8845-8427; Sangeetha Balaji 0000-0002-1566-1333; Tejashri Kannan 0009-0009-6400-5488; Naveen Jeyaraman 0000-0002-4362-3326; Shilpa Sharma 0000-0001-8695-8372; Filippo Migliorini 0000-0001-7220-1221; Madhan Jeyaraman 0000-0002-9045-9493.

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SYSTEMATIC REVIEWS

Palliative care for end-stage liver disease and acute on chronic liver failure: A systematic review

Vakaola I Pulotu Mafi, Jonathan Soldera

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Vakaola I Pulotu Mafi, Jonathan Soldera, Post-Graduate Program, Acute Medicine, University of South Wales, Cardiff CF37 1DL, United Kingdom

Corresponding author: Jonathan Soldera, MD, MSc, PhD, Instructor, School of Acute Medicine and Gastroenterology, University of South Wales, Llantwit Road, Pontypridd, Cardiff CF37 1DL, United Kingdom. jonathansoldera@gmail.com

Abstract

BACKGROUND

End stage liver disease (ESLD) represents a growing health concern characterized by elevated morbidity and mortality, particularly among individual ineligible for liver transplantation. The demand for palliative care (PC) is pronounced in patients grappling with ESLD and acute on chronic liver failure (ACLF). Unfortunately, the historical underutilization of PC in ESLD patients, despite their substantial needs and those of their family caregivers, underscores the imperative of seamlessly integrating PC principles into routine healthcare practices across the entire disease spectrum.

AIM

To comprehensively investigate the evidence surrounding the benefits of incorporating PC into the comprehensive care plan for individuals confronting ESLD and/or ACLF.

METHODS

A systematic search in the Medline (PubMed) database was performed using a predetermined search command, encompassing studies published in English without any restrictions on the publication date. Subsequently, the retrieved studies were manually examined. Simple descriptive analyses were employed to summarize the results.

RESULTS

The search strategies yielded 721 references. Following the final analysis, 32 full-length references met the inclusion criteria and were consequently incorporated into the study. Meticulous data extraction from these 32 studies was undertaken, leading to the execution of a comprehensive narrative systematic review. The review found that PC provides significant benefits, reducing symptom burden, depressive symptoms, readmission rates, and hospital stays. Yet, barriers like the appeal of transplants and misconceptions about PC hinder optimal utilization. Integrating PC early, upon the diagnosis of ESLD and ACLF, regardless of

transplant eligibility and availability, improves the quality of life for these patients.

CONCLUSION
Despite the substantial suffering and poor prognosis associated with ESLD and ACLF, where liver transplantation stands as the only curative treatment, albeit largely inaccessible, PC services have been overtly provided too late in the course of the illness. A comprehensive understanding of PC's pivotal role in treating ESLD and ACLF is crucial for overcoming these barriers, involving healthcare providers, patients, and caregivers.

Key Words: End stage liver disease; Acute on chronic liver failure; Palliative care; Liver transplantation; Quality of life

Core Tip: This systematic review addresses the underexplored utilization of palliative care (PC) in patients with end stage liver disease (ESLD) and acute on chronic liver failure (ACLF), a demographic traditionally underserved. ESLD and ACLF are characterized by grim prognoses, substantial care costs, explicit patient suffering, and elevated mortality rates. Despite liver transplantation (LT) being a curative option, accessibility remains severely limited due to barriers such as donor scarcity, financial constraints, and inadequate social support. Even among those eligible for transplantation, a significant majority of ESLD patients are referred late for PC, typically within their final couple of weeks of life. PC offers notable benefits, including amelioration of symptom burden, reduced depressive symptoms, lower readmission rates, and shorter hospital stays. However, optimal utilization of PC faces barriers such as the allure of transplants and misconceptions about PC. A comprehensive understanding of the pivotal role of PC in ESLD and ACLF treatment is crucial for all stakeholders, including healthcare providers, patients, and caregivers, to overcome these barriers. Future prospective randomized studies, irrespective of LT eligibility, are needed to strengthen the evidence supporting early integration of PC in the management of ESLD/ACLF patients.

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INTRODUCTION

Patients suffering from decompensated liver cirrhosis or end-stage liver disease (ESLD) manifest a diverse prognosis, which has demonstrated improvement since the early 2000 s. This positive trend is ascribed to an estimated reduction of around 15% in mortality rates. The decline in mortality is a consequence of the elucidation and comprehension of acute on chronic liver failure (ACLF) and the increased accessibility of emergency liver transplantation (LT) for these patients [1].

ACLF, as expounded in a widely acknowledged prospective observational study encompassing 1343 cirrhosis cases known as ACLF in cirrhosis, delineates a syndrome characterized by the presence of acutely decompensated cirrhosis (DC) or ESLD, intertwined with the failure of multiple organs. This is accompanied by a noteworthy short-term mortality rate of ≥ 15% within 28 days[2].

The classification of ACLF is predicated on the extent of organ failure and the corresponding prognosis. This classification includes grade -1 (involving one organ failure, with a 28-day mortality rate of 22%), grade 2 (entailing two organ failures, with a 28-day mortality rate of 32%), and grade 3 (involving three or more organ failures, with a 28-day mortality rate of 73%). Moreover, patients with acute decompensation (AD) classified as non-ACLF exhibit an overall short-term mortality rate of 1.9%[2-5].

It is noteworthy that approximately half of the patients diagnosed with ACLF lack a previous history of DC. However, these patients manifest a more severe manifestation of the disease compared to those with a prior history of decompensation[4]. The significance of these findings lies in their implications for understanding and managing the prognosis of patients with decompensated liver cirrhosis or ESLD, highlighting the critical role of organ failure assessment in predicting short-term mortality.

The contemporary understanding of the pathophysiological mechanisms underlying ACLF revolves around systemic inflammation as the cornerstone of its development. In contrast, ESLD or AD is considered a progression from its early asymptomatic state, termed compensated cirrhosis[1,2]. LT emerges as the exclusive curative option for individuals afflicted with either ESLD or ACLF[4]. However, the clinical implementation of this therapeutic intervention encounters various limitations attributable to factors such as elevated costs, which disproportionately impact developing nations, a scarcity of available donors, immunological rejection, disease or malignancy progression while on the transplant waiting list, active substance misuse, septic conditions, and involvement of extrahepatic organs[4].

Each patient diagnosed with ESLD and ACLF should undergo a comprehensive assessment for LT because of the significantly heightened 90-day mortality rates exceeding 20%. This imperative evaluation serves as a critical determinant in the overall management and decision-making process for patients grappling with these severe liver conditions. The recognition of these multifaceted factors underscores the complex landscape surrounding LT, necessitating a nuanced and comprehensive approach to address the diverse challenges associated with this life-saving procedure[1,2,4].

Patients diagnosed with ACLF grade 2 and grade 3 require immediate LT, given the substantial risk of short-term mortality, which escalates to 57% and 87%, respectively[2-5]. The attending physician might also consider a palliative care (PC) consultation in such a grim scenario. Historically, the utilization of PC services in managing patients with ESLD and ACLF has been found to be inadequate, primarily attributed to either sheer ignorance or a failure to comprehend the full spectrum of the underlying liver condition's progression[1-3].

PC constitutes an interdisciplinary medical approach that places emphasis on delivering the highest quality of life by optimizing symptom control and providing comprehensive psychosocial, spiritual, and practical support to both patients and their caregivers[3,4,6]. In the specific context of ESLD and ACLF, PC emerges as an alternative therapeutic avenue for patients deemed unsuitable for LT. The integration of PC into the overall management strategy acknowledges the multifaceted needs of these patients, addressing not only the physical symptoms but also the broader aspects of their well-being, ensuring a holistic and patient centered approach to care[2-5].

The intrinsic unpredictability that characterizes the trajectory of ESLD and ACLF underscores the rationale for the early integration of PC into the overall management framework. This proactive approach serves to alleviate the symptomatic toll associated with the condition, acknowledging the dynamic and evolving nature of ESLD and ACLF[3, 4]. It is imperative that all patients grappling with ESLD and ACLF receive timely referral for PC consultation, encompassing both those awaiting LT and those for whom LT is deemed unsuitable due to illness or contraindications[4].

The challenges associated with providing PC services to ESLD and ACLF patients are multifaceted. These challenges include disparities in PC accessibility among individuals from low socioeconomic strata, insufficient referrals to PC services owing to the fluctuating course of ESLD, misconceptions regarding the role of PC, and an inability to pinpoint clinical triggers for PC consultation, such as the emergence of ascites and complications stemming from portal hypertension[3,4,6]. In ESLD patients awaiting LT, marked relief in symptom burden through the strategic integration of PC referrals within the routine outpatient assessment for those awaiting LT has been demonstrated[6].

This systematic narrative review delves into evidence-based literature, critically examining the advantages of integrating PC into the comprehensive management of patients with ESLD and/or ACLF. Through a meticulous analysis of the driving forces yielding heightened quality of life and the clinical justification for PC consultation referrals within this patient cohort, this review aims to contribute valuable insights to the evolving landscape of ESLD and ACLF management.

MATERIALS AND METHODS

This narrative systemic review was meticulously conducted in strict adherence to the rigorous guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[7,8].

Data sources

In formulating the search strategy, the command employed was as follows: ("end-stage liver disease" OR "ESLD" OR "cirrhosis" OR "acute on-chronic liver failure" OR "liver transplantation" OR "ACLF") AND ("palliative care" OR "end-of-life care" OR "hospice care" OR "palliative medicine" OR "comfort care"). The searches were conducted in September 2023, utilizing the electronic databases Medline (PubMed) and Google Scholar.

No constraints were placed on the date of publication, facilitating a thorough exploration of both historical and contemporary literature. However, language restrictions were implemented, confining the search to studies published in the English language. The inclusion of studies in the review adhered to the predefined Patients, Intervention, Comparison, Outcome criteria, ensuring a methodologically rigorous selection process.

Inclusion and exclusion criteria

For this systematic review, studies focusing on patients with ESLD exhibiting evidence of at least one of the following criteria were considered for inclusion: Liver cirrhosis accompanied by a clinical manifestation of decompensation; liver cirrhosis designated for LT; liver cirrhosis undergoing evaluation for LT; liver cirrhosis characterized by a Child-Turcotte-Pugh (CTP) classification predominantly falling within category B or C within the study's cohort (Child A ≤ 40%, or mean/median CTP score > 7); patients depicted with chronic and advanced liver ailments referred for LT evaluation.

On the other hand, studies were excluded if they were composed in languages other than English, involved participants below 18 years of age, pertained to acute hepatic failure, focused on metabolic liver disorders, included patients awaiting both liver and kidney transplantation, constituted editorials, comments, and anecdotal reports, or involved a combination of cirrhotic and non-cirrhotic subjects. Additionally, failure to access the complete texts of studies or inherent elevated bias risk served as grounds for exclusion.

Study selection and data extraction

The initial screening of studies retrieved through the search command, focusing on titles and abstracts, aimed to discern papers aligned with the predefined inclusion criteria. It was imperative to exclude studies that did not adhere to the inclusion criteria, particularly those categorized as reviews and guidelines. This rigorous screening process ensured the

selection of studies that distinctly met the criteria, fostering precision and relevance in the ensuing stages.

Following the preliminary screening, the abstracts of the short-listed studies underwent a comprehensive review to ascertain their potential relevance to the research objectives. This step involved a meticulous evaluation to further refine the selection, considering the depth and specificity of each study in relation to the research focus.

The final screening phase involved a detailed assessment of the full-length papers, emphasizing the meticulous elimination of studies that did not align with the predefined inclusion criteria. This thorough scrutiny aimed to uphold the scientific rigor of the study by ensuring that the selected papers contribute meaningfully to the research objectives.

Subsequently, a comprehensive analysis of each eligible study was conducted, facilitating the standardized extraction of essential data encompassing population characteristics, study design, structural elements, results, and a concise summary. This systematic data extraction process served as a foundation for the subsequent quantitative and qualitative analysis.

The extracted data was meticulously tabulated to facilitate a structured and organized representation, enabling the identification of emerging trends and patterns within the selected studies.

RESULTS

The search strategy yielded a total of 731 references. To refine the pool of potential studies, 34 records identified as reviews during the title review stage were promptly excluded, leaving 697 records for subsequent titles and abstracts screening. During this phase, adhering strictly to the predefined inclusion criteria, 101 records emerged as eligible, advancing to the next stage for full-text retrieval. Notably, 591 records were excluded during the title and abstract screening due to a lack of alignment with the inclusion criteria.

As part of the comprehensive evaluation, full-text retrieval was conducted for the 101 eligible records and 20 records were excluded at this stage due to unavailability in full text, leaving 81 reports for in-depth analysis. Within this stage, a rigorous application of the inclusion criteria led to the exclusion of 50 papers, ensuring the final selection of studies closely aligned with the research objectives.

The subsequent data extraction phase involved 31 studies, the detailed outcomes of which are presented in Table 1. To provide a visual representation of the search strategy, a PRISMA flow diagram, depicted in Figure 1, elucidates the sequential stages of study selection and exclusion. This graphical representation serves as a transparent and comprehensive overview of the search process.

Experimental studies

Two experimental studies in patients with ESLD assessed the impact of specialist PC interventions. Shinall *et al*[9] conducted a randomized controlled trial (RCT) revealing that patients receiving PC had a lower hazard of readmission [hazard ratio (HR) = 0.36, 95%CI: 0.16-0.83, P = 0.017] and more days alive outside hospital (odds ratio = 3.97, 95%CI: 1.14-13.84, P = 0.030). However, this trial faced enrollment issues, ending prematurely with only 34% participation[9]. Bauman *et al*[6] highlighted underutilization of PC due to a lack of appropriate assessment tools for ESLD symptoms. They introduced an early PC intervention (EPCI), showing a 50% reduction in symptom burden (P < 0.05) and 43% reduction in depressive symptoms in ESLD patients awaiting LT. Limitations included a small sample size and limited follow-up, suggesting a need for future studies with larger samples and longer follow-up to validate EPCI benefits[6].

Observational-retrospective studies

Several retrospective observational studies focused on assessing PC utilization and outcomes in patients with ESLD and related conditions were reviewed.

Gupta *et al*[10] found that inpatient PC consultation reduced 30-day readmission rates and hospital stays in alcohol-associated liver disease patients with ACLF scores ≥ 2, despite study limitations due to its retrospective nature. This study highlights the impact of PC on reducing healthcare utilization in specific ESLD subgroups.

Poonja *et al*[11] highlighted that many DC patients declined or delisted for LT were infrequently referred for PC, emphasizing the need for better symptom management tools and LT-PC partnership to enhance quality of life. The study identified prevalent symptoms among this patient population, underscoring the unmet need for comprehensive PC.

Lin *et al*[12] demonstrated machine learning's predictive capabilities in managing ESLD, aiding in mortality prediction and patient classification for acute or PC needs, with implications for wider use and validation across ethnicities. This study introduces innovative technology for improving risk stratification and personalized care in ESLD.

Puentes *et al*[13] revealed critical mortality rates among ESLD patients, emphasizing the practical use of Child-Pugh and MELD-Na scores for identifying PC candidates. These scoring systems serve as valuable tools for PC decision-making in ESLD.

Hudson *et al*[14] proposed prognostic screening tools for early intervention in cirrhotic patients upon hospital admission, offering a universally applicable strategy. This study proposes a practical approach to identifying high-risk ESLD patients for timely intervention.

Medici *et al*[15] emphasized the MELD score's potential utility for implementing PC, with acknowledgment of retrospective study limitations. The MELD score emerges as a practical clinical tool for guiding PC referrals in ESLD patients.

Deng *et al*[16] linked frailty to symptom burden in cirrhosis patients, highlighting the need for comprehensive assessment and PC co-management. This study underscores the importance of holistic care in managing frail ESLD patients.

Table 1 Summary of data extracted from the systemically reviewed references

Ref.	Population	Study design	Structure	Results	Conclusion
Bauman *et al* [6], 2015	79 ESLD patients referred for LT evaluation or awaiting transplant between July 2013 and May 2014	Longitudinal, multidisciplinary, EPCI for one week pre-transplant evaluation with outpatient consultations following national guidelines. GOC discussed with patients and families until October 2014	Patients underwent EPCI with formal assessments of depression, liver-specific symptoms, psychosocial well-being, and spiritual health	Post-EPCI, there was a significant 50% reduction in symptom burden ($P < 0.05$) and a 43% decrease in depressive symptoms ($P = 0.003$). Patients with moderate to severe symptoms showed greater improvement. Assessment tools included ESAS, EPCI, and quality of life	Palliative care is underused in ESLD due to a lack of suitable distress assessment tools. EPCI effectively improves symptom burden and mood in ESLD patients awaiting transplant
Shinall *et al* [63], 2019	Patients with ESLD admitted to an urban, academic referral center. Total patients: 398293	RCT	Inclusion criteria involved ESLD diagnosis and expectation of potential mortality within 1 year. Patients were randomized into usual care or PC intervention groups with primary and secondary outcome assessments over 6 months	Among 293 eligible patients, 63 were enrolled in the RCT (31 in intervention, 32 in control). PC intervention showed reduced readmission risk (HR = 0.36, $P = 0.017$) and more days alive outside the hospital (OR = 3.97, $P = 0.030$) compared to control	PC demonstrated extended time before readmission and increased days alive outside hospital, highlighting its benefit for ESLD patients
Gupta *et al* [10], 2022	Patients admitted with decompensated alcohol-associated cirrhosis who received PC consultation	Retrospective multicenter observational study	Analysis included 78 million discharged patients (2007-2014) from national databases with ESLD diagnosis criteria including alcoholic cirrhosis or other cirrhosis with alcohol disorder and decompensation events	Out of 1,421,849 hospitalized ESLD patients, 62782 received PC. Factors like advanced age, lower income, Medicaid coverage, urban location, prolonged hospital stay, and ventilation increased odds of receiving PC. Patients treated in facilities with PC services had lower 30-day readmission rates	Increasing inpatient PC consultation for decompensated ArLD correlates with reduced 30-day readmissions, shorter hospital stays, and lower costs
Poonja *et al* [11], 2014	Adults with ESLD who were removed from or declined LT between January 2005 and December 2010 ($n = 102$)	Retrospective observational study	Primary outcome focused on DC patients referred and receiving PC Secondary outcomes included time from LT decline to death, rehospitalizations, ICU admissions, and place of death	Common reasons for LT removal or decline included noncompliance/substance abuse (26%) and severe illness/organ dysfunction (25%). Among delisted patients, 17% required renal replacement therapy, 48% had ICU admissions (median 14 days), but only 11% were referred for PC	Patients with DC declined or delisted from LT have low rates of PC referral (11%) and unclear GOC. Collaboration between LT and PC services can enhance quality of life for this patient group
Patel *et al* [25], 2017	Hospitalized adults with terminal DC (ESLD). Total patients: 59887	Cross-sectional observational study patient cohort	ESLD patients were identified using ICD-9 codes. Main outcomes included PC consultation rates during terminal hospitalization and total incurred costs, alongside demographic and comorbidity data	29.1% of hospitalized ESLD adults received PC with an average cost of $49167. Urban residents had higher PC rates, while African Americans, Hispanics, and Asians had lower rates (racial disparity). PC was associated with reduced procedure burden and cost savings of $8892	PC consultation during terminal hospitalization for ESLD is linked to cost reduction and lower procedure burden, despite racial disparities in PC access
Ufere *et al* [26], 2019	Hepatologists and gastroenterologists (396) providing care for patients with ESLD	Cross-sectional observational study patient cohort	Survey of AASLD members assessing barriers to PC and ACP delivery in ESLD patients	Most respondents (95%) cited cultural factors as a barrier to PC delivery, followed by unrealistic expectations (93%) and time constraints (91%). ACP barriers included communication issues (84%) and lack of cultural competency training (81%)	Substantial barriers hinder PC and ACP services for ESLD patients according to hepatologists and gastroenterologists. Strategies are needed to improve timely and high-quality end-of-life care for these patients
Patel *et al* [27], 2021	Study included 88 participants: 46 LT center physicians and 42 decompensated cirrhotic patients from 3 LT centers	Qualitative study using face-to-face semi-structured interviews	Interviews conducted with ESLD patients meeting specific criteria (consent, age 18 +, English proficiency, cirrhosis diagnosis, and specific symptoms) and clinicians (transplant hepatologists, surgeons, coordinators, social workers) exploring aspects of ACP	Study identified five themes related to ACP experiences: (1) Patients often considered values and preferences outside of clinical visits; (2) Optimism from transplant teams hindered discussions about dying; (3) Clinicians used discussions about death to encourage behavioral change; (4) Transplant teams avoided discussing	Decompensated cirrhotic patients lack adequate ACP throughout their illness trajectory, leading to overly aggressive end-of-life treatments. This highlights the need for improved ACP practices in this population

				nonaggressive treatment options; and (5) Surrogate decision-makers lacked preparation for end-of-life decisions	
Lin *et al*[12], 2020	Total of 903 patients: 214 from Wang Fang Hospital and 689 from Taipei Medical University	Retrospective cohort study	Inclusion criteria: Adults (> 18 years) with CLD and specific conditions, with EMR data available within 24 hours of admission. Exclusion criteria included pregnancy, cancer, and LT history	ESLD patients were categorized into acute death (within 30 days), PC (death within 1-9 months), and survived. Overall mortality rates were 283% in the training set and 22.6% in the validation set	Machine learning monitoring systems offer a comprehensive approach to assessing ESLD patient conditions. Supervised machine-learning models demonstrate superior predictive performance compared to traditional statistical methods
Vieira da Silva *et al* [22], 2023	ESLD patients presenting to a university hospital and LT center from November 2019 to September 2020	Prospective observational single-center study	Study excluded patients with previous LT, isolated acute liver failure, or another terminal disease (except hepatocellular carcinoma, HCC). PC criteria screening used the NECPAL CCOMS-ICO tool to identify patients needing PC and predicting mortality. Specific PC needs were assessed using the IPOS questionnaire for symptoms and mood	Among 54 patients, 9.3% were on the LT waiting list and 14.8% were under evaluation. NECPAL CCOMS-ICO identified 42.6% needing PC. Clinicians identified functional markers and comorbidities (47.8%) as indicating PC needs. IPOS identified multiple needs, with weakness (77.8%), reduced mobility (70.3%), and pain (48.1%) being prominent	All ESLD patients, including those awaiting transplantation, demonstrated significant PC needs. This highlights the importance of addressing PC needs across all stages of ESLD care
Beck *et al* [28], 2016	Survey conducted among 200 LT patients	Qualitative survey study	Web-based survey evaluating attitudes of LT providers and barriers to PC for patients. Examined variables included provider attitudes toward symptom management and documentation practices	Response rate was 44% (88/200). Providers agreed that LT and PC are not mutually exclusive (86%). Most suggested PC referral when death is imminent (78%). Many providers recognized patient depression (66%), but fewer consulted PC for depression (28%). Attending physicians were identified as the main barrier to involving PC (84%)	PC in LT patients a ligns with LT goals even during listing. Barriers include confusion over referral criteria
Puentes *et al* [13], 2018	Hospitalized patients with hepatic cirrhosis between January 2015 and December 2016, classified using the Child–Pugh score and MELD/Na score in January 2018	Retrospective study	Child–Pugh score assessed cirrhosis prognosis using specific parameters (TB, Bil, Albumin, PT, ascites, encephalopathy). MELD/Na score predicted survival based on Na, Cr, Bil, and INR	Patients were classified into Child–Pugh Class A (17%), Class B (48.9%), and Class C (34%). MELD/Na scores ranged > 9 (2.15%), 10–19 (46.8%), 20–29 (27.7%), 30–40 (19.1%), and > 40 (4.3%). About 51.1% had MELD/Na > 20. The study showed 59.6% of patients needing PC died within 12 months	Child–Pugh and MELD/Na scores are valuable tools to identify PC needs in liver cirrhosis patients. Early identification and comprehensive care improve quality of life by addressing physical, spiritual, family, and social needs
Hudson *et al* [14], 2017	Study included all emergency admissions with a cirrhosis diagnosis over two distinct 90-day periods (n = 83)	Retrospective study	Patients were assessed for five criteria independently scored by clinicians: (1) Child-Pugh score C; (2) ≥ 2 admissions within last 6 months; (3) Ongoing alcohol use with ArLD; (4) Unsuitability for LT; (5) WHO Performance status 3 or 4. One-year mortality was calculated using cumulative prognostic score out of 5	Analysis of 73 admissions (79.5% male, 63% ArLD, median age 54) showed that presence of ≥ 3 poor-prognosis criteria predicted 1-year mortality with sensitivity, specificity, and positive predictive value of 72.2%, 83.8%, and 81.3%, respectively. This triggered implementation of supportive care interventions	Identifying high-risk cirrhosis patients using specific criteria allows for early implementation of supportive care alongside active management to improve outcomes
Lamba *et al* [21], 2011	Study included 79 LT patients and 104 ESLD patients (n = 183)	Prospective, observational pre/post study	Interdisciplinary PC model integrated into LT service and surgical intensive care unit, focusing on family support, prognosis, and patient preferences (Part I) and interdisciplinary family meetings (Part II) within 72 hours	Baseline group (LT patients) had 21 deaths, and intervention group had 31 deaths. 85% received Part I and 58% received Part II of the intervention. GOC discussions on physician rounds increased significantly during the intervention. Do not resuscitate status increased from 52% to 81%, and withdrawal of life support increased from 35% to 68	Early integration of PC alongside curative care in surgical intensive care unit can improve EOL practices without changing mortality rates in LT patients. Interdisciplinary communication interventions facilitate consensus on GOC for dying LT patients

Medici *et al* [15], 2008	157 ESLD patients admitted to hospice service	Observational retrospective analysis	Recorded patient details included age, gender, main diagnosis, comorbidities, length of hospice stay, and development of ESLD-specific complications during hospice stay (*e.g.*, gastrointestinal bleeding, hepatic encephalopathy, tense ascites with dyspnea). MELD scores were computed at hospice entry and eventual LT	Most patients were male (67.5%) with a mean age of 57 years. Common ESLD causes were alcohol cirrhosis, hepatitis C virus infection, or both. HCC complicated 28% of cases. Common comorbidities included diabetes (18.2%), vasculopathy/hypertension (16.3%), kidney failure (11.3%), and chronic obstructive pulmonary disease (4.4%). A majority (78%) of patients died during the observation period	MELD scores can guide clinician recommendations for hospice care, aiming to increase duration beyond the current median of 2-3 weeks. Hospice referral for high MELD score patients is an effective strategy to enhance care for ESLD patients awaiting transplantation
Deng *et al* [16], 2021	233 adult cirrhosis patients evaluated for LT out patiently from July 1, 2019 to September 30, 2019	Observational retrospective analysis	Patients excluded if severe hepatic encephalopathy or non-English/Spanish speakers. Frailty assessed using liver frailty index. Symptom scores ≥ 4 triggered comprehensive assessment. ESAS score ≥ 7 indicated high symptom burden and decreased functioning. Demographic and clinical data (etiology, HCC, ascites) collected from medical records	Median age 61 years, 43% female. Frailty distribution: 22% robust, 59% pre-frail, 19% frail 38% reported ≥ 1 severe symptom (based on ESAS). Higher frailty associated with increased prevalence of pain, dyspnea, fatigue, nausea, poor appetite, drowsiness, depression, and poor well-being (all $P < 0.05$)	Frailty strongly linked to physical/psychological symptoms (pain, depression) and poor quality of life in cirrhosis patients. Frail cirrhosis patients may benefit from PC co-management to address symptoms and improve quality of life
Jung *et al* [72], 2020	101 patients with liver disease, including HCC and cirrhosis, who completed POLST at general tertiary hospitals in Seoul from February 4, 2018, to August 31, 2018	Retrospective descriptive survey analyzing decision-making practices and outcomes of life-sustaining treatment in ESLD patients with POLST	Case report form based on POLST and EMR, including patient characteristics, POLST details, life-sustaining treatment regimen, treatment outcomes, and withdrawals	63 patients (62.4%) completed their own POLST; 3 patients withdrew (2 for LT, 1 for chemotherapy). Majority were male (81.2%) with an average age of 61.8 years	Emphasizes the importance of considering LT for ESLD patients before deciding on life-sustaining treatment. Supports patient self-determination and highlights the need for effective guidelines in this context
Kathpalia *et al*[17], 2016	The study included 683 adult cirrhotic patients listed for LT at a large United States center from 2013 to 2014	Descriptive retrospective study	The study included adult cirrhotic patients newly listed for LT who either died before transplant or were too ill for transplant. Patients with certain exclusion criteria were not included. Patient demographics, disease etiology, MELD score, education level, Child-Pugh Score, presence of HCC, and insurance type were recorded from EMR	Among the 683 Listed patients, 16% (107) either died (62 patients) or were removed due to clinical decompensation (45 patients) before receiving a LT. The median age was 58 years, and most patients were male (66%), Caucasian (53%), and had Child C cirrhosis (61%) or hepatocellular carcinoma (52%)	PC services are underutilized in older, non-white patients with cirrhosis awaiting LT. Early integration of PC into transplant decision-making is recommended
Adejumo *et al* [69], 2020	The study included 67480 hospitalized patients with ESLD	Retrospective longitudinal analysis of ESLD patients hospitalized from January 2010 to January 2014	The study used a database with a 90-day follow-up after discharge, matching patients who received PC to those who did not (1:1) using propensity scores	Among the ESLD hospitalizations, 5.3% (3485) received PC, showing an annual increase from 3.6% to 6.7%. Average 30- and 90-day readmission rates were 362% and 54.6%, respectively. PC was associated with a lower risk of 30- and 90-day readmission	PC was linked to reduced readmission rates, potentially lessening the burden on healthcare resources and improving cost savings during subsequent readmissions
Low *et al*[68], 2017	The study involved 66 individuals with cirrhosis who died between April 2010 and September 2011, and 22 liver health professionals who participated in focus groups or interviews	This study used mixed methods, including retrospective case note review, qualitative focus groups, individual interviews, and qualitative focus group discussions	Researchers selected 30 out of the 66 deceased individuals with cirrhosis for data collection from their records in the 12 months before death. Additionally, semi-structured interviews and focus groups were conducted with health professionals involved in care	The study highlighted high rates of hospital admissions and symptom burden among participants with cirrhosis. Clinicians demonstrated reluctance to discuss prognosis or future care preferences due to lacking skills and confidence, resulting in delayed provision of PC	People with cirrhosis experience unpredictable disease trajectories marked by frequent hospitalizations and worsening symptoms nearing death. The study recommends implementing clinical tools to identify irreversible deterioration and fostering collaboration between liver services and PC to enhance care quality
Walling *et al* [58], 2015	The study compared 49 hospitalized veterans to 61 pre-quality improvement project veterans	This was a comparative study that retrospectively evaluated PC consultation rates among care management recipients	Veterans with cirrhosis were identified using specific ICD-9 codes and screened for ESLD based on medical records at a VA hospital. A care coordinator followed veterans from	During the intervention period, hospitalized veterans were more likely to be considered for LT (77.6% *vs* 31.1%, $P < 0.001$) and to receive PC consultation, though the latter finding did not reach statistical significance	Active case finding increased consideration for LT without reducing PC consultation rates

		compared to a prospective cohort of LT identified using the same ICD-9 codes and screening criteria over a one-year period	hospitalization through April 2013, encouraging LT evaluation consults for those with a MELD ≥ 14 and PC consults for those with a MELD ≥ 20 or inoperable HCC	(62.5% *vs* 47.1%, $P = 0.38$)	
Donlan *et al* [29], 2021	The study involved ESLD patients and their informal caregivers	This was a qualitative study involving semi-structured interviews with 15 ESLD patients and 14 informal caregivers	Interviews were conducted by a team including a gastroenterologist, study coordinator, psychologist, and oncologist, aiming to explore participants' perceptions of PC and when it should be introduced to ESLD patients	Transplant-listed patients were concerned that PC referral might impact their chance of receiving a LT. Most participants felt that ESLD patients should learn about PC soon after diagnosis	Study participants often equated PC with hospice care initially. However, after receiving education on PC, nearly all participants, including transplant-eligible and ineligible patients, supported the early introduction of PC in ESLD care
Shinall *et al* [9], 2022	The study included 24 participants from 11 institutions across the United States and Canada who participated in three focus groups	The study involved qualitative analysis of transcripts from provider focus groups followed by a community engagement studio with patients and caregivers	Three Zoom focus groups were conducted with hepatologists and PC specialists using open-ended questions. Qualitative data coding and analysis were performed following COREQ guidelines by the Vanderbilt University Qualitative Research Core, led by a PhD-level psychologist	The focus groups identified elements of specialist PC beneficial for LT patients. They also highlighted barriers to integrating PC, such as role boundaries, differences in clinical cultures, limited time and staff, and competing goals and priorities	Hepatologists, PC specialists, patients, and caregivers identified key barriers in LT patient care that specialist PC could address, including role boundaries, clinical culture differences, limited resources (time and staff), and conflicting priorities
Tombazzi *et al*[62], 2022	The study included all patients discussed in the LTC at an academic medical center in the United States between August 2018 and May 2020, totaling 769 patients	This was a retrospective descriptive study followed by cohort analysis	Out of 135 patients declined for LT, 37 (27%) received a referral to PC. Data collected included baseline demographics, MELD score, decompensation events, and reasons for transplant ineligibility. Primary outcome was PC referral, and secondary outcomes included survival from LTC decision, time from LTC decision to PC referral, and code status at PC referral	Among 769 patients discussed at LTC, 135 were declined for transplantation, and 37 (27%) received a PC referral. Patients with higher MELD scores (21-30 and > 30) had significantly higher odds of PC referral compared to those with MELD score < 20	Only a minority (27%) of patients declined or delisted for LT were referred to PC. MELD score and degree of decompensation were important factors associated with PC referral. Further exploration of this data is needed to inform future studies and establish criteria and timing for PC referral
Holden *et al* [73], 2020	The study included 397 patients with DC admitted to Indiana University Hospital in 2012	Retrospective cohort study	Patients were identified using EMR and confirmed for cirrhosis through manual chart review. Exclusions were patients under 18 years and those with prior LT. Primary outcome: Referral to PC. Secondary outcomes included hospitalization duration, medical interventions, code status limitations, LT, and mortality	Among 397 patients, 61 (15.4%) were referred to PC, 71 (17.9%) to hospice, and 99 (24.9%) to PC and/or hospice. Within one year, 50.4% of patients died. Referrals to PC and hospice were predominantly late, with 68.5% and 62.7% respectively	PC and hospice services are underutilized for patients with DC, with most referrals occurring late. Referral to PC was associated with increased comorbidity, while hospice referral was associated with greater comorbidities according to multivariable logistic regression
Peng *et al* [65], 2020	The study included all adult patients with ESLD who died during hospitalization from 2010 to 2013 in Taiwan (n = 14,247)	Retrospective cohort study using the National Health Institute Research Database, adhering to STROBE guidelines	The study focused on ESLD patients aged 18 and older who died during hospitalization. Primary outcome was ICU admission during terminal hospitalizations. Secondary outcomes were cardiopulmonary resuscitation (CPR) and mechanical ventilation during terminal hospitalizations	Among ESLD patients, 60.8% had comorbid HCC. Patients without HCC were less likely to receive PC before terminal hospitalization compared to those with HCC. Those without HCC had higher rates of ICU admission, CPR, and mechanical ventilation during terminal hospitalization	Patients with ESLD not comorbid with HCC require more attention regarding PC needs and decision-making for intensive care utilization. Prior PC was associated with reduced probability of ICU admission
Patel *et al* [23], 2020	The study included 167 veterans newly diagnosed with ESLD in 2012 at the Greater Los Angeles Healthcare System using the VA Corporate Data Warehouse	Prospective cohort study	Veterans were selected using ICD-9 codes for cirrhosis and liver decompensation. Different sampling techniques were applied to identify patients with ESLD using ICD-9 codes and chart abstraction	Among the identified patients, 62 met ESLD criteria after chart abstraction. The majority were male (98%), with a mean age at diagnosis of 61 years, and 74% were White. The quality indicator pass rate was 68%. Patients who received PC consultations were more likely to receive information care planning quality indicator	The study highlights inadequate quality of PC in veterans with ESLD. Patients who received specialty PC consultations and those affected by homelessness, drug, and alcohol abuse received better care. Combination of ICD-9 codes can effectively identify patients with ESLD

Orman *et al* [24], 2022	The study included 679 adults (age ≥ 18) with cirrhosis admitted to Indiana University Hospital between June 2014 and July 2019 who received PC	Prospective cohort study	Patients were followed from admission through 90 days post-discharge to assess outcomes. PC consults were considered EOL care for patients with imminent in-hospital death Primary outcome was unplanned 30-day readmission. Secondary outcomes included hospital length of stay, intensive care utilization, inpatient costs, discharge medications, and 90-day post-discharge mortality and costs	Among 679 patients, 74 received PC, typically later in their hospitalization. Patients receiving PC had higher Charlson comorbidity index and greater impairments in activities of daily living, social activity, and quality of interactions	PC is underutilized and often initiated late in patients with severe liver disease and functional impairment. PC may reduce healthcare utilization and increase completion of advanced directives. RCTs are needed to further evaluate PC for this population
Thandassery *et al*[18], 2022	The study compared patients with COVID-19 and cirrhosis (Group A, *n* = 1969) *vs* those with COVID-19 alone (Group B, *n* = 169257)	The study retrospectively analyzed a global multicenter database to assess mortality risk and PC referrals in patients with COVID-19 and cirrhosis	Data from 50 healthcare organizations worldwide were analyzed using a federated cloud-based network (TriNetX). Patients aged 18 to 90 years with COVID-19 were identified between January 20, 2020, and November 16, 2020	Group A (COVID-19 and cirrhosis) had a higher mortality rate (8.9%) compared to Group B (COVID-19 alone, 5.6%). The hazard ratio (95%CI) for mortality with cirrhosis was 1.59 (1.26–1.99) (*P* = 0.01). PC referrals were more frequent in Group A (4.1%) compared to Group B (2.0%). The hazard ratio (95%CI) for PC referrals with cirrhosis was 2.02 (1.39–2.94) (*P* = 0.01)	Hospitalized patients with COVID-19 and cirrhosis are at high risk of mortality and should be considered for PC referrals
Brown *et al* [76], 2016	The study included a cohort of ESLD patients (*n* = 22311)	This was a retrospective cohort study that identified hospitalized ESLD and HF patients between 2007 and 2011	The study analyzed endpoints during index hospitalization, including mortality, discharge to hospice, and length of stay. Post-discharge endpoints included all-cause mortality, rehospitalization, hospice enrollment, and days alive and out of hospital. Follow-up occurred at one and three years after discharge, comparing with a reference cohort of decompensated HF patients	One year after discharge, ESLD patients had 209 days alive and out of hospital compared to 252 days alive and out of hospital for decompensated HF patients. Inpatient mortality for ESLD was 13.5%, with all-cause mortality at 64.9%, higher than HF rates. ESLD patients had a rehospitalization rate of 59.1%, slightly lower than HF patients	The study demonstrates substantial morbidity and mortality rates associated with end-of-life care in ESLD. There is a critical need for alternative approaches to manage the care of ESLD patients
Whitsett *et al* [30], 2022	The study surveyed all United States transplant hepatology fellows enrolled in accredited fellowship programs during the 2020–2021 academic year	This was a qualitative study conducted using a national survey	The survey assessed the frequency of PC provision and fellows' comfort levels with physical and psychological symptom management, psychosocial care, communication skills, ACP, and end-of-life care	Out of 56 transplant hepatology fellows, 45 responded to the survey (79%), including 50% females (*n* = 22). Most fellows (67%, *n* = 29) trained at centers performing over 100 transplants per year. Additionally, 69% (*n* = 31) had a PC or hospice care rotation during residency, and 42% (*n* = 19) received education in PC during their transplant hepatology fellowship	The survey revealed gaps in PC experience and education during transplant hepatology fellowship, highlighting a lack of comfort in managing psychological distress and ACP. There is a desire among fellows to improve skills, particularly in symptom management
Ufere *et al* [20], 2020	The study included patients with DC evaluated for LT between January 1, 2010, and December 31, 2017 (*n* = 230)	It was a retrospective analysis of all adults (age ≥ 18 years) evaluated for LT across a network of nine acute care hospitals	The study compared healthcare utilization in the last year of life and EOL care outcomes between transplant-listed (*n* = 133) and non-listed (*n* = 97) patients. Predictors of PC and hospice care utilization were examined using multivariate logistic regression	The majority of patients (80%) died in the hospital, with 70% of them in the ICU. About 70.0% received a life-sustaining procedure during their terminal hospitalization, which did not differ between transplant-listed and non-listed patients. Transplant-listed patients had lower odds of receiving specialty PC, while patients with HCC had higher odds of receiving hospice care	Patients with DC, regardless of transplant candidacy, exhibit high rates of healthcare utilization with low utilization of palliative and hospice care. They spend most of their last 90 days of life in the hospital, where they often eventually die

ESLD: End stage liver disease; EPCI: Early palliative care intervention; GOC: Goals of care; ESAS: Edmonton symptom assessment symptom; RCT: Randomized controlled trial; PC: Palliative care; LT: Liver transplantation; AASLD: American Association for the Study of Liver Diseases; ACP: Advance care plan; CLD: Chronic liver disease; EMR: Electronic medical records; HCC: Hepatocellular carcinoma; NECPAL CCOMS tool: Strategy of identifying patients who require in palliative care in general health service; IPOS: Integrated palliative care outcome scale; INR: International normalized ratio; ArLD: Alcohol-related liver disease; EOL: End of life; POLST: Physician Orders for Life-Sustaining Treatment; LTC: Liver transplantation committee; DC: Decompensated cirrhosis; COVID-19: Coronavirus disease 2019; HR: Hazard ratio; OR: Odds ratio; ICU: Intensive care unit; HF: Heart failure; ICD-9: International Classification of Diseases, Ninth Revision; CPR: Cardiopulmonary resuscitation.

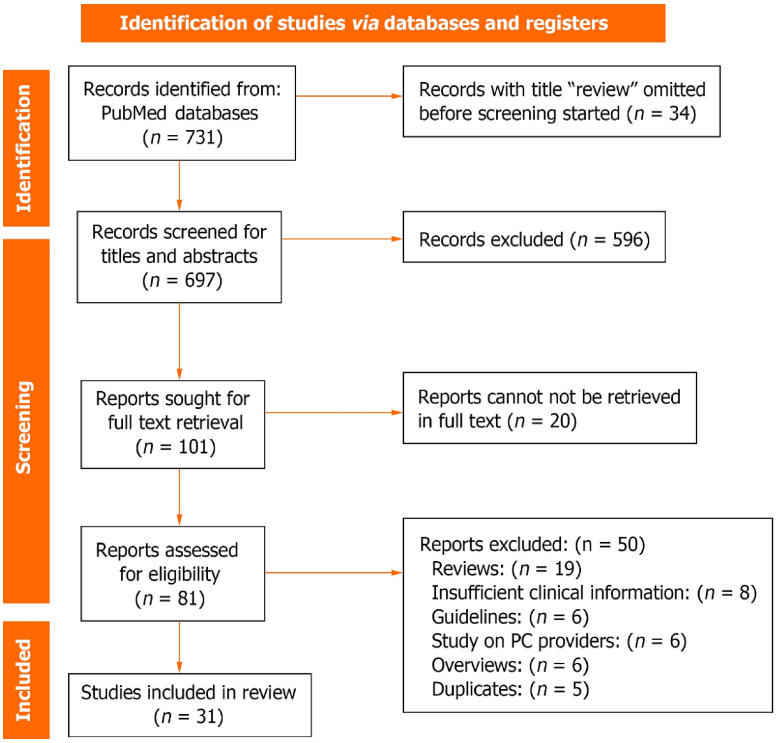

Figure 1 PRISMA search strategy for systemic review.

Kathpalia *et al*[17] underscored the potential benefits of PC for cirrhotic patients facing LT-related mortality, advocating for early PC integration into decision-making. This study emphasizes the role of PC in improving outcomes for ESLD patients awaiting LT.

Thandassery *et al*[18] and Trebicka *et al*[19] linked ESLD and COVID-19 mortality, prompting PC considerations during pandemics, with retrospective study limitations. These studies highlight the unique challenges and considerations for PC in ESLD patients during public health emergencies.

Ufere *et al*[20] addressed gaps in PC utilization and training, necessitating better education and broader study designs to enhance care for advanced liver disease patients. This study emphasizes the need for improved PC education and integration into ESLD care.

Observational-prospective studies

Several prospective observational studies highlight the importance of integrating PC into the care of patients with ESLD.

Lamba *et al*[21] demonstrate that interdisciplinary communication interventions can facilitate early consensus on goals of care for terminally ill LT service patients, enhancing end-of-life care practices without altering mortality outcomes.

Vieira *et al*[22] emphasize the universal need for PC among ESLD patients, regardless of transplant eligibility. However, the study's limitations include a single-hospital sample and heterogeneous subgroup distribution, which could introduce bias.

Patel *et al*[23] identify inadequate PC quality in a veteran population diagnosed with ESLD, suggesting the use of International Classification of Diseases, Ninth Revision codes for patient cohort identification. The study's limitations include a small sample size and single-center data.

Orman *et al*[24] find that PC is underutilized and provided late to patients with severe liver disease, despite its association with reduced healthcare utilization and greater completion of advanced directives. Randomized trials are needed to evaluate PC's efficacy in this population.

Observational studies-qualitative studies

A series of qualitative studies shed light on the challenges and barriers surrounding PC utilization and advance care planning (ACP) for patients with ESLD.

Patel *et al*[25] revealed low rates of PC consultation alongside high healthcare costs for ESLD patients, indicating racial and ethnic disparities in PC access. They propose targeted quality improvement initiatives to address these disparities.

Ufere *et al*[26] surveyed hepatologists and gastroenterologists, identifying cultural factors and unrealistic expectations as major barriers to PC and ACP utilization. Insufficient communication about end-of-life care and late engagement in ACP were also highlighted.

Patel *et al*[27] found that patients with DC received inadequate ACP, leading to overly aggressive life-sustaining treatments at the end of life. This study underscores the need for improved ACP throughout the illness trajectory.

Beck *et al*[28] suggested clear referral criteria, such as the MELD score, to expand PC access for LT patients. Educational interventions targeting attending physicians could enhance PC utilization.

Donlan *et al*[29] conducted educational interventions to dispel misconceptions about PC among ESLD patients and caregivers, emphasizing its role in enhancing illness understanding and coping mechanisms.

Shinall *et al*[9] identified barriers in LT patient care, including role boundaries and differences in clinical cultures, proposing comprehensive symptom assessment and support for caregivers to improve care quality.

Whitsett *et al*[30] highlighted gaps in PC education and confidence among transplant fellows, advocating for early consideration of palliative medicine and hospice in ESLD management due to its comparable morbidity and mortality rates to heart failure.

These qualitative studies collectively emphasize the need for targeted interventions, improved education, and enhanced interdisciplinary collaboration to optimize PC utilization and ACP for patients with ESLD.

DISCUSSION

ESLD is the apex of the progression of CLD to cirrhosis, decompensation, and chronic liver failure. Despite LT being proven curative for patients with ESLD, the availability of the procedure is restricted by donor availability, active substance abuse, financial constraints in developing countries, and progression of disease among wait-list patients including extrahepatic organ involvement and sepsis[3]. In this systemic review, we examined the evidence-based literature focusing on the advantages of integrating PC into the management of patients with ESLD and ACLF. PC encompasses achievable goals that include symptom control and interventions that favorably alter the natural course of the disease to offer curative intent[31]. More so in this review, we discuss the disease course of ESLD and ACLF, the role of PC in the management of these patients, the challenges, and barriers it encountered in evidence-based practice, an acknowledgment of the limitations of this study, and lastly the recommendations for future research on the integration of PC in the management of ESLD and or ACLF.

Unlike clinical treatment which aims at curing disease, PC is a medical specialty that focuses on helping people with serious illnesses get relief from the symptoms, pain, and side effects they experience. PC does not aim at curing disease so it can be provided along with curative treatment and may begin at the time of diagnosis. PC is appropriate for every stage of a serious illness, from diagnosis until the end of your life. In the context of ESLD and ACLF, PC emerges as an alternative therapeutic avenue for patients deemed unsuitable for LT[30,32-34].

Additionally, there is a clear unmet need for comprehensive PC, as evidenced by the infrequent referral of DC patients for PC, highlighting the necessity for better symptom management tools and collaboration between LT and PC services. Innovative approaches like machine learning show promising predictive capabilities in ESLD management, aiding in risk stratification and personalized care. Furthermore, the use of practical tools such as Child-Pugh and MELD-Na scores can effectively identify PC candidates, facilitating timely intervention and decision-making.

ACLF

These studies underscore the impact of PC on reducing healthcare utilization, such as reducing readmission rates and hospital stays, particularly in specific ESLD subgroups like alcohol-associated liver disease with ACLF scores ≥ 2.

According to Bajaj *et al*[32], the guideline panel, comprising six experts in hepatology and two guideline methodologists, officially presented ACLF practice recommendations in the *American Journal of Gastroenterology*[32]. The authors provided insights into the unique similarities, differences, and limitations of the three most widely used ACLF definitions: European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF; Europe), Asian-Pacific Association for the Study of the Liver (Asia), and North American Consortium for the Study of ESLD (NACSELD; North America). They suggested defining ACLF as a "potentially reversible condition in patients with chronic liver disease with or without cirrhosis that is associated with the potential for multiple organ failure and mortality within 3 months in the absence of treatment of underlying liver disease, liver support, or LT"[32].

In the EASL-CLIF criteria, ACLF occurs in patients with DC who develop additional organ failures. The NACSELD criteria were established later, primarily for patients hospitalized with cirrhosis and bacterial infections. These two criteria are essentially modifications of the EASL-CLIF criteria, where ACLF is defined by the presence of at least two extrahepatic organ failures, including shock, HE grades 3 or 4, renal replacement, and/or mechanical ventilation[35].

The CLIF consortium (CLIF-C) organ failure is associated with high mortality, and the score determines individual thresholds for organ failures, which may include all organs, including the liver[36]. The concept of ACLF, although debated in the last decade, has gained momentum with the publication of clinical guidelines, signifying its global acceptance[36]. However, despite several clinical study attempts, disease-modifying therapies for ACLF, such as granulocyte-colony-stimulating factor[37], the unselective interleukin-1 (IL-1) inhibitor Anakinra[38], or selective IL-1 beta inhibitor canakinumab[39], have failed to establish due to the complexity of its underlying pathophysiology, which is not yet well understood[32].

Currently, there is no approved or broadly accepted standard treatment option to modify the disease course, and short-term mortality rates range between 30%-50%, making LT the only curative approach[33-36]. However, a shortage of donor organs and numerous contraindications limit access to transplantation to a small proportion of ACLF patients. The complexity of treatment strategies, involving multiple organ systems and various medical specialties, underscores the pressing need for guidelines for diagnostic and therapeutic procedures in ACLF[33-36].

The scores developed by the EASL-CLIF-C have been shown to be accurate predictors of patient mortality[40-43], even in specific events in the course of the disease, such as spontaneous bacterial peritonitis[44,45], acute variceal bleeding[46,47], sepsis[48] and hepatorenal syndrome[49,50]. It is no surprising at all that a very robust study found that a CLIF-C ACLF score cutoff ≥ 70 identified patients with a 100% mortality within 28 days, indicating that these patients may reach

a threshold of futility for further ongoing intensive support, and the best treatment options may include PC[51]. A retrospective study was conducted on hospitalized patients with cirrhosis admitted between January 2015 and December 2016, utilizing the Child–Pugh score and the MELD/Na score in January 2018. Approximately 51.1% of the patients had a MELD/Na score > 20, while 48.9% had a score < 20. The study findings indicated that 59.6% of patients had died within 12 months, suggesting that a MELD score > 20 could serve as a referral threshold for LT patients to PC[13]. These results highlight the significant need for PC among this patient population.

ESLD

The transition from compensated to DC and ESLD is universally recognized by the occurrence of clinical complications, including ascites, hepatic encephalopathy, gastrointestinal bleeding, and jaundice[52]. This transition process can follow two distinct pathways: AD and progressive, non-AD (NAD). AD is characterized by the first or recurrent grade 2 or 3 ascites within less than 2 weeks, the first or recurrent acute hepatic encephalopathy in patients with previously normal consciousness, acute gastrointestinal bleeding, and any type of acute bacterial infection[36]. AD and ACLF predominantly occur in patients with a history of previous decompensation, representing further decompensation. The most severe form of AD is ACLF, primarily triggered by alcoholic hepatitis or infections[36,52]. Regardless of the cirrhosis etiology, AD manifests as ACLF in approximately 16% of cases; pre-ACLF in 17%; unstable decompensation in 22%, characterized by persistent albeit unstable inflammatory status resulting in further AD events within 1 year; and stable decompensation in 48%, with a stable decrease of systemic inflammation and no further AD for at least 1 year[53].

In contrast, NAD is characterized by the progressive development of any single event (58%-72%) or any combination (28%-42%) of slow ascites formation, hepatic encephalopathy grade 1-2 or higher if manageable in an outpatient setting, or progressive jaundice in non-cholestatic cirrhosis[36]. NAD is mainly represented by the first decompensation, occurring in 58% to 72% of patients, and usually does not require hospitalization[52]. Even when presenting with two or more decompensating events, a significant proportion of these patients may be managed as outpatients or in the day-hospital setting. This also applies to many patients with further decompensation represented by refractory ascites and mild to moderate recurrent encephalopathy free of other complications[19]. Thus, it appears that AD and NAD impact the clinical course of cirrhosis differently, with AD mostly representing further decompensation and NAD mostly the first decompensating event.

PC in this context

These studies collectively emphasize the importance of holistic care, early PC integration into clinical decision-making, and the necessity for improved PC education and integration into ESLD care to enhance patient outcomes, especially during unique challenges like public health emergencies.

The American Association for the Study of Liver Diseases (AASLD) defines PC as "multidisciplinary, specialized medical care that addresses the physical, spiritual, and psychosocial needs of patients with serious illness and their caregivers"[31,54]. According to the World Health Organization, PC is "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering using early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual"[55]. AASLD emphasizes that PC can be provided at any stage of a serious illness and concurrently with disease-directed and curative treatments, including organ transplants[56]. Over the past decade, there has been an expansion in the body of evidence supporting early PC, extending to individuals with non-malignant conditions which carry a poor prognosis and intense suffering such as cirrhosis[56,57]. Some authors recognize the challenge clinicians face in determining the ideal timing for involving specialized PC teams due to the unpredictable disease trajectory and the potential for curative LT[58]. Overall, the majority of studies included in this review advocate for the early initiation of PC for patients with cirrhosis who develop ESLD or ACLF. This suggests that the diagnosis of cirrhosis represents the earliest point at which PC should be offered to these patients, making it the preferred stage to initiate PC.

From the outset, the aim of the study is to comprehensively investigate the evidence surrounding the benefits of incorporating PC care of patients with ESLD and/or ACLF. This systemic review addresses the underexplored utilization of PC in patients with ESLD and acute on chronic liver disease. The study focuses on the evidence based literatures that sought the advantages of integrating PC into the comprehensive management of patients with ESLD and ACLF. Thus aiming to contribute valuable insights to the evolving landscape of ESLD and ACLF management. In these studies, the diagnosis of ESLD and ACLF was made by a liver specialist or a qualified physician in the field, who then referred the patient to a PC at various stages of his or her life. The experience and education level of the healthcare personal who provide the PC are not even acknowledged in the studies included in this systemic review. PC management typically involves a team comprising physicians, nurses, chaplains, social workers, and other providers[31].

Globally, there is a growing recognition of the benefits of PC across disease states, including DC or ACLF. Evidently, a substantial body of evidence supports the integration of curative and PC approaches for patients with DC. Outpatient PC in patients with DC is associated with improved symptoms, enhanced care coordination, and better anticipatory planning [56,57]. The AASLD, through its Practice Guidelines Committee, has provided PC guidance specifically for patients with cirrhosis, addressing issues relevant to adult patients with DC. The decision to commission guidance rather than a guideline stems from the paucity of RCT on PC in DC[31]. While PC can be considered irrespective of the cirrhosis stage, the notable physical, psychosocial, and financial burden in this group has led to the development of guidance tailored to adult patients with DC[31].

PC, though underutilized, addresses the myriad challenges encountered by patients with DC or ESLD and their families. For example, a significant underutilization of PC services, particularly in older, non-white patients with cirrhosis on the LT waitlist was observed[11,59], which was corroborated by the National Inpatient Survey[60]. The lack of PC support has a negative impact on the quality of life of non-transplant candidates with ESLD[11,59]. Although an increase

PC services utilization has been observed in the past decade[25,60], only a few ESLD patients declining or delisted for LT are referred for PC services[11,58,59], and they are commonly referred within a few days or weeks before their death[17,61]. Therefore, it is paramount to advocate for the systemic implementation of PC principles and resources to alleviate the physical and emotional burden on the ESLD patient population and their families[62].

Although, a very relevant limitation that might contribute to the underutilization of PC in ESLD is the lack of tools identifying distressing symptoms correlating with the optimal time for PC referral[6]. It is important to notice that low rates of PC consultation in patients with ESLD might incur into significant costs for these terminally ill patients[23,25,27,28,63,64] and an increase in undesired suffering, as ESLD patients receive ACP consultations too late in the course of their disease[23,26]. PC referral during hospital admissions that concludes in death is often belated and inefficacious, as it often fails to reduce anxiety symptoms[65]. Despite all the addressed above, the hepatology community recognizes PC as underutilized in ESLD and ACLF[65]. Nevertheless, pre-emptive PC intervention in the management of patients with ESLD can result in increase in time to the first readmission and more days alive outside the hospital for admitted ESLD patients[63].

LT stands as the sole cure for ESLD and ACLF, but annual LT rates remain stagnant due to various obstacles such as donor availability, financial constraints, active substance use, mental health disorders, and lack of social support[66]. Clinical scoring systems, including the CTP score, MELD, and ACLF grade, have been developed to predict mortality in cirrhosis patients[29]. ACLF grade at 3-7 days post-admission, MELD score and CLIF-C ACLF scores may identify patients for whom continued care is futile[6,34,51,67]. Although, it is rather challenging to identify the point of irreversible liver deterioration warranting referral for PC[18,68], machine learning models might help us distinguish patients with better expected survival[22].

Disparities in PC referral extend to the delivery of PC in cirrhosis patients specifically. Financially and socially vulnerable groups are less likely to receive PC referrals upon hospital admission[36]. The misconception that PC is synonymous with end of life care persists in medical settings, that can be persistently propagated by attending physicians, potentially contributing to its underutilization in the transplant setting[28]. Also, the misconception that is a synonym to hospice care is also very common. It is important that fellow physicians, patients and their families receive education on PC, so to recognize its potential to support their understanding of illness and coping[26,29].

Evidence based benefits of PC in the management of ESLD and or ACLF

While the impact of PC on patients with ESLD and ACLF remains an understudied area, innovative care models have emerged to enhance the utilization of PC in these patients. For example, patients who denied or were delisted from LT or which experienced worsening MELD scores on the transplant list can enrolled in hospice care, and some of these patients might be successfully transplanted while in hospice care[39]. Also, PC consultation might reduce readmission rates and hospital stay in patients with cirrhosis[17,63], while improving physical and physiological suffering[6].

A study conducted by Adejumo *et al*[69] reported that PC consultation was associated with a lower risk for 30- and 90-day readmissions (HR = 0.42, 95%CI: 0.38–0.47 and 0.38, 95%CI: 0.34–0.42, respectively). This association resulted in reduced burden on healthcare resource utilization and improvement in cost savings during subsequent readmissions[69]. Lamba *et al*[21] implemented a single-centered, 2-tiered structured intervention, assessing automatic PC integration for cirrhosis and LT patients admitted to the Surgical Intensive Care Unit (SICU)[21]. The first part focused on reviewing prognosis, advanced directives, and symptom management within 24 hours of SICU admission. The second part involved a family meeting with both primary and PC teams to review the goals of care. The outcomes of this intervention included increased goals of care meetings (from 2% to 38%), increased do not resuscitate rates (from 52% to 81%), increased withdrawal from life support (from 35% to 68% of cases), and a decreased SICU mean length of stay by 3 days, all achieved without a change in mortality rates. This suggests that only patients undergoing futile care had life-sustaining care withdrawn. Additionally, interdisciplinary communication interventions with physicians and families in the SICU may lead to earlier consensus around goals of care for dying LT service patients. Early integration of PC alongside aggressive, disease-focused, curative care in the SICU for LT patients can be accomplished without a change in mortality and can improve end of life care practices in such patients[21].

These studies collectively indicate a benefit with PC across the continuum of care in heterogeneous patient populations, particularly those struggling with uncertainties such as the population with DC, which experiences significant stress, anxiety, and decreased quality of life[67]. Early PC referral could provide a benefit to caregivers of patients with cirrhosis who also suffer while caring for loved ones with this illness. Early PC integration has been shown to reduce depression and anxiety among caregivers, such as spouses, children, and parents[70].

Barriers in PC for patients with DC

Cirrhosis is linked to a diminished health-related quality of life, posing challenges due to various stressors encompassing physical, cognitive, psychological, and social aspects. Studies have consistently revealed that patients with DC face variable mortality rates ranging from 20% to 80% over five years. The disease trajectory is progressive, marked by declining health, increasing symptom burden, and frequent hospitalizations. While LT has proven to be a curative option, only a minority of patients survive to receive it[70]. There is an unmet PC need for cirrhosis patients and their caregivers, with only a few of them receiving PC or hospice care referrals, often occurring late in the disease course[61,71,72].

Several identified barriers hinder the implementation of PC for patients with ESLD and/or ACLF, such as a shortage of specialty PC providers, the absence of evidence-based referral criteria, a lack of role clarity between specialists, the stigma associating PC with "giving up" on curative treatments, insufficient provider training, competing demands on providers' time, and prognostic uncertainty[26]. Additionally, many symptoms experienced by individuals with ESLD are highly liver-specific and are longitudinally managed by liver teams. The process of transplant waitlisting and evaluation itself acts as a barrier to PC due to potential conflicts between transplantation and PC, although these patients undergoing

transplant evaluation tend to receive lower-quality end of life care[58,64,73]. Notably, PC competencies for hepatologists have not been developed, as hepatology training does not routinely include PC training.

AASLD guideline statements emphasize that patients with ESLD and their caregivers frequently face substantial unmet PC needs across psychological, physical, social, financial, and spiritual dimensions. The recommendations advocate for the assessment of unmet PC needs and the consideration of specialty PC consultation for all patients with DC and their caregivers. Importantly, the guidance clarifies that disease-directed care, such as transplantation evaluation and listing, should not preclude the delivery of PC or specialty PC consultation for patients with DC.

Clearly, obstacles impeding the delivery of quality PC for patients with ESLD or ACLF include a shortage of PC specialists and inadequate training for healthcare providers, including hepatologists, as PC training is typically not integrated into hepatology training programs. Therefore, it is imperative to mandate PC training for healthcare professionals in subspecialty hepatology departments who are directly responsible for the care of patients with ESLD/ACLF [74-77].

Acknowledging the shortage of specialty PC providers, the AASLD recommends that hepatology clinicians take a pivotal role in providing primary PC services to patients with cirrhosis. This role includes conducting symptom assessment and management, facilitating basic ACP activities such as identifying surrogate decision-makers, offering counselling, and making referrals for additional support when necessary and feasible[31].

Artificial intelligence (AI) holds significant promise in the field of healthcare, particularly in prognosticating patients with complex conditions such as LT, ESLD or ACLF[78-80]. By leveraging advanced algorithms and machine learning techniques, these systems can analyze vast amounts of patient data, including clinical variables, imaging studies, and laboratory results, to identify patterns and predict disease progression[81-84]. In the context of PC for patients with ESLD or ACLF, AI-driven prognostic models could assist healthcare providers in selecting those individuals who are most likely to benefit from PC interventions. This tailored approach may optimize resource allocation and improve outcomes by ensuring that PC services are directed towards those who stand to benefit the most.

Our study exhibits several limitations. Primarily, due to the retrospective nature of our discharge database, our analysis is susceptible to coding errors and missing data. While transplant patients represent a minority group, the non-transplant patient group is inadequately assessed in only a few studies. The prospective and retrospective studies utilized to elucidate the impact of PC in ESLD and/or ACLF predominantly consist of non-randomized trials, observational studies, or relatively small-scale investigations. Notably, the transplant and ineligible transplant populations differ, each harboring unique sources of suffering and care disparities. Consequently, findings from studies in one population may lack generalizability to the other, necessitating separate investigations.

Future directions for the effective implementation of PC into clinical hepatology involve commitments to bridge the research gap, advocate for essential health policy changes, instigate relevant cultural shifts, and foster essential clinical innovation. Prospective and randomized trials on integrated PC interventions for patients with ESLD and ACLF are crucial, with a specific focus on evaluating the PC needs of both transplant and non-transplant patient groups. Emphasis should be placed on assessing symptom burden and quality of life rather than solely focusing on the intervention's impact on mortality. Collaborative efforts between LT and PC services could enhance the quality of life in this patient population.

CONCLUSION

ESLD and ACLF impose a substantial burden of clinical complications, leading to patient suffering and poor prognosis. Despite LT being the sole recognized cure for ESLD and ACLF, it remains accessible only to a minority of patients. PC represents a specialized area of clinical intervention aimed at enhancing the quality of life for individuals with advanced cirrhosis. This involves advanced care planning, alleviation of physical symptoms through timely interventions, and provision of emotional support to both the patient and their family. Regrettably, the utilization of PC is infrequent, and referrals typically occur late in the course of patients with ESLD and ACLF. Ideally, PC should be initiated upon the diagnosis of ESLD or ACLF and be sustained throughout the entire trajectory of the illness. Overcoming existing barriers and integrating PC early in the treatment continuum, including alongside active interventions such as LT, would maximize benefits for patients before the end of life and reduce costs for the broader healthcare system. To facilitate improvement in this regard, there is a need for more researches particularly prospective randomized control trials assessing the impact of integrated PC services in the early management of patients with ESLD and ACLF, irrespective of transplant eligibility.

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FOOTNOTES

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Country of origin: United Kingdom

ORCID number: Jonathan Soldera 0000-0001-6055-4783.

Corresponding Author's Membership in Professional Societies: Federação Brasileira De Gastroenterologia; Sociedade Brasileira de Hepatologia.

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