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EDITORIAL

Importance of methodological considerations in documenting psychological trauma

Gentian Vyshka, Fatime Elezi, Tedi Mana

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Abstract

The documentation of psychological trauma is obviously a challenge to clinicians while they are diving deep into remote events related to their clients or patients. The potential role of psychological trauma in the early developmental stages, and even the existence of adverse childhood experiences, is important to prove, yet it is difficult to do so. A diverse range of methods have been applied, all of which presumably benchmark a big therapeutic step; however, these enthusiastic methods frequently do not last for long. While hypnosis supporters, Freudian and Neo-Freudian disciples can be acute enough to enhance and uncover suppressed memories, modern psychiatry relies mostly on diversely structured interviews. Functional magnetic resonance and its related subtleties might help, but the questions that remain unanswered are numerous and confusing. Connecting early experiences with long-term memory while identifying psychological trauma its importance for the individual's growth trajectory; thus, it remains an intriguing issue.

Key Words: Psychological trauma; Adverse childhood experiences; Post-traumatic stress disorder; Self-reporting; Hypnosis; Magnetic resonance imaging

Core Tip: The documentation of psychological trauma is a delicate issue with important clinical, ethical and legal implications. Interviews, self-reporting, hypnosis and recent sophisticated imaging techniques have been proposed and tried. While each method has intrinsic advantages and drawbacks, it is important for scholars to specify their chosen approach while denoting the value and limitations of the findings.

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INTRODUCTION

Remote psychotrauma, especially in the early stages of human development, deserves special attention with regard to later psychiatric morbidities. This issue has long since been of particular value as even ancient authors highlighted the role of stress and trauma in the aftermath of catastrophic life events.

Of interest might be that early sources grant no time delay between psychotrauma and its effects on the human psyche. However, months or possibly years may be required for the full picture of posttraumatic stress disorder to arise; this might be true for Homer's Odysseus, who experiences flashbacks and intrusive memories of lost friends while in captivity on Calypso's island, although the legendary author sketches no clear timelines. This notion of time and relativity is older than Einstein's discovery.

Macbeth demonstrated the full picture of psychotrauma soon after the killing of his rival[1]. Charles IX experienced hallucinations and nightmares the day after the Saint Bartholomew massacre: […] the solitary hours of Charles IX were rendered terrible by a repetition of the cries and groans which assailed his ears during the massacre of Saint Bartholomew [2].

Therefore, it is clear that in remote historical settings, the timeline of psychotrauma following a stressful event is different from what it seems to be in current lines of thought. The immediacy of reaction(s) is disputable but remains present.

Self-reporting and structured interviews

The form of trauma reporting in a structured interview differs from the self-reporting found in most available questionnaires; however, the authors generally speak through their characters as if the experiences were their own. Trauma reporting recently transcended the necessity of a close relationship between the physician (therapist) and the patient (client), as questionnaires can be completed online as well. Thus, the effects of psychotrauma might be communicated *via* the internet[3].

It is clear, however, that patient interviews and self-reports have limitations. Memories of remote and early traumatic experiences are often suppressed or erased. Furthermore, identifying participants whose responses are likely dishonest or unreliable is challenging[3]. Documentation requires objectivity; hence, the value of an interview remains restricted. Even when equipment and staffing are adequate, different issues (for example, retraumatization) might lead to the loss of information[4].

Hypnosis and psychoanalysis

The advent of hypnosis and psychoanalytical methodologies provided new perspectives for obtaining the requested information. In 1889, Oppenheim elaborated on some of Erichsen's ideas and coined the term 'traumatic neurosis'. Another French author (Brissaud) pushed the notion further and spoke of 'sinistrosis'[5]. While Erichsen (1866) proposed an organic nature of traumatic events, the London surgeon Page argued in 1885 that it was not physical injuries but rather fright, fear, and alarm that caused the disorder he termed "nervous shock"[6,7]. These views and those of other contemporaries prompted Charcot's pupil, Sigmund Freud, and his apostles to dig deeper into the traumatic unconscious[8,9].

The milestone Freudian publications, namely, 'Interpretation of dreams' (1900) and 'Beyond the pleasure principle' (1920), shed unprecedented light on the internalization of psychological trauma and its elaboration, although not everyone—perhaps even less his contemporaries—shared Freud's opinions[10,11].

Criticism aside, hypnosis was developed before the nineteenth century, yet French scholars maintain its worth; Janet referred to hypnosis as 'influence somnambulique'[12]. Nevertheless, apart from the intrinsic problems of hypnosis, hypnotherapy and all other subtleties of the technique somehow failed to stand the test of time. The changed status of awareness in hypnosis leading to profound relaxation and free production of recollections of remote traumas (if present) does not necessarily serve as documentation of trauma. Mnestic lacunae, confabulations and inconsistent statements arise, even with an experienced therapist. To add more to the controversy, Dreikurs suggested, "Hypnosis will not continue as a therapeutic procedure, despite its present tremendous appeal and increasingly wide use"[13].

Functional neuroimaging and biochemistry

Neuroimaging and neurochemistry have made significant progress in the last half-century. This progress has had clear implications in psychiatry, clinical psychology and psychotrauma.

Table 1 Documenting psychological trauma

Methodology	Advantages	Disadvantages
Self-reporting, structured interviews and questionnaires	Online surveys possible	Interviewer dependent
	User friendly	Participant motivation
	Therapeutic alliance	Low response rate
	Culturally shaped	Risk of retraumatization
	Standardizing of results	
	Quantifiable	
Hypnosis and psychodynamic/psychoanalytical approach	Recall of suppressed memories	Mnestic lacunae
	Recollections of remote traumas and of adverse childhood experiences	Confabulations
	Person centered	Inconsistent statements
	Potentially of treatment value	Potential for false memories
	Exploring the subconscious	Unsuitable for psychotic patients
MRI (functional neuro-imaging)	Objective data/findings	Methodology still not well standardized
	Reproducible	Ethnic and age-related changes to be considered
	Images availability and storage of high quality	Relatively costly

MRI: Magnetic resonance imaging.

Structural magnetic resonance imaging studies on traumatized children and adolescents have revealed abnormalities in numerous brain regions[14]. An impressive number of structures seem involved or imputed. The amygdala has been the focus, with measurements of its volume; the same is true for the hippocampus, brain cortex and limbic system as a whole[15,16]. Most studies have focused on children and childhood trauma, therefore encompassing an age range when important developmental changes occur. This bias is unneglectable but is not the only factor involved. Individual, racial and ethnic changes in volumetric parameters could also alter imaging findings. Researchers have strived to draft reliable and accurate methodologies; however, dilemmas remain.

Psychotrauma has an important effect on the brain's neurotransmitter systems. Therefore, a search is warranted for biochemical markers of trauma, in spite of their delicate and dynamic equilibrium. The hypothalamic pituitary adrenal axis is clearly relevant in stress responses; additionally, several neurotransmitters appear to be involved, such as serotonin and amino acids[17]. Interestingly, some biological therapies have tried to prevent post-traumatic stress disorder symptoms; an example is administering intranasal oxytocin, which is a hypothalamic hormone with a wide range of neural effects[18].

Table 1 summarizes some of the novelties and drawbacks intrinsic to most of the abovementioned methodologies. In a nonexhaustive approach, authors have tried to focus on the main characteristics of each technique, which obviously have numerous and specific features.

CONCLUSION

The theme of psychological trauma and its long-term after-effects is of particular interest in neuroscience. However, this issue still needs systematization. Documenting a psychologically remote and traumatic event might be problematic but of high value when medico-legal and forensic issues are at stake, even with the unfortunate result of retraumatization[19].

When producing results, clinicians must clearly report the methodology used for documenting psychological trauma. By doing so, everyone should clearly understand the limitations of the findings without raising unnecessary doubts about their validity.

FOOTNOTES

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OPINION REVIEW

ChatGPT in action: Harnessing artificial intelligence potential and addressing ethical challenges in medicine, education, and scientific research

Madhan Jeyaraman, Swaminathan Ramasubramanian, Sangeetha Balaji, Naveen Jeyaraman, Arulkumar Nallakumarasamy, Shilpa Sharma

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Abstract

Artificial intelligence (AI) tools, like OpenAI's Chat Generative Pre-trained Transformer (ChatGPT), hold considerable potential in healthcare, academia, and diverse industries. Evidence demonstrates its capability at a medical student level in standardized tests, suggesting utility in medical education, radiology reporting, genetics research, data optimization, and drafting repetitive texts such as discharge summaries. Nevertheless, these tools should augment, not supplant, human expertise. Despite promising applications, ChatGPT confronts limitations, including critical thinking tasks and generating false references, necessitating stringent cross-verification. Ensuing concerns, such as potential misuse, bias, blind trust, and privacy, underscore the need for transparency, accountability, and clear policies. Evaluations of AI-generated content and preservation of academic integrity are critical. With responsible use, AI can significantly improve healthcare, academia, and industry without compromising integrity and research quality. For effective and ethical AI deployment, collaboration amongst AI developers, researchers, educators, and policymakers is vital. The development of domain-specific tools, guidelines, regulations, and the facilitation of public dialogue must underpin these endeavors to responsibly harness AI's potential.

Key Words: Artificial intelligence; ChatGPT; Open artificial intelligence; Education; Research

Core Tip: Chat Generative Pre-trained Transformer's potential applications span medicine, education, and scientific research, with a focus on addressing its limitations and ethical concerns. Emphasizes the importance of developing guidelines and fostering collaboration between artificial intelligence (AI) developers, tech companies, researchers, and academic publishers. The key areas for future advancements, such as enhancing AI capabilities, addressing biases, and promoting the ethical use of AI tools have been outlined.

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INTRODUCTION

"Chat Generative Pre-trained Transformer (ChatGPT) is an advanced artificial intelligence (AI) language model developed by OpenAI, based on the Generative Pre-trained Transformer (GPT)-4 architecture. Stemming from the original GPT model inspired by the 2017 Transformer architecture, successive iterations culminated in ChatGPT, which generates human-like text and performs tasks like text completion, summarization, and translation. Despite its remarkable capabilities, ChatGPT faces limitations such as sensitivity to input phrasing, plausible yet incorrect responses, and inconsistent world knowledge. Ongoing research aims to enhance the model's performance and address these challenges". That is an exemplary introduction to the topic of this paper, offered by ChatGPT when asked to explain its nature and historical development within a 100-word limit. It serves as an apt teaser to the scope of capabilities of the system. Within a week of its release, ChatGPT reached one million users, reflecting its wide acceptance and potential impact[1-4]. The model has evolved from GPT-1 through GPT-3, with the latter using 45 TB of data to enhance its ability to generate coherent sequences of words, code, and data. The latest iteration, GPT-4, was released on 14 March 2023. However, it still faces limitations such as the inability to consistently answer semantic, factual, and ethical questions, as well as the presence of biases and prejudices[5-8]. Despite these drawbacks, early reactions to ChatGPT have been largely positive, with users acknowledging its transformative potential across various domains. This review article provides an overview of the current state of ChatGPT, discussing its applications, challenges, and potential impact. Additionally, we will explore possible measures to incorporate ChatGPT into the healthcare and scientific realms, ensuring its utility is maximized while mitigating risks.

AI AND HUMAN INTELLIGENCE: COMPLEMENTARY FORCES SHAPING THE FUTURE OF SCIENCE AND EDUCATION

AI technology, particularly large language models (LLMs) such as ChatGPT, has demonstrated remarkable capabilities in generating human-like text, answering questions, and providing explanations[9,10]. These advancements have significantly impacted various fields, including medicine[11-13], law[14,15], and academia[9,16-18]. ChatGPT has the potential to revolutionize science by speeding up the article writing and editing process, allowing researchers to focus on their research[19-22]. In education, AI chatbots like ChatGPT can offer students individualized learning experiences, assistance in learning new languages, tutoring and homework help, and answers to challenging questions[23].

AI systems, such as ChatGPT, have shown potential in various fields, including medical education, clinical decision support, and genetics[9,12,13,15,16]. For instance, ChatGPT has been evaluated in the context of the American Heart Association Basic Life Support and Advanced Cardiovascular Life Support exams, performing reasonably well overall, with accuracy varying depending on the question type[15,24]. In another study, ChatGPT was compared to human respondents in addressing genetics questions, showing similar performance but excelling in memorization-style questions[12,13]. Additionally, ChatGPT performed well on standardized exams such as AMBOSS-Step1, AMBOSS-Step2, NBME-Free-Step1, and NBME-Free-Step2 datasets[12,13].

However, it is essential to acknowledge the significance of human involvement in scientific research, as humans are responsible for posing hypotheses, designing experiments, and interpreting results[25]. Thorp[25] emphasizes the role of machines as tools but highlights that the scientific record ultimately results from human endeavors grappling with critical questions. Furthermore, OpenAI and DeepMind have developed AI systems, ChatGPT and AlphaCode, capable of producing lines of code. Although these systems have the potential to automate certain tasks in large software engineering projects, understanding human needs can be challenging, as these needs may be difficult to describe with

machine-readable specifications[11].

Limitations and potential misuse of AI raise concerns about their impact on human intelligence[23,26,27]. Neural network-based LLMs may pose a challenge for scientific thinking, as they are trained on past information and may struggle to think differently from the past, potentially hindering social and scientific progress[28]. Additionally, biases and inaccuracies may arise from the quality of training datasets[23]. Irene Solaiman, a researcher of the social impact of AI at Hugging Face, has expressed concerns about relying on these models for scientific thinking[28].

As AI systems continue to evolve, it is crucial to strike a balance between AI advancements and human intervention. AI technology can enhance various aspects of human life, but the significance of human involvement in tasks such as posing hypotheses, designing experiments, and interpreting results should not be overlooked[25]. AI systems can be viewed as tools that complement and extend human intelligence rather than replacing it. While AI has the potential to augment human intelligence, it is unlikely to completely take over, as human creativity, critical thinking, and adaptability remain indispensable in various aspects of life and scientific research.

CHATGPT IN HEALTHCARE

ChatGPT has demonstrated significant potential in various healthcare-related applications, such as medical education, radiologic decision-making, clinical genetics, and patient care[9,12-16]. Its use in medical education has shown promise as an interactive tool to support learning and problem-solving[9]. ChatGPT performed at or near the passing threshold for all three United States Medical Licensing Exam (USMLE) exams and demonstrated a high level of concordance and insight in its explanations without any specialized training or reinforcement[13].

ChatGPT has potential applications in healthcare education, research, and practice, such as improving scientific writing, enhancing research equity and versatility, streamlining workflow, saving time, and improving health literacy[16,21,29]. In the context of nursing education, O'Connor[23] suggests using a variety of assessment methods to reduce the risk of automated answers in students' written work, while emphasizing the importance of educating students about academic integrity and the value of critical thinking and scientific writing. AI chatbots like ChatGPT have the potential to be valuable tools for tailored learning experiences in education, providing personalized learning experiences for students, assisting with language acquisition, providing homework help and tutoring, and answering questions to aid in understanding complex concepts[23]. A publication discusses how doctors can use ChatGPT to write medical summaries for patients, emphasizing the importance of considering patient acceptance of new technology and its potential negative effects[17]. However, concerns have been raised about the lack of transparency and accountability in AI-generated content[30].

Research by Rao *et al*[12] suggests that specialized AI-based clinical decision-making tools will emerge in the future, highlighting the potential of using ChatGPT for radiologic decision-making and finding it feasible and potentially beneficial for improving clinical workflow and responsible use of radiology services. Another paper by Kung *et al*[13] concludes that LLMs, such as ChatGPT, have the potential to enhance the delivery of individualized, compassionate, and scalable healthcare by assisting with medical education and potentially clinical decision-making. In the field of clinical genetics, Duong and Solomon[15] found that ChatGPT did not significantly differ from humans overall in answering genetics questions, but performed better on memorization-type questions than critical thinking questions. The study also revealed that ChatGPT frequently provided different answers when asked the same question multiple times, with plausible explanations for both correct and incorrect answers[15]. Fijačko *et al*[24] tested ChatGPT's accuracy in answering questions related to life support and resuscitation, revealing that it could provide accurate answers to a majority of the questions on the American Heart Association's Basic Life Support and Advanced Cardiovascular Life Support exams. Furthermore, ChatGPT may assist with individualized, compassionate, and scalable healthcare delivery[13].

In neurosurgical research and patient care, ChatGPT has been explored for its potential role in gathering patient data, administering surveys or questionnaires, and providing information about care and treatment[14]. However, the implementation of these technologies should be approached carefully to ensure effectiveness and safety[14]. The potential of combining biotechnology and AI to tackle global issues and advance sustainable development goals is examined in a paper, which covers the wide range of AI applications in the life sciences, including decision support, natural language processing, data mining, and machine learning[31]. The authors emphasize the value of reproducibility in the development of AI models and highlight current research issues and challenges in these fields[31]. Another article explores the use of computational systems biology in stem cell research, emphasizing the value of computational methods in understanding the intricate biological mechanisms underlying stem cell differentiation and regeneration[32]. The article also highlights the importance of interdisciplinary partnerships between computational and experimental biologists to advance stem cell research. Furthermore, it discusses the application of machine learning and deep learning algorithms in stem cell research, serving as an example of how computational systems biology can advance our knowledge of stem cells and their potential therapeutic uses[32].

AI-powered chatbots, like ChatGPT, have the potential to improve patient outcomes by facilitating communication between patients and healthcare professionals, informing patients about their care and treatment using natural language processing[14]. In the context of neurosurgical research, chatbots can speed up the process of data collection and analysis by gathering information from a large number of patients and may be useful for longitudinal studies, which must track patient outcomes over time[14]. In a study that investigates various ChatGPT prompting strategies for breast cancer screening and breast pain, it was suggested that ChatGPT can be used to help radiologists choose the best imaging modalities, potentially enhancing clinical workflow and encouraging the prudent use of radiology services[12]. An article covering the third year of the coronavirus disease-19 pandemic, along with various topics like computer-based testing

(CBT), study design, ChatGPT, journal metrics, and appreciation for reviewers, emphasizes the benefits of CBT and suggests adding more multimedia test items to better represent real-world clinical scenarios[33]. The significance of the study design and the application of ChatGPT for data analysis are also discussed in the article[33].

ChatGPT has demonstrated significant potential in various healthcare-related applications, ranging from medical education to clinical decision-making and patient care. Its implementation in these fields has yielded notable results, but it is essential to approach the integration of such technologies carefully to ensure effectiveness, safety, and ethical considerations.

NAVIGATING THE ETHICAL AND QUALITY CHALLENGES OF AI-GENERATED CONTENT IN MEDICAL EDUCATION AND RESEARCH

The use of AI models such as ChatGPT in medical education, decision-making, scientific writing, and research has demonstrated their capabilities and potential benefits[9,12,13,15,21,22,29]. However, their utilization comes with potential risks and challenges, including ethical, copyright, transparency, legal issues, and concerns related to the generation of content difficult to distinguish from human-generated content[16,26]. Moreover, there are issues of bias, plagiarism, lack of originality, inaccurate content, and incorrect citations[16,34]. Several articles emphasize the importance of transparency, integrity, and truth in scientific research and highlight the potential risks associated with the use of AI tools like ChatGPT[20,26]. To address these concerns, the development of appropriate guidelines, regulations, and technologies for detecting AI-generated outputs and ensuring the safe and responsible use of ChatGPT and other LLMs in healthcare, academia, and research has been proposed[16,26,27,34]. The academic community must address these challenges by investing in the development of robust quality control measures for AI-generated content, including stringent human supervision, validation of generated content, and ensuring that AI-generated outputs meet high standards of accuracy, originality, and integrity[29,34]. In addition, funders, publishers, and research institutions should adopt clear policies to encourage openness and public understanding of the use of AI-generated content[20].

Several key issues need to be discussed, including the potential for AI-generated content to be used unethically, the need for transparency and honesty, the risk of manipulating public opinion or decision-making, the necessity of policies and guidelines, and the potential for AI-generated content to transform research practices and publication[20]. Furthermore, academic publishers should engage in discussions about the implications of AI-generated content and create comprehensive guidelines for publishing such content[30]. Notably, according to recent articles, it can be difficult for journal editors to recognize and reject papers written by AI because these models can often produce texts that look very similar to those written by humans[22]. The use of GPT-3 as a co-author in a study published in the journal Oncoscience has sparked a debate about authorship conventions in the context of AI-generated content[35]. While some experts argue that AI shouldn't be given credit for writing, others highlight their role in generating ideas and producing papers. This ongoing discussion may lead to changes in authorship conventions in the future[35].

The rise of AI models like ChatGPT presents both opportunities and challenges in the fields of medical education, scientific writing, and research. Addressing the ethical, legal, and quality concerns associated with AI-generated content requires the collective efforts of the academic community, publishers, and AI developers. By proactively establishing guidelines, regulations, and policies, the potential benefits of AI-generated content can be realized while minimizing the risks associated with its misuse.

BALANCING THE BENEFITS AND ETHICAL IMPLICATIONS OF CHATGPT IN HEALTHCARE AND EDUCATION

ChatGPT, a powerful AI tool with potential applications across various fields, has been the subject of numerous studies and discussions. Despite its promise in reducing the time required for tasks, it has several limitations and ethical implications that need to be considered, particularly in sensitive fields like healthcare and education[11,20,22,28-30,36]. One primary concern is the accuracy of the information generated by ChatGPT, as it heavily depends on the quality of its training data[23,37]. The risk of biased or misleading results due to poor-quality datasets is particularly relevant in fields like medical education and clinical decision-making, which require high levels of precision[12,13,24]. Such inaccuracies may negatively impact patient outcomes and damage the reputation of the medical community, while in the realm of education, they could lead students astray and impede learning[25,26,29,34]. O'Connor[23] warns against relying on automated tools like ChatGPT to detect plagiarism in nursing education, suggesting a combination of assessment methods, including oral presentations and objective structured clinical examinations, along with smaller pieces of scientific writing. This approach would reduce the risk of automated answers in students' work and emphasize the importance of academic integrity, critical thinking, and scientific writing skills. Additionally, other papers discourage the use of ChatGPT or similar technologies for writing research articles or cheating on assignments[10,26]. Another limitation of ChatGPT is its inability to perform well on tasks requiring critical thinking or reasoning[15,36]. Duong and Solomon [15] acknowledges that the model's performance may not generalize to all types of genetics questions or contexts, as it performs better on memorization-type questions than on critical thinking ones. This indicates that relying solely on AI models like ChatGPT may not be sufficient for addressing complex tasks in various fields, including healthcare and education. Moreover, ChatGPT is prone to generating fake references and citations, a phenomenon referred to as "hallucination" or "stochastic parroting"[22]. This poses a significant challenge for journal editors, as the output may

contain fabricated information, undermining the credibility of scientific research. The potential misuse of ChatGPT for plagiarism also raises concerns[10,16,23,26,36], which could disrupt traditional methods of assigning essays and lead to a decline in academic integrity.

In addition to the aforementioned concerns, the utilization of ChatGPT poses several other challenges, including the dangers of blind trust, excessive regulation, dehumanization, misaligned optimization targets, information overload, false forecasting, and the need for self-reference monitoring[38-40]. A study found that there are worries about the possible dangers of using GPT-3 for online radicalization and extremism. The model can be manipulated to amplify extremist ideologies, generate polemics reminiscent of past attackers, and propagate harmful beliefs. Efforts should be made to understand and mitigate these risks effectively[41]. Another study emphasizes the need to handle privacy and Personally Identifiable Information retention issues when employing AI-powered chatbots, especially in delicate situations like summarising cover letters. It underlines the requirement for responsible AI use and the creation of privacy protection measures[42]. Moreover, language models like ChatGPT can give rise to various detrimental outcomes, such as discrimination, toxicity, information hazards, misinformation propagation, malicious exploitation, issues with human-computer interaction, and environmental impacts[39,40]. These challenges underscore the significance of responsible usage and achieving a balance between regulation and innovation.

The integration of AI-generated content raises questions about authenticity, accountability, privacy, and security[1,18]. As a result, there is an urgent need for guidelines and regulations to ensure the safe and responsible use of ChatGPT and other LLMs. Chatterjee and Dethlefs[27] emphasizes the responsibility of tech companies like OpenAI to provide solutions to manage potential misuse and ensure the ethical use of powerful AI models. The Lancet article also calls for investment in detecting problematic outputs and establishing editorial policies that keep up with evolving technology to ensure the safe and ethical use of AI tools like ChatGPT in scholarly publishing[34]. The reliance on LLMs like ChatGPT for scientific thinking may impede social and scientific progress, as these models are trained on past information and may not be able to think differently from the past[28]. Researchers and academics should remain vigilant in their use of AI tools, emphasizing human involvement in hypothesis formulation, experimental design, and interpretation of results to ensure that the scientific record remains a product of human endeavor in grappling with critical questions[25].

Other key ethical issues brought up by the use of ChatGPT include those bias, authorship, privacy and security, transparency, abuse, and privacy and security. One major concern is the potential for bias in ChatGPT's responses, stemming from biases present in the training data, model bias, and non-representative data labelers. This bias can perpetuate and amplify societal biases, leading to unfair and discriminatory outcomes. Privacy and security are also significant issues, as ChatGPT collects data during training, including potentially sensitive personal information, and user interactions with the system may inadvertently disclose personal details, posing risks if obtained by malicious entities. Another ethical concern is the lack of transparency in ChatGPT's decision-making process and the limited disclosure of technical details by OpenAI, making it challenging for users to have control over the generated content and understand the model's limitations. Furthermore, there are concerns regarding the potential for abuse, including the spread of misinformation and the impersonation of individuals using ChatGPT[38,40].

A review of the primary literature on AI-assisted psychosis risk screening in adolescents focuses on two specific methods: chatbot-based screening and analysis of large-scale social media data. The authors highlight ethical issues as the primary challenge in utilizing AI for psychiatric risk screening. They emphasize the need for compliance with the biomedical ethical principles of respect for autonomy, non-maleficence, beneficence, and impartiality[43]. A different study on ChatGPT's moral authority shows that it has the potential to enhance users' moral judgement, but also emphasizes its inconsistency and capability to taint judgement. Users underestimate its power, making responsible use and instruction in digital literacy necessary to effectively understand its recommendations[44]. Another paper, on the other hand, offers proof that language models developed using reinforcement learning from human feedback (RLHF) are capable of "moral self-correction" by avoiding damaging outputs when specifically told to do so. This ability, which involves the models' capacity for comprehension and instruction following, arises with larger models trained with RLHF. The results point to the possibility of teaching language models to follow moral standards, providing cause for cautious hope[45]. A review of the primary literature on AI-assisted psychosis risk screening in adolescents focuses on two specific methods: Chatbot-based screening and analysis of large-scale social media data. The authors highlight ethical issues as the primary challenge in utilizing AI for psychiatric risk screening. They emphasize the need for compliance with the biomedical ethical principles of respect for autonomy, non-maleficence, beneficence, and impartiality.

While ChatGPT offers numerous benefits, its limitations and ethical implications must be carefully considered. Publishers, funders, and researchers must establish clear rules and regulations regarding the use of ChatGPT and similar tools in academic research[11,20,22,28-30,36,38-40]. For instance, in healthcare, AI-generated summaries using patient data should be manually reviewed by a healthcare professional before use, taking into account patient acceptability and potential consequences of technology failure[17]. Transparency and accountability should be prioritized by researchers and developers by disclosing data on bias, privacy, and system constraints. Vulnerable users should be given extra protection, and it's crucial to communicate clearly about ChatGPT's capabilities and restrictions. ChatGPT responses should be justified and given only in response to specific requests. The accuracy of ChatGPT's responses can be improved by including domain-specific knowledge through expert-curated data. At the same time, users must validate information, tell facts from fiction, comprehend ramifications, communicate clearly, and be aware of terms and conditions. Regulators and politicians should strive for a balanced strategy that steers clear of overregulation and prevents information and communication concentration. To handle complex ethical issues, ethicists need to work in conjunction with specialists from a variety of professions[38]. It is advised, in terms of regulation policy, to put measures in place that stop the abuse of ChatGPT in academic settings, such as using different exam formats and applying AI content detectors for plagiarism detection. The issue of including ChatGPT as a co-author in academic works should be addressed with clear norms and disclosure requirements. It's important to note that ChatGPT-generated content isn't protected by copyright[40]. The

development of risk assessment frameworks and tools to evaluate the potential risks connected to language models should be an area of focus of future studies. It is necessary to incorporate disciplines like ethnographic research and human-computer interaction into the methodological toolbox for language model analysis. Furthermore, to create efficient plans for resolving identified hazards, technological and sociotechnical mitigation research is required. To establish normative performance levels, benchmarking initiatives should be conducted with input from all participants. To fully understand the possible advantages and overall social impact of language models, a thorough investigation should be done[39]. Overall, a cautious and well-considered approach is necessary for the integration of AI tools like ChatGPT, with an emphasis on maintaining human involvement in critical aspects of research, assessment, and decision-making processes. By doing so, we can ensure the responsible and ethical use of AI while leveraging its benefits in various fields.

THE FUTURE OF AI AND HUMAN INTELLIGENCE - INTEGRATING CHATGPT RESPONSIBLY

The ChatGPT has demonstrated remarkable potential in various fields, including medicine, education, law, and scientific research[9,11,15,16,18]. This large language model exhibits proficiency in answering questions, producing well-referenced writing, assisting in drafting papers, and providing support for clinical decision-making[9,12,13,15,21]. However, it is important to recognize the limitations and potential risks of AI, as human intelligence, creativity, and critical thinking remain essential components of scientific inquiry and progress. AI tools should be viewed as complementary rather than a replacement for human expertise. In medical education and clinical decision-making, ChatGPT has been found to perform at or near the passing threshold for USMLE[13], highlighting its potential as an interactive medical education tool and in assisting with radiologic decision-making, streamlining clinical workflow, and improving responsible use of radiology services[12]. Nevertheless, its application in these fields should be approached with care, acknowledging its limitations, the risk of biased or misleading results, and the importance of human involvement in the decision-making process[23,25,29].

In scientific publishing, ChatGPT has demonstrated the capacity to accelerate the writing and editing process[21]. However, concerns about the authenticity and accountability of AI-generated content have been raised[30,34]. Researchers suggest that academic publishers engage in discussions about the implications of AI-generated content and establish comprehensive guidelines for publishing such content[30]. Moreover, some studies emphasize the need for collaboration in preventing potential misuse of AI models like ChatGPT and call for tech companies to take responsibility for managing potential misuse[27]. An article published in Nature highlights the issues that require attention, such as the tasks that should be delegated to LLMs, the qualifications and skills necessary for researchers, the stages of the AI-assisted research process that need human verification, and the laws required to deal with LLMs[20]. There should also be discussions on how LLMs can be used to educate and train researchers, how researchers and funders can encourage the development of independent, open-source LLMs, and what standards of quality should be expected of LLMs. Further topics include how LLMs can advance open science principles and research equity, as well as the legal ramifications LLMs may have on scientific practice[20].

The development of ChatGPT's ability to interact with humans naturally and ask follow-up questions to reduce bias holds great promise for its future applications[27]. By using reinforcement learning to optimize the model, ChatGPT becomes more robust and capable of sustaining longer conversations with users. The potential of ChatGPT extends beyond the examples mentioned in the paper, including prospects for its use in various industries such as customer service, education, and mental health[27].

As AI technologies continue to advance, they have the potential to revolutionize numerous fields, including healthcare, education, and scientific research. However, there are several key considerations for future developments, as highlighted by the cited research: (1) Enhancing AI capabilities: Future AI models should aim to improve their performance on critical thinking tasks, as well as memorization-type questions, to be more effective in assisting human experts in various fields [15]; (2) Addressing biases: AI developers should work to minimize biases in AI systems, as these biases can limit the effectiveness and ethical use of AI tools[25]; (3) Ensuring ethical use: Tech companies and researchers must prioritize the ethical use of AI tools and develop strategies to prevent misuse[27]. This includes investing in methods to detect problematic outputs and establishing editorial policies that can adapt to evolving technology[34]; and (4) Fostering collaboration: The integration of AI and human expertise should be encouraged, promoting a collaborative approach that leverages the strengths of both AI and human intelligence[10]. The challenges of ChatGPT is depicted in Figure 1.

By focusing on these key areas, future advancements in AI can help address current limitations and ensure that the technology is employed responsibly and ethically. Through this approach, AI can be harnessed to improve healthcare, education, and scientific research, all while maintaining the importance of human intelligence and critical thinking.

CONCLUSION

ChatGPT has shown significant potential in revolutionizing various fields, including science, healthcare, and education, by accelerating processes, enhancing personalization, and providing valuable support to professionals and learners alike. Despite its capabilities, it is important to recognize that ChatGPT is not a substitute for human intelligence and its use comes with an array of ethical, legal, and quality-related challenges that need to be addressed to harness its full potential. Establishing clear guidelines and usage policies is essential to ensure the responsible integration of ChatGPT in academic and professional settings. This includes maintaining transparency in AI-generated content, acknowledging the potential

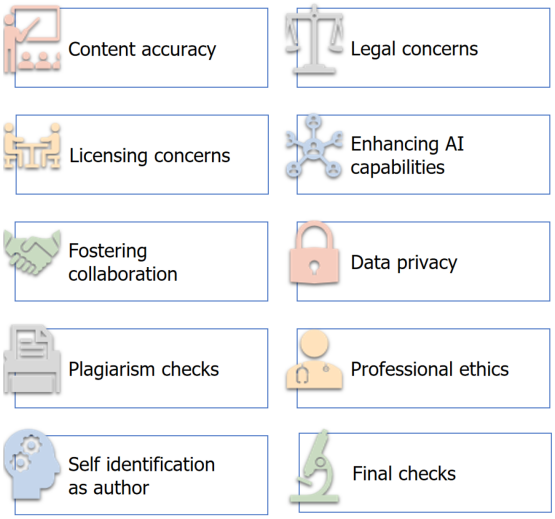

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Figure 1 Challenges of ChatGPT.

for misinformation and plagiarism, and promoting adherence to quality standards. Furthermore, as AI systems like ChatGPT continue to advance, continuous research, interdisciplinary collaboration, and dialogue among stakeholders are crucial in addressing the limitations, risks, and ethical implications of this emerging technology.

In the healthcare sector, for instance, striking a balance between the benefits of AI assistance and the potential risks associated with misinformation is of utmost importance. Close monitoring, human verification, and careful consideration of patient acceptability are necessary to mitigate these risks. Similarly, in education, it is essential to maintain academic integrity and discourage any unethical use of ChatGPT while exploring its potential for personalized learning experiences. As the landscape of AI-assisted research and applications continues to evolve, it is important to examine the broader implications of ChatGPT and similar tools on the job market, legal frameworks, and societal values. The development of open-source LLMs, the establishment of standards of quality, and the evaluation of legal ramifications are topics that warrant further exploration.

While ChatGPT holds great promise in transforming various industries and enhancing research and learning experiences, it is essential to adopt a cautious and responsible approach to its integration. By fostering interdisciplinary collaboration, ongoing research, and proactive policy development, the research community can ensure that conversational AI is utilized ethically, effectively, and responsibly, paving the way for innovative applications that positively impact society.

FOOTNOTES

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REVIEW

Compensated liver cirrhosis: Natural course and disease-modifying strategies

Ramesh Kumar, Sudhir Kumar, Sabbu Surya Prakash

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Abstract

Compensated liver cirrhosis (CLC) is defined as cirrhosis with one or more decompensating events, such as ascites, variceal haemorrhage, or hepatic encephalopathy. Patients with CLC are largely asymptomatic with preserved hepatic function. The transition from CLC to decompensated cirrhosis occurs as a result of a complex interaction between multiple predisposing and precipitating factors. The first decompensation event in CLC patients is considered a significant turning point in the progression of cirrhosis, as it signals a drastic decline in median survival rates from 10-12 years to only 1-2 years. Furthermore, early cirrhosis has the potential to regress as liver fibrosis is a dynamic condition. With the advent of effective non-invasive tools for detecting hepatic fibrosis, more and more patients with CLC are currently being recognised. This offers clinicians a unique opportunity to properly manage such patients in order to achieve cirrhosis regression or, at the very least, prevent its progression. There are numerous emerging approaches for preventing or delaying decompensation in CLC patients. A growing body of evidence indicates that treating the underlying cause can lead to cirrhosis regression, and the use of non-selective beta-blockers can prevent decompensation by lowering portal hypertension. Additionally, address-ing various cofactors (such as obesity, diabetes, dyslipidaemia, and alcoholism) and precipitating factors (such as infection, viral hepatitis, and hepatotoxic drugs) that have a detrimental impact on the natural course of cirrhosis may benefit patients with CLC. However, high-quality data must be generated through well-designed and adequately powered randomised clinical trials to validate these disease-modifying techniques for CLC patients. This article discussed the natural history of CLC, risk factors for its progression, and therapeutic approaches that could alter the trajectory of CLC evolution and improve outcomes.

Key Words: Compensated cirrhosis; Compensated advanced chronic liver disease; Clinical decompensation; Cirrhosis reversal; Disease-modifying agents; Acute-on-chronic liver failure

Core Tip: Compensated liver cirrhosis might be reversible if the underlying cause is treated before the disease progresses. The median survival for these individuals is typically 10-12 years; however, after the first decompensation, it drastically drops to 1-2 years. As a result, the outcomes of such patients can be significantly improved by integrating a number of disease-modifying therapy strategies that address complex pathophysiology, risk factors, and triggering events linked with disease progression. This article discussed the natural course of compensated liver cirrhosis, risk factors for its progression, and potential therapeutic strategies to favourably influence its natural evolution and enhance outcomes.

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INTRODUCTION

The prevalence and mortality associated with liver cirrhosis (LC) continue to increase despite improvements in knowledge and medical care. According to data from the United States, the annual number of LC-related deaths has risen by 65%, while the number of hospitalisations for LC has nearly doubled in a decade[1,2]. LC has traditionally been regarded as a singular entity with a continuum of increasing degrees of severity until death or liver transplantation. Recently, these paradigms have shifted, leading to the recognition of LC as a heterogenous condition with varying prognosis across the different stages[3,4]. The term "compensated liver cirrhosis" (CLC) is used to describe LC without one or more decompensating events, such as ascites, hepatic encephalopathy, variceal haemorrhage (VH), and jaundice [5]. After experiencing a decompensation event, LC patients are always classified as decompensated LC (DLC) because the pathogenic mechanisms that caused the decompensation persist. When LC patients were separated into two groups based on decompensating events, the median 1-year survival in CLC patients was 95% compared to 61% in DLC patients [6]. Therefore, the first decompensation in CLC patients is regarded as a prognostic watershed due to a substantial reduction in median survival from 10-12 years in CLC to only 1-2 years in DLC[6].

LC has long been viewed as the end stage of chronic liver disease (CLD). However, this perception has started to shift in the past two decades. Wanless *et al*[7] were the first to describe the reversal of LC, and since then numerous series of LC patients with diverse aetiologies have demonstrated the same[7,8]. Patients with CLC remain asymptomatic and undiagnosed for the first few years[9]. Despite being asymptomatic, between one-third and one-half of CLC patients have varices and clinically significant portal hypertension (CSPH) at the time of diagnosis[10-12]. Over time, CLC patients develop several risk factors that increase their susceptibility to clinical decompensation, such as rising portal pressure, systemic inflammation, and haemodynamic changes. Moreover, certain triggers including bacterial infection, medications, or alcohol can acutely precipitate decompensation. When the underlying cause of CLC is eliminated early on, a significant proportion of patients experience cirrhosis regression[7,8].

Even when regression of LC is not possible, there are variety of evolving strategies for preventing or delaying decompensation in such patients. Therefore, the prognosis of such patients can be greatly enhanced by early diagnosis of CLC. However, the medical community has predominantly focused its efforts on managing and improving the outcomes for patients with DLC, with little attention given to the medical management of CLC. In order to enhance the ease of diagnosis of advanced CLD noninvasively using transient elastography, the Baveno VI consensus introduced the new term "compensated advanced CLD" that encompasses CLC and CLD with advanced fibrosis[13]. Due to efficient noninvasive testing tools, more and more LC patients are now being recognised at an early compensated stage[14]. This offers the gastroenterologists and hepatologists greater opportunities to intervene and alter the trajectory of the natural evolution of CLC. This article discussed the natural history of CLC, risk factors for its progression and decompensation, and potential therapeutic strategies to change the course of the illness and improve the outcomes.

NATURAL HISTORY OF CLC

The natural progression of LC is characterised by a continuum from a long silent compensated phase to a more progressive symptomatic decompensation phase (Figure 1). As LC progresses over time, patients develop a variety of risk factors, including altered liver architecture, portal hypertension (PHT), systemic inflammation, and haemodynamic alterations that increase the risk for clinical decompensation. Decompensation may occur insidiously due to slowly increasing portal pressure and deteriorating hepatic function, often referred to as non-acute decompensation (AD)[5]. However, different triggering events, such as bacterial infection, alcohol, bleeding, medications, or a flare-up of liver disease, can lead to AD within days, which may progress to acute-on-chronic liver failure (ACLF). In patients with CLC, decompensation represents a turning point in terms of mortality risk, patient quality of life, and propensity for hospitalisation.

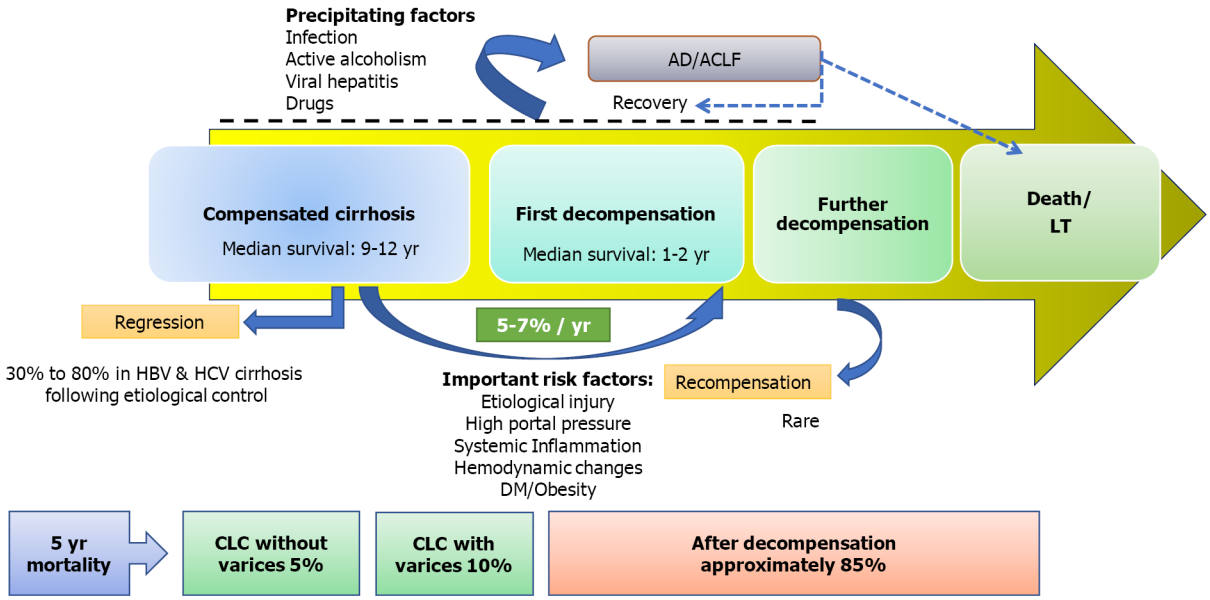

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Figure 1 Natural course of patients with compensated liver cirrhosis. The natural progression of cirrhosis is characterised by a continuum from an asymptomatic compensated phase to a symptomatic decompensation phase. The rate of transition from a compensated to a decompensated stage is about 5%-7% each year. The 5-year mortality rate in compensated cirrhosis without or with varices is 5% and 10%, respectively. There are several known factors associated with decompensation such as high portal pressure, persistent etiological injury, systemic inflammation, and haemodynamic alterations. In addition, several types of triggering events, such as bacterial infection, alcohol, viral hepatitis, or medications, may cause acute decompensation (AD) and acute-on-chronic liver failure (ACLF). Prompt and effective control of etiological factors are associated not only with regression of compensated cirrhosis but also with recompensation of decompensated cirrhosis (data adapted from references 3, 6, 18, and 31). CLC: Compensated liver cirrhosis; DM: Diabetes mellitus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; LT: Liver transplantation.

In a systematic review, pooling of data from relevant studies, revealed that the survival of patients with LC varied from 1 mo to 186 mo, with a median survival > 12 years for CLC and 1.8 years for DLC[6]. The rate of transition from a compensated to a decompensated stage is approximately 5%-7% each year[15]. Ascites is typically the first sign of decompensation in most studies. Overall, the 5-year mortality rate in CLC patients is only 1.5% for those without CSPH, 5.0% for those with CSPH but no varices, and 10.0% for those with CSPH and varices, highlighting the significance of PHT in mortality risk[3]. Therefore, CLC patients without varices and without CSPH constitute a highly compensated group with a very low mortality risk[6].

The first decompensation of CLC does not always indicate a point of no return in the natural course of LC. Emerging data suggests that although it is an uncommon occurrence, recompensation of DLC is possible if the underlying cause of LC is suppressed[16]. Recompensated cirrhosis is indeed a real condition, and the Baveno VII consensus has provided a standard definition for it[17]. Similarly, it is now more widely acknowledged that CLC can regress to a non-cirrhotic stage when etiological factors are promptly controlled[7,18]. Liver fibrosis is a dynamic condition, and early LC, which lacks extracellular matrix crosslinking and marked angiogenesis, can even revert into normal architecture[19].

FACTORS ASSOCIATED WITH DECOMPENSATION OF CLC

The transition from CLC to DLC occurs as a result of a complex interaction between predisposing and precipitating factors (Table 1). The development of PHT is the key factor causing the switch from CLC to DLC[10,20-22]. In a study, patients with a hepatic venous pressure gradient (HVPG) < 10 mmHg had a 90% probability of not developing clinical decompensation over 4 years. As the HVPG rises above 10 mmHg, which signifies CSPH, the risk of decompensation begins to rise[10]. VH typically occurs when HVPG is higher than 12 mmHg[15]. Another study found that CLC with a baseline HVPG > 20 mmHg had a 47% risk of decompensation in mean duration of just 1.6 years[21]. There is also growing evidence that long-term use of non-selective beta-blockers (NSBBs) significantly reduces the risk of decompensation[22]. Thick fibrous septa and small nodules observed in liver biopsy specimens of CLC patients are associated with CSPH and an increased risk of decompensation[23-25]. Ongoing liver damage caused by etiological factors also increases the risk of decompensation. This is supported by the finding that attaining a sustained virological response (SVR) in hepatitis C virus (HCV)-cirrhosis and maintaining viral suppression in hepatitis B virus (HBV)-cirrhosis significantly lowers the incidence of decompensation[26-29]. The neurohormonal and inflammatory alterations in LC contribute to decompensation in the form of ascites by causing splanchnic vasodilatation and lymphatic dysfunction[30-32].

Table 1 Factors associated with decompensation of compensated liver cirrhosis

Risk factors for non-acute decompensation	Precipitating factors for acute decompensation
Thick fibrous septa and micronodularity on liver biopsy	Bacterial infection
Persistent liver injury by etiological factor	Active alcoholism
High portal pressure	Gastrointestinal haemorrhage
Systemic inflammation & hemodynamic changes	Consumption of hepatotoxic drug/alternative medicine
Metabolic risk factors: DM, obesity, and dyslipidaemia	Superinfection or flare of viral hepatitis
Genetic risk factors: *PNPLA3* G/G genotype	Major surgery and general anaesthesia

DM: Diabetes mellitus; *PNPLA3*: Patatin-like phospholipase domain-containing protein 3.

Several metabolic factors have also been found to influence the risk of decompensation[33-36]. CLC patients with diabetes have a higher risk of developing any decompensating event than those without diabetes[33]. Obesity has a negative impact on the natural course of CLC, regardless of aetiology, and increases the risk of decompensation[34]. Sarcopenia and myosteatosis, which are common in CLD with various aetiologies, appear to promote the progression of CLD to advanced stages[35]. Another study found that the *PNPLA3* G/G genotype, involved in triacylglycerol hydrolysis, was associated with a 2-fold increase in the probability of decompensation[36]. Gut dysbiosis, characterised by a loss of beneficial commensals and an increase in pathogenic organisms, significantly influences the natural course of LC patients[36-40]. Furthermore, cirrhosis-associated immune dysfunction, involving both immune deficiency and proinflammatory immune cell activation, contributes to haemodynamic disturbances and PHT, accelerating the development of decompensation[41-43].

Bacterial infection can cause AD by escalating the intensity of systemic inflammation and PHT. In a large prospective study of 1672 patients with compensated HCV-related or HBV-related cirrhosis, bacterial infections preceded and precipitated decompensation in 13% of patients over a 5-year period[44]. Overall, bacterial infection is considered to be the most frequent precipitant of AD (22%-29%) and ACLF (33%-50%)[45]. Alcoholic hepatitis can cause decompensation in patients with CLC through various mechanisms[46,47]. AD and ACLF frequently develop in patients with LC undergoing surgery [48]. In a study using an animal model of CLC, it was discovered that extrahepatic surgery raises the portal pressure during the postoperative period, leading to decompensation[49]. Other situations where decompensation can develop in patients with CLC include superimposed viral hepatitis, consumption of hepatotoxic medications, and vascular thromboses[50].

DISEASE-MODIFYING TREATMENT STRATEGIES

The present strategy for managing patients with LC is centred on strategies intended to avoid or treat complications, without giving much thought to their effects on the natural history of LC. There is a need to pay more attention to agents that target key points in the complex pathophysiology of LC. The ideal goal of a disease-modifying medication should be the regression or reversal of cirrhosis. If this is not possible, the next goal should be to prevent or at least delay the progression of the disease. Growing evidence suggests that addressing the underlying cause of LC and reducing PHT by NSBB have positive impacts on the natural history of patients with CLC[7,8,22,26,29]. Moreover, such patients may potentially benefit from addressing a number of cofactors and precipitating factors that have a negative influence on the natural course of LC[51]. Thus, effective disease-modifying treatment strategies might include: (1) Removal of etiological factors; (2) Pathophysiology-oriented therapy; (3) Management of adverse cofactors like obesity, DM, dyslipidaemia, and alcoholism; (4) Anti-fibrotic and regenerative therapies; and (5) Elimination of precipitating factors that lead to AD/ACLF.

Removal of etiological factors

The main prerequisite for fibrosis regression is the cessation of liver injury, which is accomplished through therapeutic control of causal factors. Regression of LC has been extensively described in patients with HBV-related and HCV-related cirrhosis after aetiological treatment (Table 2). Nevertheless, robust data supporting the regression of non-viral causes of LC are generally lacking.

Viral cirrhosis: Dienstag *et al*[26] reported regression of LC in 73% (8/11) of patients following 3 years of lamivudine therapy. In another prospective study, treatment with adefovir dipivoxil for up to 240 wk resulted in regression of bridging fibrosis or cirrhosis in 58% (7/12) of patients[27]. Pegylated interferon and ribavirin combination therapy has been shown to reduce liver fibrosis following SVR. Combination therapy led to the reversal of LC in 49% of patients in a pooled data analysis from four randomised controlled trials (RCTs) that included 153 patients with HCV-cirrhosis at baseline[52]. Though data are still evolving, a recent study found that direct-acting antivirals were effective in reducing fibrosis based on FibroScan[53]. In a systematic review of 463 patients with HBV-cirrhosis, regression of LC was observed in 33% to 80% of patients following sustained viral suppression. Meanwhile, LC regressed in 33% to 100% of 58 patients

Table 2 Impact of etiological treatment on regression of liver cirrhosis

Ref.	Study design	Drug/duration	Patients, *n*	Baseline LC	Main results
Dienstag *et al*[26], 2003	Prospective, partially randomised	Lamivudin/3 yr	63 CHB	11	LC regressed in 8 of 11 patients (73%)
Hadziyannis *et al*[27], 2006	Prospective	Adefovir dipivoxil, up to 240 wk	125 CHB	4	58% had reversal of bridging fibrosis/cirrhosis; 3 of 4 LC patients had reversal
Marcellin *et al*[29], 2013	Randomised trial	TDF/adefovir for 48 wk then open-label TDF	641 CHB	96	71 of 96 (74%) became non-cirrhotic at 5 yr
Poynard *et al*[52], 2002	Pooled data from RCTs	IFN/PEG-IFN + RBV	3010 CHC	153	The reversal of LC was observed in 75 patients (49%)
Mauro *et al*[53], 2018	Retrospective	DAAs/IFN + RBV	112 HCV-infected LT recipients	37	Regression of fibrosis in 43% of LC (16/37)
Lassailly *et al*[55], 2020	Prospective	Bariatric surgery	180 obese NASH	9	At 5 yr, fibrosis regression was seen in 68% of advanced fibrosis and 33% of patients had reversal of LC
Sanyal *et al*[54], 2022	Data from two RCTs	Simtuzumab or selonsertib or placebo	1135 NASH patients, 709 (62%) had Ishak stage 6 fibrosis	709	LC regression occurred in 16% (176/1135). Drugs were not better than placebo
Dufour *et al*[64], 1997	Retrospective	Immunosuppressant	8 AIH cirrhosis	8	LC regressed in all
Czaja *et al*[63], 2004	Retrospective	Corticosteroid	87 AIH	14	LC regressed in 4 of 14 patients
Bardou-Jacquet *et al*[66], 2020	Retrospective	Venesection	106 patients with haemochromatosis	66	LC regressed in 15 of 66 (23%) during median follow-up of 9.5 yr

AIH: Autoimmune hepatitis; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C; DAAs: Direct-acting antivirals; HCV: Hepatitis C virus; IFN: Interferon; LC: Liver cirrhosis; LT: Liver transplantation; NASH: Nonalcoholic steatohepatitis; PEG-IFN: Pegylated interferon; RBV: Ribavirin; RCT: Randomised controlled trial; TDF: Tenofovir disoproxil fumarate.

with HCV-cirrhosis following SVR[28]. This suggests that once the causal element is removed early in the course of CLC, progression is halted and cirrhosis regression occurs in a significant number of patients.

Non-viral cirrhosis: Weight loss through lifestyle changes improves fibrosis in patients with nonalcoholic steatohepatitis (NASH), but its effects on NASH-cirrhosis per se are still poorly understood. In a recently published study involving 709 patients with compensated NASH-cirrhosis from two RCTs on simtuzumab and selonsertib *vs* placebo, regression of LC was observed in 135 patients during a median follow-up of 16.6 mo. Notably, the impact of the drug was not better than placebo, indicating the influence of lifestyle modification[54]. Another study that assessed the long-term effects of bariatric surgery in 180 obese patients with NASH found significant regression of fibrosis at 5 years after surgery. The fibrosis decreased in 70.2% of patients, disappeared in 42.0% of patients, and 33.0% of patients with baseline LC became non-cirrhotic[55]. However, the outcomes of RCTs on a variety of compounds that target the metabolic/inflammatory pathways of NASH-cirrhosis have been dismal[56-59]. In a recent RCT with emricasan, an oral pan-caspase inhibitor, there was a small treatment effect on HVPG reduction in compensated NASH cirrhosis; however, the drug was overall ineffective in improving clinical outcomes[56]. Belapectin, an inhibitor of galectin-3 that was earlier found to reduce liver fibrosis and PHT in rats, was proven to be ineffective in human NASH-cirrhosis[57].

Abstinence from alcohol improves the prognosis in all stages of alcohol-related LC; nevertheless, there is scant clinical support for fibrosis/cirrhosis regression in alcoholic liver disease[60-62]. In one study, patients who were abstinent *vs* those who were not showed a 3-year decompensation likelihood of 32.4% *vs* 60.0%, respectively[60]. Early alcohol abstinence after LC diagnosis was found to be a significant predictor in survival, with abstinent patients having a 72% survival rate at 7 years compared to 44% in patients who continued to consume alcohol[61]. Reversibility of hepatic fibrosis has also been documented in autoimmune hepatitis patients[63,64]. A study on corticosteroid-treated autoimmune hepatitis has revealed regression of histological LC from 16% to 11%[63]. Ursodeoxycholic acid treatment may halt disease progression and improve the survival of patients with primary biliary cholangitis, but it appears to be less effective in promoting fibrosis regression[65]. In a retrospective analysis of patients with haemochromatosis treated with venesection, LC regression was observed in 15 out of 66 (23%) over a median period of 9.5 years[66].

Pathophysiology-oriented therapy

NSBB: In patients with LC, CSPH appears to be an important pathophysiologic driver of the first decompensating event [10,20-22]. The onset of PHT is primarily caused by elevated portal blood inflow resistance resulting from architectural

distortion (fixed component) and increased elevated hepatic microvascular tone (dynamic component). The increased hepatic vascular tone is attributed to decreased intrahepatic vasodilators, primarily nitric oxide (NO), and increased production of vasoconstrictors such as angiotensin, endothelins, and prostanoids. Portosystemic collaterals appear later, heralding splanchnic vasodilation, increased splanchnic blood flow, and hyperkinetic circulation, all contributing to further raise portal pressure. The only pharmacological class that is still recommended for long-term treatment of PHT is NSBB. Importantly, NSBBs are only beneficial in patients with CSPH and not in those with subclinical PHT because they reduce portal venous flow, and significant hyperdynamic circulation only develops once CSPH is set[67]. Adequate responses to NSBBs are associated with a lower incidence of decompensating events and improved survival rate, indicating a positive influence on the natural history of LC (Table 3).

According to current recommendations, patients with high-risk varices should have NSBBs or endoscopic variceal ligation (EVL) as primary prophylaxis for VH[68]. While choosing between NSBBs and EVL, the patient's preferences, tolerance, side effect profile, and contraindications can all be taken into account[69]. Importantly, NSBB, in addition to being as effective as EVL at preventing VH, has the added benefit of lowering the risk of decompensation and mortality [22,70-73]. Among commonly used NSBBs, propranolol and nadolol reduce portal pressure by reducing portal venous inflow by blocking β_1 and β_2 adrenergic receptors, whereas carvedilol has additional intrinsic vasodilatory activity because of its anti-α-adrenergic activity and its ability to increase NO release[74]. Moreover, carvedilol has been observed to cause greater reduction in HVPG compared to propranolol or nadolol[75,76]. Carvedilol might be especially useful for patients with CLC, where a higher hepatic vascular resistance is the main cause of PH[76,77].

The emerging evidence strongly indicates that NSBBs can prevent decompensation in patients with CLC. The PREDESCI trial, a multicentre, double-blind, RCT, studied whether the administration of NSBBs over an extended period of time prevents the development of clinical decompensation and increase survival in CLC patients with CSPH[22]. In this study, 201 patients with CLC with CSPH were randomly assigned to receive NSBBs or a placebo. After a median follow-up of 37 mo, the NSBB arm showed considerably lower rates of clinical decompensation compared to the placebo arm [17% *vs* 27%, hazard ratio (HR): 0.51, 95% confidence interval (CI): 0.26-0.97]. Among decompensating events, decreased incidence of ascites (20% *vs* 9%) was the main effect of NSBB. However, the PREDESCI trial hinged the choice of NSBB on the HVPG response to intravenous propranolol, which is impracticable for a large population of patients. In a recent competing-risk time-to-event meta-analysis that included 352 patients with CLC, 181 carvedilol-treated patients, and 171 controls from 4 RCTs, long-term carvedilol therapy was associated with a decreased risk of decompensating events and improved survival. Carvedilol decreased the risk of decompensation, mainly ascites, with a subdistribution HR of 0.506 (95%CI: 0.289-0.887), and the risk of death with a subdistribution HR: of 0.417 (95%CI: 0.194-0.896)[78].

Statins: Several studies have been published in recent years on the beneficial effects of statins in patients with LC. The benefits include a decrease in portal pressure, favourable effects on sinusoidal endothelial function, hepatic microcirculation, and liver fibrosis[79]. In the first such study of statins in LC, simvastatin was found to increase NO generation in liver sinusoids and reduced intrahepatic vascular resistance[80]. Furthermore, it was found that simvastatin had an additive effect with NSBB on HVPG reduction[81]. Several moderate-quality studies have suggested that the use of statins in CLC lowers the risk of hepatic decompensation and mortality[82-84]. In a large study from Taiwan, including 1350 patients with LC, statin use decreased the risk of decompensation, mortality, and hepatocellular carcinoma in a dose-dependent manner. With statins, the incidence of decompensation was 61% lower in HBV-cirrhosis and 49% lower in HCV-cirrhosis[85].

In a recent systematic review and meta-analysis, statins were associated with a 46% reduced risk of hepatic decompensation and a 46% lower risk of mortality in patients with LC[86]. Notably, LC patients who benefit from statins are mainly those with Child-Pugh classes A or B but not those with Child class C. In DLC, simvastatin at higher doses may even cause rhabdomyolysis and hepatotoxicity[87,88]. Therefore, despite a strong case for statins being helpful for patients with LC, more evidence from high-quality RCTs is required before they can be regularly recommended for patients with CLC. Until then, it is safe to presume that patients with CLC with dyslipidaemia should not be denied statin therapy.

Anticoagulant: As LC progresses, endothelial damage and occlusion of small hepatic veins causes parenchymal extinction, which contributes to tissue collapse and architectural distortion[8]. Furthermore, studies have shown that the oral anticoagulant rivaroxaban and the low molecular weight heparin enoxaparin lower intrahepatic vascular resistance in cirrhotic rat models[89,90]. These beneficial effects of anticoagulants were attributed to a decreased intrahepatic microthrombosis, hepatic stellate cell deactivation, and increased NO bioavailability. In a small RCT, a 12-mo regimen of enoxaparin in patients with LC with a Child-Pugh score of 7 to 10 appeared to prolong survival and delay the emergence of hepatic decompensation[91]. In a recent meta-analysis, use of antiplatelet agents was associated with a 32% decreased risk of hepatic fibrosis[92]. Still, more data are required before a conclusive statement can be made about the usage of anticoagulants and antiplatelet agents in CLC patients.

Management of co-factors

Weight loss and glycaemic control: Obesity is a condition characterised by systemic inflammation and immunological dysregulation that is linked to poor clinical outcomes in LC patients, including decompensation[34,93]. Obese patients with LC have higher levels of inflammatory cytokines, increasing the risk of decompensation through a systemic inflammatory response[94]. Obesity has a negative impact on the course of CLC across all aetiologies, regardless of portal pressure or liver function. In a study including 161 patients with CLC, clinical decompensation occurred in 15% of lean, 31% of overweight, and 43% of obese patients during a median follow-up of 59 mo[34]. Class III obesity was found to be an independent risk factor for the development of ACLF in a recent study using data registries[95]. Hence, weight loss

Table 3 Impact of non-selective beta-blockers on portal hypertension, variceal haemorrhage, decompensation, and survival in patients with liver cirrhosis

Ref.	Study population	Intervention	Study design	Sample size, *n*	Study conclusion
Poynard *et al* [70], 1991	LC patients with oesophageal varices	Propranolol, nadolol *vs* placebo	Meta-analysis of 4 RCTs	589	Both propranolol and nadolol were effective in preventing first VH and reducing the mortality associated with VH
Tripathi *et al* [71], 2009	LC patients with grade II or more varices	Carvedilol *vs* EVL	RCT	152	On intention-to-treat analysis, carvedilol had lower rates of the first VH compared to EVL (10% *vs* 23%)
Gluud *et al* [69], 2012	LC patients with high-risk varices without prior VH	NSBBs *vs* EVL	Meta-analysis of 19 RCTs	1504	Both EVL and NSBB reduced VH (RR: 0.69 and 0.67) without difference in mortality rates
Sinagra *et al* [75], 2014	LC patients with PHT	Carvedilol *vs* propranolol	Meta-analysis of 5 studies	175	Carvedilol reduced PHT significantly more than propranolol
Bhardwaj *et al*[76], 2017	LC patients with small varices	Carvedilol *vs* placebo	RCT	140	Carvedilol is safe and effective in delaying the progression of small to large oesophageal varices in LC patients
Zacharias *et al*[77], 2018	Adults with LC and varices	NSBBs	Meta-analysis of 10 RCTs	810	Carvedilol was more effective at reducing the HVPG. However, it was not better than traditional NSBBs with regard to the mortality, VH, or adverse events
Malandris *et al*[72], 2019	LC patients requiring primary or secondary prevention of VH	Carvedilol, NSBBS, EVL	Meta-analysis of 13 RCTs	1598	Carvedilol was as efficacious and safe as standard-of-care interventions for the primary and secondary prevention of VH. Also, carvedilol was associated with lower all-cause mortality compared to EVL
Sharma *et al* [73], 2019	LC patients with large oesophageal varices and no prior history of VH	NSBB, isosorbide-mononitrate, carvedilol, and EVL alone or in combination	Meta-analysis of 32 RCTs	3362	NSBB monotherapy decreased all-cause mortality and the risk of first VH. Additionally, NSBB carried a lower risk of serious complications compared with EVL
Villanueva *et al*[22], 2019	CLC patients and CSPH	Propranolol, carvedilol *vs* placebo	RCT	201	Long-term treatment with β blockers could increase decompensation-free survival in patients with CLC with CSPH, mainly by reducing the incidence of ascites
Villanueva *et al*[78], 2022	LC patients with CSPH	Carvedilol *vs* EVL/no treatment	Meta-analysis of 4 RCTs	352	Long-term carvedilol therapy reduced decompensation and significantly improved survival

CLC: Compensated liver cirrhosis; CSPH: Clinically significant portal hypertension; EVL: Endoscopic variceal ligation; HVPG: Hepatic venous portal gradient; LC: Liver cirrhosis; NSBBs: Non-selective beta-blockers; PHT: Portal hypertension; RCT: Randomised controlled trial; RR: Relative risk; VH: Variceal haemorrhage.

may be an effective therapeutic strategy for obese patients with cirrhosis[96,97]. Following bariatric surgery, the advantages of weight loss have been established in obese patients with LC[96]. Nonetheless, bariatric surgery is not generally recommended for people with CLC and is contraindicated in DLC. Patients with LC may be safely recommended to change their lifestyles under the care of a dietician with the aim to reduce body weight.

In LC patients, the prevalence of abnormal glucose regulation, including type 2 DM and hepatogenous diabetes, is quite high (20% to 70%)[98,99]. This high incidence appears to be due to poor insulin clearance and dysfunctional pancreatic beta cells[98]. Hyperinsulinemia is also implicated in vasodilatory and antinatriuretic effects in patients with CLC[100]. Impaired glycaemic indices in LC are associated with disease progression, decompensation, complications, and poor outcomes[101,102]. Hence, maintaining appropriate glycaemic control can benefit the course of LC. However, standardised diabetes management for LC patients has not been established yet. In addition to lifestyle modification, oral hypoglycaemic agents can be used in LC patients up to Child-Pugh class B, while insulin is recommended for LC at all stages.

Alcohol abstinence: Abstinence from alcohol reduces the risk of decompensation and improves outcomes in all stages of alcohol-related LC[60-62]. Early alcohol abstinence after diagnosis of LC is important for a better outcome[61]. According to a meta-analysis of seven cohort studies involving 1235 patients with alcoholic cirrhosis, at least 1.5 years of abstinence is required before a statistically significant difference in survival between the abstinent and alcohol consumption groups can be observed[103].

Diet, salt, and physical activity: Dietary interventions should include a target protein intake of 1.2-1.5 g/kg/d and regular aerobic exercise to prevent or ameliorate sarcopenia, which is associated with poor outcomes in LC patients[104-106]. In a recent prospective study, 16 wk of personalised hypocaloric normoproteic diet and 60 min per week of supervised physical activity were found to reduce body weight and portal pressure in overweight/obese patients with

CLC[107].

Many observational studies have found an inverse relationship between coffee consumption and LC[108,109]. According to two recent meta-analyses, coffee drinkers had a lower risk of developing LC than non-drinkers[108,109]. Unfortunately, these meta-analyses may not have adequately controlled the bias and confounding factors due to the low quality of the observational studies. Prospective RCTs are needed to establish the impact of coffee consumption on fibrosis regression in CLC patients.

Most of the scientific societies do not recommend sodium (salt) restriction for patients with CLC. However, preascitic LC patients have been found to retain sodium when faced with a high salt intake[110]. It is believed that a new steady state of sodium balance is eventually achieved in such patients primarily because of increased levels of atrial natriuretic peptide, inhibition of the renin-angiotensin-aldosterone system, and suppression of sympathetic activity, which prevent sodium retention and the formation of ascites. Jalan *et al*[111] reported that the severity of PHT contributed to the abnormalities of sodium handling in patients with CLC. Therefore, it would be intriguing to determine whether salt restriction could prevent the development of ascites in CLC patients with CSPH.

Correction of vitamin D deficiency: The liver plays a crucial role in 25-hydroxyvitamin D metabolism. Vitamin D deficiency and insufficiency are highly prevalent in patients with CLD (64% to 92%), where they are associated with poor outcomes[112]. Emerging evidence suggests protective effects of vitamin D against hepatic fibrogenesis[113,114]. However, vitamin D supplementation had no beneficial effects in animal models of LC and pre-existing fibrosis[115]. In a recent RCT, vitamin D treatment did raise the serum levels of 25-hydroxyvitamin D in patients with LC, but indicators of liver fibrosis did not improve[116]. The disappointing results can be attributed to the small sample size and short study period, calling for larger and longer studies in the LC population. Nevertheless, LC patients who are vitamin D deficient should receive treatment because LC itself is associated with an increased risk of osteopenia and fracture.

Regenerative therapies and investigational drugs

The potential of cell treatments to improve liver regeneration and modify the course of liver disease has garnered a lot of attention in recent years. There are many different cell types that can be employed to treat LC or fibrosis; however, mesenchymal stem cells (MSCs) are the most often used cell source (73%). Research using animal models have demonstrated that MSC therapy can reduce liver fibrosis, improve liver function, and lessen liver injury[117]. Clinical studies using MSCs for cirrhosis have demonstrated their efficacy in improving liver function; however, large-scale, stratified studies in various CLD settings are required to draw a robust conclusion[117-120]. Also, patients with advanced LC with liver failure, rather than CLC, have been the focus of the majority of clinical trials on stem cells. There is significant heterogeneity between published studies in terms of the type, dose, and method of stem cell delivery, and data accuracy, making it a difficult interpretation[121].

Granulocyte-colony stimulating factor (G-CSF) serves as an alternative to exogenous stem cell infusions by mobilising haematopoietic stem and immune cells. Some RCTs on G-CSF have reported improved survival in patients with ACLF [122,123]. However, in a recent multicentre, open-label, RCT, G-CSF with or without haemopoietic stem cell infusions did not improve liver dysfunction or fibrosis in patients with CLC. Moreover, these medicines were associated with a higher frequency of unfavourable events[124]. Therefore, because of conflicting results, G-CSF is not currently advised for use in CLC patients.

Recent developments in important pathophysiologic pathways linked to PHT in LC have revealed a number of novel possible treatment targets. These include intrahepatic abnormalities associated with inflammation, fibrogenesis, and microvascular changes[57-59,81,125-128]. Some medications, including phosphodiesterase-5 inhibitors, farnesoid X receptor agonists, endothelin-A receptor antagonists, and amino sulphonic acid taurine, have been found to lower PHT, which may be useful in reducing decompensation in CLC patients[125-128]. However, more solid and consistent evidence is required regarding the safety and effectiveness of these medicines. Currently, there are no pharmacotherapies for fibrosis that have been licensed, but research on antifibrosis medications has made significant strides in recent years, especially with regard to medications for nonalcoholic fatty liver disease-related fibrosis[129]. It seems that treatment with a single medication may not be sufficient to treat advanced liver fibrosis due to the complexity of the hepatic fibrosis process, which involves interactions between many cell types including immune cells, hepatic stellate cells, and hepatocytes. Therefore, more studies are needed to determine combination therapies using drugs that have several modes of action.

Elimination of precipitating factors

Several precipitating events can lead to abrupt worsening of clinical condition of LC patients by causing ACLF[130,131]. Furthermore, CLC patients experience a more severe form of ACLF than patients with prior decompensation episodes. Thus, controlling such precipitating variables can thereby significantly reduce cirrhosis-related morbidity and mortality. Antibiotic prophylaxis and prompt, judicious antibiotic treatment can aid in the prevention of ACLF triggered by infection[132]. Prophylactic antibiotics in conjunction with effective gastrointestinal bleeding management can prevent precipitating ACLF.

Another important preventive strategy is vaccination for viral hepatitis. For all LC patients, hepatitis B vaccine is advised. However, compared to normal subjects, patients with cirrhosis achieve lower seroprotection rates following HBV vaccination (mean response rate of 47%)[133,134]. Hepatitis E virus (HEV) and hepatitis A virus (HAV) superinfection is another well-known cause of ACLF in endemic areas[135]. While many nations recommend HAV immunisation for CLD patients, routine vaccination is not advised in some areas, such as India, where the prevalence of HAV antibodies in CLD is apparently greater than 90%. Recombinant HEV vaccines have also been developed but are not

widely available or approved across the world[136]. When vaccination is not an option, general preventive measures like improvement of sanitary conditions and the provision of clean water might decrease the incidence of HEV/HAV-induced ACLF.

CONCLUSION

The life expectancy of patients with CLC is often high, and many of them may be candidates for cirrhosis regression. Therefore, to facilitate the early detection of CLC, medical professionals should employ noninvasive techniques in all CLD patients. Early diagnosis of CLC offers the opportunity to treat underlying causes and prevent or halt the progression of liver disease. For viral cirrhosis, and to a lesser extent non-viral cirrhosis, fibrosis regression may result in cirrhosis reversal when the underlying cause of CLC is treated before progression. The transition from compensated to decompensated cirrhosis is mainly driven by PHT. This transition is accompanied by a dramatic decline in the median survival rates. NSBBs are currently the cornerstones of treatment for PHT, although a number of emerging therapies may pave the way for tailored multimodal strategies in the future. Some more recent drugs have shown promise in decreasing PHT, but more reliable and consistent data are needed to determine their safety and efficacy in LC patients. Furthermore, there are several known risk factors and triggering events for the decompensation of CLC that need to be taken care of. Regardless of the aetiology of CLC, evolving disease-modifying approaches might lead to a paradigm change and a decrease in the burden, morbidity, and mortality associated with LC.

FOOTNOTES

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REVIEW

Telemedicine in inflammatory bowel diseases: A new brick in the medicine of the future?

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Abstract

Inflammatory bowel disease (IBD) is a chronic digestive disease that requires continuous monitoring by healthcare professionals to determine the appropriate therapy and monitor short-term and long-term complications. The progressive development of information technology has enabled healthcare personnel to deliver care services to patients remotely. Therefore, various applications of telemedicine in IBD management have evolved, including telemonitoring, teleconsulting, teleducation, telenursing, telenutrition, and telepathology. While evidence has been provided for some telemedicine applications, targeted studies are still required. This review summarises the major studies that have evaluated telemedicine and its application in the management of IBD.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Telemedicine; Telemonitoring; Telenutrition; Telepathology; Teleducation; Telepsychology

Core Tip: The progressive development of technology has provided new telehealth tools for gastroenterologists to manage patients with inflammatory bowel disease. Through online platforms, simple e-mails, phone calls, and websites, physicians can monitor patients, adapt therapies, summon patients in case of alerts or red flags, and communicate with them. However, there is a need to scientifically test these methods by comparing them with the standard of care to determine whether these forms of care are superimposable, or at least comparable.

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INTRODUCTION

Inflammatory bowel diseases (IBD) include ulcerative colitis (UC) and Crohn's disease (CD). They are characterised by chronic, self-sustained digestive inflammation with a relapsing and remitting course that leads to disability, reduced quality of life (QoL), and increased healthcare costs[1].

At present, the exact etiopathogenesis of IBD remains to a large extent, unclear. However, it is believed that it may be the product of a series of complex interactions between genetic (as well as genomic and epigenomic) factors related to the colonic mucosal immune system and gut microbiota. This creates an imbalance in gastrointestinal inflammatory homeostasis by activating the inflammatory process and upregulating proinflammatory cytokines at the expense of anti-inflammatory cytokines[1]. IBD has a significant epidemiological burden. The incidence and prevalence of IBD are steadily increasing, with the highest incidence rates in Western and Northern Europe and North America. The most frequent age range at diagnosis is 16–35 years, and about 6%–7% of newly diagnosed patients are children younger than 15 years[2].

The chronic and relapsing nature of IBD poses the problem of inducing and maintaining remission to avoid developing short-term and long-term complications, disability, and the onset of neoplasia[3,4]. To this end, it is mandatory to continuously monitor various outcomes (*e.g.*, clinical, biochemical, and endoscopic) to weigh the therapeutic efficacy in both the initiation and maintenance phases of treatment to reduce the recurrence rate and minimise complications[5]. Such monitoring is traditionally performed during regular outpatient visits, determination of hematochemical indices, and instrumental investigations, mainly endoscopic exams[5].

However, there is an increasing need to initiate a digital transition in IBD medicine to achieve multiparametric clinical benefits, ranging from increased therapeutic adherence to close monitoring with feasibility in terms of economic sustainability and reduction in healthcare costs[6,7].

The gradual shift from symptom-oriented to prevention-oriented approaches has promoted and accelerated the development of mobile health technologies with the potential to radically transform healthcare delivery[8].

Despite the availability of various digital health tools, there are still no specific codified recommendations regarding which telehealth tools are the best for patients with IBD, the precise indications and contraindications, or the outcomes they can weigh most effectively and safely.

This Narrative Review aims to provide primary evidence on telemedicine applications, specifically in the setting of IBD.

TELEMEDICINE: GENERAL CONSIDERATIONS

Telemedicine: Definitions and applications

Telemedicine uses technological tools to provide medical care (from diagnosis to treatment) from a distance[9].

The need for a proper definition of telemedicine is challenging in the early stages of testing and implementation. More than fifteen years ago, a peer review of one hundred and four different definitions of telemedicine allowed telemedicine to be defined as "Telemedicine being a subset of telehealth, uses communications networks for delivery of healthcare services and medical education from one geographical location to another, primarily to address challenges like uneven distribution and shortage of infrastructural and human resources"[10].

Several aspects must be addressed when approaching the subject of telemedicine. First, while it offers the possibility of providing care with greater immediacy and constancy, and at a potentially better cost-benefit ratio, there are several aspects to be considered. Specifically, those related to privacy, confidentiality, and the need to achieve adequate information transparency with prior informed consent well-stated by the patient have already been stigmatized[9].

Telemedicine is not a particularly recent technique, but pioneering examples were found even before the 2000s. The telepsychiatry system was established in 1959 at the University of Nebraska School of Medicine[11]. However, the modern era of telemedicine occurred later in 1968 when a multispecialty telemedicine system was established at Massachusetts General Hospital and offered to workers and passengers at Logan International Airport[11].

Examples of national telehealth programmes can be identified later, in the 1980s, by the Norwegian government to provide health services to isolated portions of the population in rural areas with difficult access to health care. Similar services were offered in Australia, Canada, Japan, and the United States[12]. Since the 1990s, telemedicine has undergone marked growth in the technologies used and territorial implementation[11].

Bashshur *et al*[13] presented a telemedicine taxonomy by identifying three dimensions (functionality, application, and technology). Functionality, in turn, is divided into consultation, diagnosis, mentoring, and monitoring applications, and into specialty, disease, site, and treatment. Finally, technology was divided into synchronicity, networks, and connectivity. This is called the "three-dimensional model"[13].

Synchronicity is an important term in the telemedicine glossary in that telemedicine can be carried out as much in an "asynchronous" sense as in the case of diagnostic images or surveys as in a "synchronous" mind, for example, in remote medical examinations[14]. The need for greater connectivity has increased dramatically in recent decades. This can be partly explained by the extensive advances in digital technology, which have made it increasingly easy to connect patients and healthcare providers remotely[14]. Easy access to scientific sources also lays the foundation for continuing medical education at a distance[12]. This could also be relevant in the field of IBD, given the continuous progress made in medical and surgical science in this field.

Telemedicine offers several benefits. The first is the possibility of improving access to health services and increasing the spread with which these are delivered[12]. Second, it is possible to enhance the degree to which patients and healthcare providers are informed while setting up systems for quality control and improving the feasibility of screening programmes[12].

As telemedicine should affect IBD, we need to consider that it is a chronic condition with a very often unpredictable course and epidemiology that deeply affects younger populations[15]. Telemedicine can interject itself into these difficulties and provide support in monitoring the disease (telemonitoring), providing medical care and choices (teleconsulting), educating patients about IBD and its management (teleducation), and managing the nutritional aspects (telenutrition) (Figure 1).

Already two meta-analyses on telehealth in IBD have shown that current evidence may justify a role for it in the treatment of IBD[16,17]. This finding seems to be most evident for QoL in adolescents and in the reduction in the number of outpatient visits[16].

The patient's point of view: Perspectives and beliefs related to telehealth

Regardless of the remote care technique employed, IBD patients must benefit and accept it. Several studies before and after the coronavirus disease 2019 (COVID-19) pandemic weighed the expectations and perspectives of IBD patients in this regard. However, while there are benefits of non-invasive and continuous healthcare, there is also a need to ensure equity in the delivery of telemedicine and assurance of confidentiality[18]. Therefore, the voice of the patient, the recipient of these services, must be carefully heard.

A systematic review conducted by Al Khoury *et al*[19] identified that the highest expectations experienced by patients with IBD were pain control, endoscopic reporting in the normal range, and adequate QoL. Additionally, some patients wanted to be informed by gastroenterologists about their IBD. However, one of the most interesting elements that emerged was the propensity of patients toward e-health tools that were deemed feasible and acceptable.

Beyond healthcare, e-health resources are also potential sources of information for patients with IBD. For example, an extensive survey involving more than 300 patients with IBD revealed that, while the healthcare team was the preferred source of medical information, the second favourite source was the Internet[20]. Approximately 80% of the participants had searched the Internet for information about IBD, and approximately 30% did so at least once a week. In this study, patients were given a website for consultation, as recommended by health professionals.

This survey provides a source of food for further research. First, there probably needs to be an effort by health professionals to alert patients to potential sources of misinformation on the Web. Indeed, the concept of "infodemic" to which patients are subjected has emerged with COVID-19 more and more strongly[21].

Several surveys were conducted during the pandemic to weigh the beliefs and perceptions of physicians involved in managing IBD and patients suffering from healthcare consequences.

Patient beliefs regarding the relationship between IBD and COVID-19 are among the major issues to be addressed by busy gastroenterologists during the pandemic.

For example, a Portuguese survey recorded how patients believed they were at an increased risk of severe COVID-19 if they had active IBD or were taking corticosteroids within three months[22]. In addition, Pellegrino *et al*[23] reported a reduction in therapeutic adherence during outpatient follow-up during the COVID-19 pandemic at a referral IBD centre in southern Italy by employing a remote questionnaire-based interview.

Additionally, in an Indian survey, patients reported similar fears aimed at patients in remission in most or all-controlled clinical activities in which telemedicine methods had also been applied in most of the sample[24]. The authors reported reduced involuntary adherence (due to the unavailability of medication, financial constraints, and difficulty in reaching dedicated health facilities) with increased disease activity. In addition, the authors recorded an involuntary need to switch therapies due to the unavailability of previous therapies.

In addition, a French survey examined how telemedicine met with some success in terms of preference by healthcare personnel and a sample of patients during the COVID-19 pandemic[25]. However, an element that emerged in this survey was the need for a filter because disease flare-ups require in-person consultation.

Indeed, one cannot analyse the changes forced by the restrictions of the pandemic on remote medicine systems without considering that not all age groups have overlapping adaptive capacities. Moum *et al*[26], for example, showed in an analysis of more than 500 patients with IBD that although the preferred follow-up method was outpatient visits, the under-50 age group preferred telephone follow-up more than the older age group. Unsurprisingly, another study showed

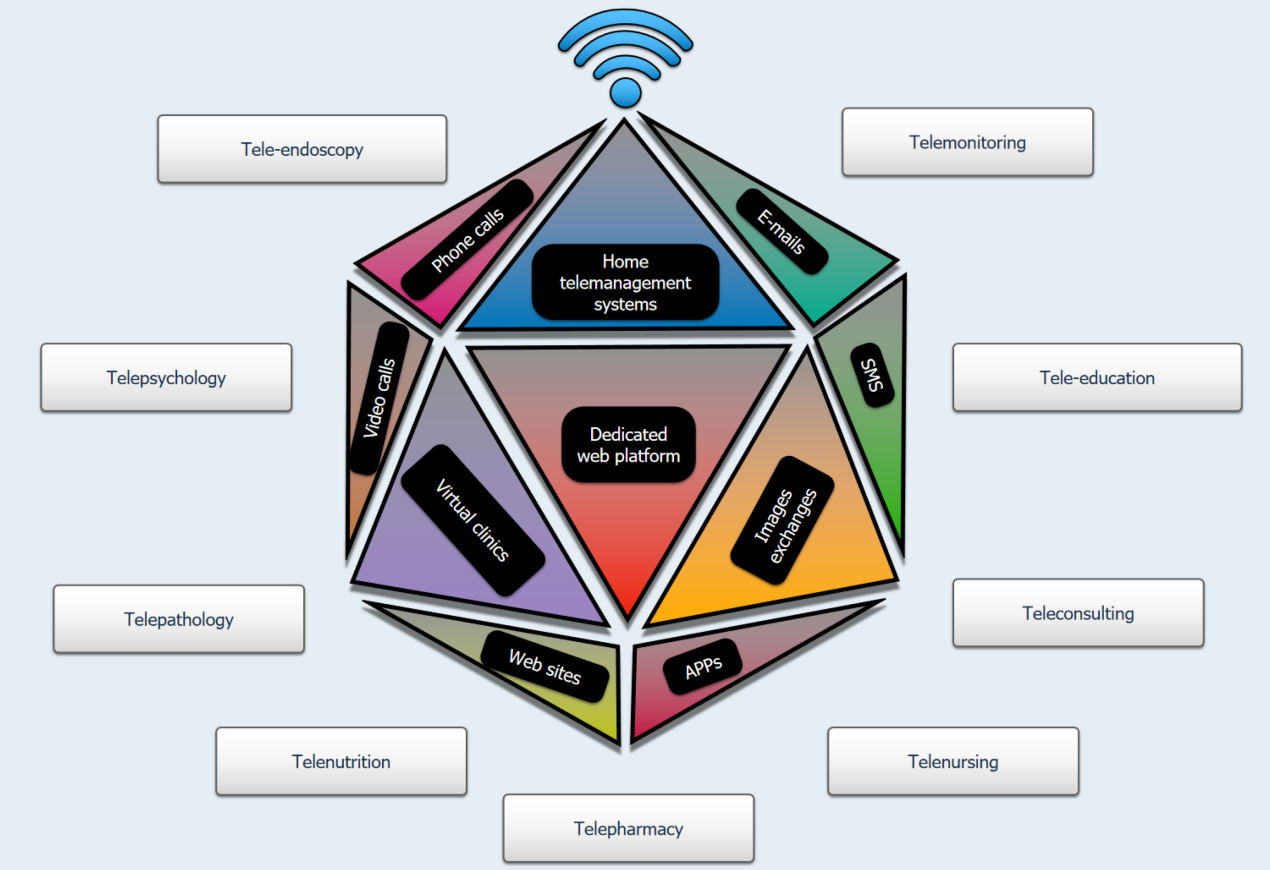

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Figure 1 Telehealth modality proposed in the management of inflammatory bowel diseases. Various data-obtaining and telecommunication systems can be established between patients and physicians engaged in the direction of inflammatory bowel diseases (IBD) management. Combining these data and interactions leads to the genesis of various telemedicine applications in the IBD setting to ensure a range of outcomes (*i.e.*, clinical, therapeutic, diagnostic, nutritional, psychological, *etc.*).

that younger patients were more prone to use telemedicine[27]. However, other evidence has shown encouraging results regarding the involvement of older adults in telemedicine systems, especially with the advent of the COVID-19 pandemic [28].

Another system by which patients with IBD can receive remote healthcare is through social media (*e.g.*, Facebook, Instagram, LinkedIn, Twitter). A survey conducted in 2020 on over 100 patients with IBD (with an average age of 47 years) showed that Facebook and Instagram were the social networks most frequently used by patients. Of these, approximately 30% used social media concerning their IBD (*i.e.*, for information about IBD, for support and coping strategies, to improve their anxiety levels, and to connect with other IBD patients)[29]. In addition, most participants (72.3%) reported wanting to receive telemedicine through society.

The use of social services for this purpose was also evaluated in settings where healthcare became complex, that is, in rural locations. For example, an experiment conducted in the rural community of West Virginia involving over 600 patients with IBD confirmed that Facebook and Instagram were the preferred social platforms, and over 90% of the sample desired to receive care from their physicians through them[30].

Ultimately, different voices emerged in different geographical settings, with a common matrix of good acceptability/preference for telehealth tools by IBD patients.

The COVID-19 pandemic helped accelerate the implementation of telemedicine in the management of IBD: From pandemic damage to the possibilities of remote medicine

In 2019, the outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a beta-coronavirus, arose in the Wuhan district of China and gradually acquired characteristics defined as a pandemic by the World Health Organization [31]. Although the diction of SARS-Cov-2 emphasizes the primary pulmonary involvement of the disease, it has gradually emerged that the condition could also affect the gastrointestinal tract as much as nonspecific clinical manifestations (such as vomiting/nausea, abdominal pain, and diarrhoea), as with direct organ damage as in hepatitis[32]. Furthermore, gastrointestinal involvement is associated with a worse intrahospital prognosis and requires intensive care[32]. Nevertheless, severe gastrointestinal disorders related to COVID-19 have been reported[33-35]. Additionally, suspicions have been raised regarding the possible role of SARS-CoV-2 in triggering the onset of *de novo* IBD[36]. The gastroenterological world has been strongly advocating preserving patients with IBD and those who are chronic and require continuous care over time. Telemedicine has accelerated abruptly to address this need[37]. The COVID-19 pandemic has

drastically occupied beds in hospital facilities, resulting in the closure of outpatient facilities for emergency management and the reshuffling of healthcare personnel by redirecting them to COVID-19 centres. Therefore, the need for telemedicine arose from an unquantifiable set of requirements for IBD patients, impacted by the priority that COVID-19 patients had acquired (such as management of moderate-severe cases, severe acute UC, complicated CD, chronic control of biologic therapy, and oncologic surveillance of patients with long-standing IBD)[38].

Telemonitoring during pandemics has often been mandated in territories affected by lockdowns. Nevertheless, an economic analysis has also suggested telemonitoring as a cost-effective strategy for improving quality-adjusted life-years and costs of care[39].

All these events have, in the gastroenterology research landscape, resulted in substantial growth of studies examining the potential of telehealth in the IBD patient (Figure 2).

TELEMONITORING IN IBD

Definitions

Medical telemonitoring is a continuous or non-continuous monitoring process generally applied to chronic diseases, allowing healthcare providers to monitor and interpret patient data to make decisions about the health of the monitored patient[40]. Over time, several modalities have been outlined for applying information technology to telemonitoring for IBD. For example, some studies have examined home tele management systems and website-based systems as the most straightforward systems for the exchange of emails or phone calls between physicians and patients[41].

Many studies conducted on telemonitoring also included telemonitoring components because they provided information and educational content to patients about their IBD[42,43].

Cross group's experiences with the home automated tele management system

The United States Cross Group evaluated several applications of the home automated tele management (HAT) system for IBDs in subsequent studies. The HAT system consists of three elements: A patient unit, a server supporting decision-making, and a web portal for physicians[44]. However, this system has not been applied to many patients with IBD. The first component was a laptop that served patients for self-testing. This concept is based on the genesis of alerts exhibited to clinicians (*i.e.*, alert systems) from a dedicated web system when the patient's self-reported values exceed certain predetermined thresholds. The main variables collected by the authors were based on a numerical scale to weigh symptoms, compliance with medical therapy, body weight, and adverse events related to treatment.

In 2006, the first uncontrolled and nonrandomised pilot study enrolled five patients with CD and five with UC (almost all Caucasians) with a mean age of approximately 48 years. None of the patients exhibited severe disease activity. Several interesting findings emerged from the study, including the fact that 20% of the participants had not been previously educated about computer use. All patients found HAT feasible and easy to use without a special commitment to their daily lives by ensuring weekly completion[44].

The same group conducted a subsequent HAT-based study in 2007 on 25 patients with IBD, with a mean age of 43 years. In this study, the feasibility and patient acceptance of HAT re-emerged. During the study, which took place over six months of follow-up, there was a reduction in disease activity and indices of inflammation (*i.e.*, C-reactive protein and erythrocyte sedimentation rate). This was also accompanied by an increased QoL and patient self-awareness of IBD[45].

The authors also evaluated patients' preferences for HAT by confirming their acceptability in a survey of patients included in HAT studies[46].

Finally, the cross-group conducted a randomised controlled trial on HAT targeting 25 UC patients on HAT *vs* 22 on the standard of care with a follow-up in both groups of one year[47]. However, during the study, 11 patients dropped out of the HAT group, and at the end of the follow-up, the authors concluded that there was a lack of reduction in disease activity as well as a failure to increase therapeutic adherence. Nevertheless, corrective analyses revealed a modest increase in QoL. However, this study was limited by its small sample size, which might have revealed only gross differences between the groups; the fact that there was a significant proportion of patients in long-term remission; and the dropout rate in the intervention group.

Ultimately, this system showed excellent patient acceptability and feasibility in all studies. However, as described, the data on QoL and impact on therapeutic compliance and disease activity were discordant and inconclusive, probably because of the small sample size common to all three studies.

However, these experiences, while home-based, have been among the starting points for more modern expressions of telehealth and do not require special hardware devices to be placed in patients' homes.

The gradual evolution toward more immediate systems: The "Constant-Care" web-based telemonitoring

The rapid and recent evolution of the Internet has resulted in the development of numerous online computer platforms, from real-time chat systems and emails to online portals dedicated to health. Thus, the concept of eHealth (the use of telecommunications and information technology in healthcare services) emerged. The concept of eHealth has been introduced for the development of portable medical devices.

A Danish group employed a web-based telemonitoring system called Constant-Care embedded explicitly in a dedicated website (www.constant-care.dk), validated in an initial study conducted over a decade ago in 21 patients with mild-to-moderate UC[48]. The authors assessed various outcomes from education (*i.e.*, knowledge of IBD), QoL, anxiety, and depression levels. While no particular impact was recorded on the QoL and mood (*i.e.*, anxiety and depression), the systems showed excellent feasibility and acceptance by patients and increased knowledge of their disease. The same

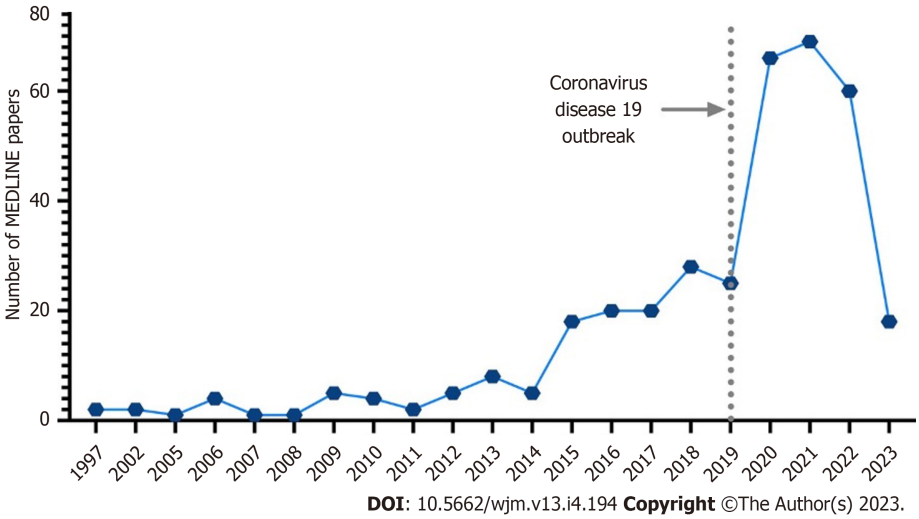

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Figure 2 Trends in telehealth research before and after the coronavirus disease 2019 outbreak. Conducting a simple search in papers indexed in MEDLINE, it is glaring how since 2019 (the year in which the onset of today's coronavirus disease 2019 pandemic falls), there has been significant growth in papers produced combining telehealth with inflammatory bowel diseases (IBD). We also note, predictably, that before 2019 the mass of papers on IBD gradually showed a gradual growth trend in the period 1992-2008. The search for such data in this figure stopped on 2 April, 2023.

group later conducted a randomised controlled trial on the same platform, including over 300 patients with mild-to-moderate UC on first-line therapy with 5-aminosalicylate acid derivatives, randomised into two groups (constant care *vs* usual care) for one year[49]. In contrast to the first study, in addition to the confirmation of feasibility/acceptance by patients, there was an increase in therapeutic adherence and QoL compared to the control and a decrease in the number of outpatient visits and the average patient/year costs. However, there was no impact on the frequency of IBD flare-ups, hospitalisation, or surgical outcomes.

Moreover, the Constant-Care platform has been used to optimise infusion sessions in patients with CD undergoing intravenous therapy with infliximab. In detail, Pedersen *et al*[50] in an initial pilot study included 27 patients with CD on maintenance infliximab therapy for 52 wk of follow-up (reached in the majority of the sample). The authors recorded the platform data regarding symptomatology and CD activity of the patients weekly, and faecal calprotectin levels were recorded weekly. All these parameters were computed into a score (*i.e.*, inflammatory burden score) adopted by the authors to classify patients into a visual colour system (green, yellow, or red zones) to refer yellow and red patients for medical consultation. An interesting element emerging from this pilot study was the high rate of therapeutic change: 39% of the sample obtained therapeutic optimisation, while 50%, on the contrary, achieved longer intervals between infusion sessions. Pedersen *et al*[51] applied the same platform in a prospective open-label study targeting 95 patients with mild-to-moderate UC on mesalazine therapy for three months showing excellent results on the therapeutic adjustment of its dosages. Patients were required to complete the simple clinical colitis activity index each week and their faecal calprotectin values were recorded. Again, the authors, employing these variables, calculated an equal inflammatory burden score, similar to what was done in a previous study of CD patients. There was a significant reduction in the simple clinical colitis activity index score and faecal calprotectin levels. Through this form of monitoring, the authors reduced the dosage of mesalazine in a quarter of the patients at week 3, in half of the subjects at week 5 and in almost all patients (88%) at week 12.

Subsequently, Carlsen *et al*[52] applied a monthly Constant-Care web application (www.young.constant-care.com) to paediatric patients with IBD, significantly reducing outpatient visits and school absences in the constant-care group compared to the control group, which followed classic quarterly outpatient monitoring. There were no significant differences in therapeutic adherence or QoL between the intervention and control groups. An interesting finding was the excellent acceptability (81% adherence) in a complex setting, such as paediatrics.

Other experiences based on telemonitoring systems using web-based systems

Other web-based portals have been implemented to establish telemonitoring for patients with IBD. For example, de Jong *et al*[53], in 2017, examined a telemonitoring system (myIBD Coach) in a randomised trial. This system is a webpage accessible from tablets and smartphones for the monthly monitoring of disease activity levels, therapeutic adherence, adverse drug events, nutritional status, anxiety and depression levels, and other outcomes (such as physical activity and patients' ability to self-manage). Physicians can monitor these parameters, communicate with patients, and use the e-learning modules. The authors assigned more than 450 patients to the myIBD Coach group and 444 to the usual care group. The study's primary results were a significant reduction in hospital access for outpatient visits and the number of hospitalisations in the myIBD Coach group.

A further randomised trial compared the web-based system on the platform "Telemonitorización de la Enfermedad de Crohn's Disease y Colitis Ulcerosa or Telemonitoring of Crohn's Disease and Ulcerative Colitis" (TECCU) *vs* usual care and telemedicine by phone calls by examining clinical outcomes (*i.e.*, clinical remission at week 24, QoL, therapeutic adherence, adverse events to therapies, social activities, hospitalisations, IBD surgery, number of outpatient visits)[54]. In

these three study arms (21 patients per group) consisting of patients on immunosuppressive therapy, the TECCU group had the highest remission rate, the best disease activity scores, and reduced faecal calprotectin values.

Cross *et al*[55], to overcome the limitations of the HAT system, also evaluated another web-based telemedicine system [*i.e.*, telemedicine for Patients with IBD (TELE-IBD)] based on text messages. A three-arm randomised trial (TELE-IBD administered every week, TELE-IBD every two weeks, and a standard care group) involved more than 300 patients with IBD with at least one disease flare-up tracked in the previous two years. The trial showed improved disease activity and QoL, and reduced hospitalisations in the TELE-IBD group; however, no clear superiority of TELE-IBD over the standard of care was demonstrated. Schliep *et al*[56] conducted a follow-up analysis of the data from the already mentioned TELE-IBD trial by Cross *et al*[55], who conducted a specific analysis on the levels of depressive symptoms (assessed with the Mental Health Inventory 5) and QoL (set using the Short Form 12) and showed that text message-based monitoring did not increase depressive symptoms and QoL.

A trial based on web-based telemonitoring with text messages was conducted by Bilgrami *et al*[57] in 222 IBD patients with at least one exacerbation in the previous two years compared with usual care. Again, no particular difference emerged in the outcomes assessed between the telemonitoring and standard of care groups (*i.e.*, self-efficacy and patient activation).

An additional platform in this context is the EasyMICI-MaMICI® studied in a randomised controlled trial directed at patients with active IBD *vs* standard of care and showed improved QoL and satisfaction in the included patients (*i.e.*, 54 IBD patients) and reduced outpatient visits[58]. EasyMICI-MaMICI® includes a smartphone-accessible app (EasyMICI) and online portal system (MaMICI). This platform provides a method for data collection and enables communication between users and caregivers.

Ghoshal *et al*[59], in 2021, employed a web-based platform video/audio consultation during the COVID-19 pandemic in 50 IBD patients reviewing IBD activity, anxiety levels, QoL, and probable COVID-19 symptoms, and recorded a comparable SARS-Cov-2 infection rate in IBD *vs* non-IBD controls, and QoL comparable or better than before the pandemic.

Ultimately, web-based systems have been among the most abundantly tested and have provided interesting results, as described above, regarding first-level outcomes in IBD (*i.e.*, clinical remission rates and hospitalisations).

More accessible telemonitoring systems: Use of phone calls, text messages, e-mails or apps

Telehealth strategies that do not use complex online platforms or home-based telemonitoring systems should certainly be included in the analysis of telemonitoring, as well as in systems that have tools within everyone's reach, such as simple short message service messages, emails, or even simpler phone calls between healthcare caregivers and patients with IBD.

Examples of such methodologies can already be found several years ago. In 2009, a retrospective study was conducted by Torrejón Herrera *et al*[60], who aimed to collect care data from the Crohn's Colitis Care Unit at Vall d'Hebron University Hospital in Spain over nine years (*i.e.*, 1999 to 2007). They collected data from 1784 patients and observed how remote tools (telephone and fax) were employed more often than presential activities. The Crohn's Colitis Care Unit also used a web-based system (which recorded over 3500 registered IBD users and over 150000 visits).

Other examples can be traced to the paediatric population. For instance, Heida *et al*[61] telemonitored 160 patients aged 10 to 19 years through the use of e-mail and phone calls. They found an increase in the patients' self-efficacy and acceptance of telemedicine. The authors also recorded significant economic gains and reduced the number of in-person visits in the telemonitoring group.

Pinto *et al*[62] telemonitored 21 patients with CD and 56 patients with UC *via* telephone calls during the COVID-19 pandemic through a collection of patient-reported outcomes to assess disease activity and adopt treatment adjustments.

Few studies have examined cell phone applications as tools for IBD settings. Among them, a study conducted by Echarri *et al*[63] evaluated the Harvey-Bradshaw index self-administered *via* an app (*i.e.*, the MediCrohn Study) by patients to determine if their results agreed with the same index calculated in the hospital by a physician. The study found a high percentage of concordance between the Harvey-Bradshaw index assessed by the app and that assessed by the physician. Another study by McCombie *et al*[64] using a telemonitoring system for outpatients employing two smartphone apps (*i.e.*, "IBDsmart" for symptoms and "IBDoc" for faecal calprotectin monitoring) and comparing it with usual care leaned toward the efficacy and acceptability of the telemonitoring system finding it particularly effective when used in patients with mild to moderate disease not recently diagnosed with a reduction in outpatient visits. Similar results were reported in a randomised trial by Östlund *et al*[65]. Again, participants found self-monitoring using a home faecal calprotectin assay and a digital application feasible and appreciated.

Finally, the study conducted by Zhen *et al*[66] involved the use of an app (*i.e.*, "HealthPROMISE") by patients with IBD to monitor the condition after one year of data collection showed no improvements in QoL between patients followed through the app and those undergoing standard care; however, patients reported an increase in their understanding of the nature/causes of their condition after the period of using the app, a statistically significant decrease in IBD-related hospitalisations and emergency room visits was also found.

TELECONSULTING IN IBD

Teleconsulting provides healthcare consultation *via* telecommunications, directed by healthcare personnel to patients. Therefore, many of the aforementioned studies on telemonitoring inevitably have a teleconsulting component. In addition, many of the telemonitoring systems and platforms studied are aimed at providing consultations to patients to make diagnostic or therapeutic choices. However, over time, experiences aimed at studying teleconsulting (in isolation),

its impact on clinical practice, and the significant outcomes of IBD have emerged.

A preliminary study conducted by Krier *et al*[67] used a real-time imaging-based system (*i.e.*, Solar Digital Unity software, San Diego, CA, United States) capable of integrating audio-visual communication between physicians and patients as well as the ability to share digital content (such as diagnostic images) to care for 34 veterans with IBD. The authors demonstrated that, through this follow-up system of telemedicine outpatient consultation *via* video calls, a similar level of patient satisfaction was achieved as that obtained from in-person encounters concerning indices such as attention to patient concerns and the physician's perceived skill level. The interviewed physicians welcomed the technical and informational qualities of the telemedicine sessions.

In addition, in the retrospective experience of the Crohn's Colitis Care Unit at Vall d'Hebron University Hospital in Spain by Torrejón Herrera *et al*[60], much of the care provided to patients over the nine years of reviewed care was *via* teleconsulting.

In the Highlands and Scottish Isles, the study conducted by Ruf *et al*[68] showed that Virtual Care clinics can be a safe and effective model of patient-centred care for patients with IBD living in remote areas, allowing enormous potential for time and cost savings.

Li *et al*[69] evaluated whether a telemedicine-based IBD clinic could provide a high-quality, low-cost alternative to traditional care. Telemedicine clinics are based on virtual appointments with IBD specialists using an Internet-connected device. Patients completed a pre-visit survey reporting information about their disease activity, a post-visit study about their experience during the web appointment with the specialist, the time and money saved by not having to travel to the visit, and their preferences for future visits. At the end of the study, 77% of the patients reported that they preferred web appointments, again demonstrating the applicability of web monitoring systems as an alternative to outpatient visits to save time and money without compromising quality of care.

Gastroenterologists and IBD specialists can also benefit from the educational potential of telemedicine as it provides a forum to discuss patient cases with complex diagnostic or treatment dilemmas. Live inter-institutional interdisciplinary videoconference education (IBD LIVE) is an example of a multisite, multidisciplinary videoconference platform. The participating members included gastroenterologists, surgeons, pathologists, radiologists, and other medical specialists. The objectives of each session included a review of evidence-based data and exchange of inputs for managing patients with IBD[70].

TELENUTRITION IN IBD

IBD causes significant digestive changes that require careful evaluation and monitoring by clinical nutritional specialists. Therefore, attention has also been paid to telemedicine (although few studies are available) for the possibility of providing nutritional care to patients with IBD remotely (telenutrition).

In addition, the nutrition of patients with IBD must be adapted not only to the patient's clinical-demographic and anthropometric characteristics, but also to changes in disease activity in situations in which therapeutic fasting and parenteral nutrition may be necessary[71].

While many of the studies conducted in telemedicine have primarily focused on modifying medical-therapeutic parameters for outcomes directly related to IBD disease activity, another concept is also emerging. Given the lack of need for a physical examination in many dietitian encounters, telenutrition could fit into this context and address the nutritional needs of IBD patients[72].

Similar to the previously discussed telemedicine applications, the nutritional aspect has also been dramatically affected by the COVID-19 pandemic, and there have been many efforts to provide chronic patients with remote nutritional care [73,74].

Thus, telenutrition can investigate various aspects such as weight history, food intolerance, diet setting, evaluation of diet response, hunger assessment, monitoring, and therapeutic adjustments of enteral and parenteral nutrition therapy [75]. However, in the available studies, the study design was not always explicitly outlined for the remote assessment of nutritional status. This outcome is often one of the other outcomes examined (*e.g.*, disease activity and therapeutic adherence).

For example, Ehrlich *et al*[76], in 2012, proposed an app (*i.e.*, "GI Buddy") available for iPhones or also *via* a dedicated website in which patients 13 years of age and older entered data related to patient-reported medical outcomes but also dietary logs. In other words, there was a categorisation of data that the patients could input: Symptoms, treatment, diet, and lifestyle.

Later, there was a nutritional component in a previously described study by de Jong *et al*[53] employing the myIBD Coach app. A teleducation service also provides educational modules for nutrition and IBD.

Other teleconsulting experiences (*e.g.*, the Promoting Access and Care through Centres of Excellence Telemedicine Program) included the nutritionist experience in IBD as part of the team and consultation[77].

An Indian congressional communication at the 17th Congress of the European Crohn's and Colitis Organization presented a digital health platform designed explicitly for telenutrition (*i.e.*, IBD NutriCare)[78]. This application, available for both Android and iOS, allows the recording of dietary variables based on over 600 Indian recipes, as well as other clinical parameters of disease activity. These data were then used to analyse the nutrients consumed by patients to provide real-time tracking of the diet of the monitored IBD patients.

In conclusion, evidence for telenutrition in patients with IBD is particularly scarce and has not increased, even during the COVID-19 pandemic. Therefore, more efforts from the research community on IBD and nutrition are undoubtedly desirable to test new tools and further validate those already available to improve chronic nutritional care and properly

manage patients with IBD.

TELEDUCATION IN IBD

There are not many studies conducted exclusively on teleducation. Instead, many of the studies conducted in other branches of telehealth have included teleducation components. Some examples are the telenutrition platforms explained above. As stated, de Jong *et al*[42,53] included in the "MyIBD Coach" platform specific e-learning modules delivered to patients with IBD. Central among these modules was the discussion of IBD in general and the importance of immunosuppressive and biological therapies and traditional treatments (*i.e.*, mesalamine). In addition, the authors educated patients on "self-management", that is, adopting strategies to prevent/reduce symptoms. Also completing these modules were sections on influenza vaccination, anxiety and depression. As mentioned above, an authentic "educational curriculum" was also provided in the TELE-IBD platform[43]. In this system, each participant received educational advice once or twice a week (depending on which intervention arm they belonged to). In addition, healthcare providers could also send educational messages exempt from this temporal logic concerning, for example, advice during flu seasons. Similarly, the web-based platform "Constant-Care" also hosted educational training on the website[48].

SPECIAL APPLICATIONS

Telepathology

Care for patients with IBD is also achieved through accurate diagnosis of histologic specimens both at the time of the first diagnosis, where differential diagnosis between CD and UC becomes crucial, and during follow-up endoscopic investigations and colorectal cancer surveillance.

In telepathology, a remote consultation with a pathologist is achieved by transmitting digital images. The main telepathology experiments conducted in the field of IBD have primarily targeted the burden of interobserver variability in diagnosing IBD-associated dysplasia/cancer, which often requires evaluation by multiple pathologists.

In the early 2000s, Odze *et al*[79] weighed the utility of telepathology and interobserver variability in detecting UC-associated dysplasia in approximately forty cases of UC. Four pathologists reviewed the slides of the haematoxylin-eosin images of UC. The degree of concordance among the pathologists was fair, with a kappa (κ) of 0.4 and worse results were observed for low-grade or indefinite dysplasia. However, the resolution of the images had not yet reached the current quality levels, so much so that, in this study, the same pathologists had generally given an upgrade in the degree of dysplasia on direct evaluation of the slides, but not in telepathology. The method used to obtain images was a Twin Cam MX-700 digital camera (Fuji film) provided with a (for use with a microscope) ocular device (I. Miller Precision Optical Instruments Inc., Philadelphia, PA, United States).

Later, Odze *et al*[80] recorded telepathology in the same setting involving seven pathologists (of whom only one was an expert in digestive pathology). A dynamic Apollo Telepath system (Apollo Telemedicine, Falls Church, VA, United States) was deployed for image transmission. However, the κ was poor (k = 0.32), with a worse level for low-grade and indefinite dysplasia.

However, subsequent studies have shown more encouraging results. For example, Wu *et al*[81] involved four Chinese pathologists in examining fifty IBD colonic biopsies digitized using the Aperio system (Leica Biosystems). The degree of agreement among the pathologists was much higher (k = 0.68) for interpreting IBD-associated neoplasms. Moreover, an interesting aspect of the study was the comparison of this agreement with that of four pathologists in the United States. In this case, the κ was greater than 0.74.

Further experience was provided by the Italian Group for the study of the Inflammatory Bowel Disease (*i.e.*, IG-IBD) pathology group[82]. In this study, 20 pathologists with experience in digestive pathology evaluated 54 diagnostic blocks from 30 colonoscopies in patients with IBD. Dysplasia detection showed a moderate degree of agreement (κ = 0.48).

Ultimately, telepathology could be of great help in the management of patients with IBD. Guidelines recommend that the evaluation of dysplasia in patients with IBD, given the increased risk of colorectal cancer compared to the general population, should be performed by pathologists experienced in IBD[83]. However, IBD referral centres are not always available in all geographic regions; therefore, telepathology could provide valuable support in such settings.

Telenursing

IBD nurse practitioners are increasingly gaining importance in clinical life[84-87], even in post-surgical stoma management but little evidence is available on telenursing (*i.e.*, remote nursing care provided to patients with IBD)[88].

Cook *et al*[89] reported in 2010 on the application of telenursing to address cognitive and emotional barriers to therapeutic adherence of mesalazine in patients with UC. A large sample of > 200 patients was included in a nurse-managed telephone follow-up programme to increase therapeutic adherence through cognitive-behavioural and motivational techniques. Ultimately, the authors recorded a significant increase in therapeutic adherence after the telenursing programme.

In a study by Del Hoyo *et al*[90], nurses played a role in telemonitoring IBD patients *via* telephone assistance, showing encouraging results from a cost-effective perspective. Specifically, telenursing experience showed a 67% probability of producing economic savings per additional quality-adjusted life-year compared with standard care.

Squires *et al*[91] found that a nurse-operated telephone advice line is a cost-effective intervention that allows patients to avoid going to the hospital when unnecessary and saves money in primary and secondary care.

A similar study by Sanromán Alvarez *et al*[92] found increased telephone consultation requests by nurses and a decreased need for medical consultations, with savings on care amounting to 73.603 euros from 2009 to 2011.

Ultimately, the role of IBD nurses in telehealth has yet to be well evaluated in the literature and could show strong potential in managing chronic patients such as IBD patients and providing relevant support to medical staff. In addition, a large proportion of these studies employed nurses as ancillary elements through phone calls. Studies in which IBD nurses could play a more primary role would perhaps be desirable since they often spend the most time with patients with IBD.

Telehealth as a tool to determine anxiety-depressive disorders in the IBD patient and the initial experiences on telepsychology

It is increasingly emerging that the gut-brain axis plays a role in the pathogenesis of IBD as it affects the course of the disease, such that bidirectional communication with a mutual influence between the brain and gut is realised[93]. The bidirectionality in the gut-brain axis is one of its gnoseological pillars, in that the prevalence of anxiety-depressive disorders reaches about 30% in patients in remission and increases to about 70% in patients with active IBD[94]. During the COVID-19 pandemic, it was also observed in Italy that, during the first lockdown, there were particularly high rates of anxiety, depression, and poor sleep quality in patients with IBD in remission[95]. Nonetheless, anxiety-depressive disorders may also influence the frequency of disease flare-ups in patients with IBD, potentially leading to an increased frequency of flare-ups, an often more aggressive presentation, increased rates of hospital readmission, and an increased risk of surgical intervention[94]. However, this issue is not always adequately addressed in managing IBD and often takes a back seat. Unsurprisingly, some studies have reported that, in some settings, up to 70% of patients with anxiety-depressive disorders (even severe ones) are not treated by a dedicated specialist[96-98].

The different psychological techniques applied to IBD include cognitive behavioural therapy (CCBT), social support, stress management, and targeted techniques[98,99]. Many studies that have weighed the impact of psychology on managing IBD have also included remotely performed treatments.

Therefore, telemedicine and telepsychology interventions could be promising alternatives for patients with IBD who need them. In addition, web-based psychological interventions have proven effective in other situations, such as treating depression and anxiety[100,101], insomnia[102], and irritable bowel syndrome[103,104].

Some of these projects are currently underway. One example is the randomised trial by Evans *et al*[94] known as the "ACTforIBD" program. The latter is based on acceptance-commitment therapy (*i.e.*, a technique specifically for patients with IBD and concomitant psychopathological comorbidities) to address unresolved problems related to chronic IBD. This technique will be administered to patients by dedicated psychological therapists in one-hour sessions for eight weeks.

Schliep *et al*[56] additionally conducted a posthoc analysis of data from the TELE-IBD trial[55]. They extrapolated the variables of mental health (assessed using the Mental Health Inventory 5) and QoL (assessed with the Short Form 12 questionnaire). They compared a group that received telemedicine with a control group (*i.e.*, standard of care). The TELE-IBD method, which is mainly based on text messages, did not positively affect depressive symptoms or the QoL.

Other studies have attempted to provide CCBT psychotherapy to remote patients with IBD by comparing it with the in-person standard of care. For example, McCombie *et al*[105] showed that CCBT is associated with improved disease activity and QoL, including anxiety and depressive symptoms, in the first 12 wk. However, these results were not confirmed at six months. However, patients with less than 50% adherence to the CCBT program had many outcomes at six months. Therefore, future research should focus on adherence to psychological therapies.

Telepsychology has also provided interesting results regarding adherence to conventional therapy for IBD. For example, Hommel *et al*[106] offered behavioural therapy with four 60–90-minute sessions to patients with IBD and measured therapeutic adherence with the pill count strategy; they reported interesting results, although not significant, about a 29% increase in adherence to mesalazine.

Tele-endoscopy

Patients with IBD require recurrent assessment with quality endoscopic methods[107] as much in initial diagnosis as in monitoring and oncologic surveillance, so much so that endoscopic outcome is the focus of the most up-to-date "Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II)" consensus[108].

To consider the application of telemedicine in endoscopic evaluations, one can turn to the concept of “tele-endoscopy”.

Tele-endoscopy has already been generally proposed for digestive diseases and, in particular, for geographically remote regions[109-112].

However, to the best of our knowledge, no study has been explicitly designed for IBD.

Telepharmacy

Telehealth can also be applied to dispense drugs to patients with IBD through remote contact between the patient and the pharmacist. However, no ad hoc studies have been designed for such applications in the treatment of IBD.

However, there are some initial data on home delivery services set up during the COVID-19 pandemic. For example, in one communication by Ruiz Garcia *et al*[113], they addressed patients with immune-mediated diseases receiving home medication delivery. Among them there were seven IBD patients corresponding to 6.03% of the sample.

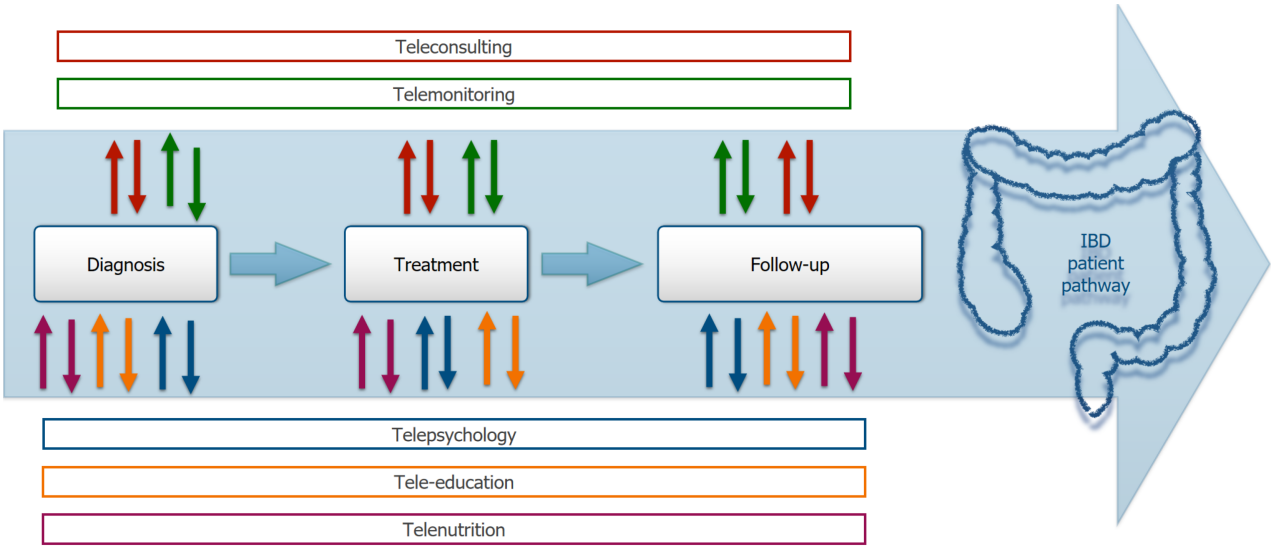

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Figure 3 Inflammatory bowel disease patient telemedicine pathway. Based on the current evidence, various telemedicine applications are across the entire inflammatory bowel diseases management, from diagnosis to treatment setting and short-term and long-term monitoring of its effectiveness. Nevertheless, such telehealth applications are bidirectional. That is, they may have the potential to be both active (provided by the physician, psychologist, nurse or nutritionist, *etc.*) and passively requested by the patient from their healthcare managers on needs. IBD: Inflammatory bowel diseases.

CONCLUSION

In conclusion, IBD is a complex disease with many variables in its management, and a disease course that is rarely predictable. Close monitoring of this type of patient is necessary, as they require constant and continuous care, especially when the disease flares. Regular follow-up is also needed to determine whether the therapy is achieving its target. As highlighted by the STRIDE-II consensus, the goal is to ensure a QoL that overlaps that of the general population with the help of medicine. Telemedicine can intervene by meeting the needs of these patients (Figure 3). Many telehealth applications have been studied; however, other applications require considerable attention and new evidence. It is still necessary to study tele-endoscopy, telepharmacy, telesurgery or telerehabilitation in the context of IBD and studies are still awaited. In addition, telehealth has several limitations to consider. That is, it is not clear, under what precise conditions the telehealth medical examination can be superimposed on the in-person examination. It is not yet defined what spectrum of patients may or may not be followed with such remote modalities, although much of the literature addresses patients with mild-to-moderate IBD and not necessarily in advanced therapy. The absence of an objective examination that can be done in attendance is certainly another limitation to consider. Indeed, to achieve these goals, one needs systems that integrate patient-reported symptom data with objective data (*i.e.*, laboratory tests and instrumental examinations) so that the telehealth visit can be as reliable as possible.

Conversely, there is a need to evaluate which patients may be compliant with such systems and can use them fully. There are, however, exciting perspectives and evidence, as outlined in this review on telemonitoring, that make, in any case, telehealth a tool certainly to be considered in the management of chronic patients such as those with IBD. In addition, psychological monitoring tools (considering how much these patients suffer from anxiety-depressive disorders compared to the general population) should be encouraged.

In addition, in many realities, the COVID-19 pandemic was an unexpected and dramatic event, an opportunity for telemedicine systems to be an obligatory and ready solution to solving the medical care shortage. In this context, these efforts, as the pandemic epidemiological situation improves, should not be thwarted and represent an important starting point for the continued implementation of telehealth systems. In addition, the robust research growth that there has been with COVID-19 should similarly not come to a halt. All of these would enable the collection of additional evidence, as much real-life as the result of clinical trials, that could hopefully stimulate precise recommendations from the world's major IBD guidelines.

FOOTNOTES

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Utilization of online systems to promote youth participation in research: A methodological study

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Abstract

BACKGROUND

Online surveys can align with youth's increased use of the internet and can be a mechanism for expanding youth participation in research. This is particularly important during the coronavirus disease 2019 (COVID-19) pandemic, when in-person interactions are limited. However, the advantages and drawbacks of online systems used for research need to be carefully considered before utilizing such methodologies.

AIM

To describe and discuss the strengths and limitations of an online system developed to recruit adolescent girls for a sexual health research study and conduct a three-month follow up survey.

METHODS

This methodology paper examines the use of an online system to recruit and follow participants three months after their medical visit to evaluate a mobile sexual and reproductive health application, *Health-E You/Salud iTu*™, for adolescent girls attending school-based health centers (SBHCs) across the United States. SBHC staff gave adolescent girls a web link to an online eligibility and consent survey. Participants were then asked to complete two online surveys (baseline and 3-month follow-up). Surveys, reminders, and incentives to complete

them were distributed through short message service (SMS) text messages. Upon completing each survey, participants were also sent an email with a link to an electronic gift card as a thank-you for their participation. Barriers to implementing this system were discussed with clinicians and staff at each participating SBHC.

RESULTS

This online recruitment and retention system enabled participant recruitment at 26 different SBHCs in seven states across the United States. Between September 2021 and June 2022, 415 adolescent girls were screened using the Qualtrics online survey platform, and 182 were eligible to participate. Of those eligible, 78.0% (n = 142) completed the baseline survey. Participants were racially, geographically, and linguistically diverse. Most of the participants (89.4%) were non-White, and 40.8% spoke Spanish. A total of 62.0% (n = 88) completed the 3-month follow-up survey. Limitations of this system included reliance on internet access (*via* Wi-Fi or cell service), which was not universally available or reliable. In addition, an individual unrelated to the study obtained the survey link, filled out multiple surveys, and received multiple gift cards before the research team discovered and stopped this activity. As a result, additional security protocols were instituted.

CONCLUSION

Online systems for health research can increase the reach and diversity of study participants, reduce costs for research personnel time and travel, allow for continued study operation when in-person visits are limited (such as during the COVID-19 pandemic), and connect youth with research using technology. However, there are challenges and limitations to online systems, which include limited internet access, intermittent internet connection, data security concerns, and the potential for fraudulent users. These challenges should be considered prior to using online systems for research.

Key Words: Online recruitment; Adolescents; Sexual and reproductive health; Mobile data; Methodology paper; Data security

Core Tip: Online systems for health research have the potential to reach larger and more diverse audiences than traditional in-person recruitment methods. It can also decrease the cost and time necessary to recruit participants in person. This paper provides a case study of the online system developed and used to evaluate *Health-E You/Salud iTu*™, an interactive mobile sexual and reproductive health application (app) for adolescent females used in conjunction with school-based health centers. This study demonstrates the strengths and limitations of online systems used for research.

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INTRODUCTION

Online systems were widely used prior to the coronavirus disease 2019 (COVID-19) pandemic; however, COVID has increased the need for researchers to consider alternative methods to continue their study activities remotely[1,2]. Online systems to recruit and consent participants in research studies can be more time-efficient and reduce costs associated with traditional, in-person approaches[3,4]. More recently, online recruitment efforts for health research have been conducted with targeted web-based strategies on social media platforms[2,5,6]. However, online recruitment can also be useful for clinic-based sampling to evaluate interventions aimed at improving clinical care. In addition, online recruitment methods may be particularly effective for adolescents, given their increased use of mobile technologies, including smartphones, tablets, and laptops[7,8]. There is value beyond recruitment; online systems can be used to automatically send participants links to follow-up surveys, reminders to complete follow-up surveys, and distribute e-gift card incentives[9,10].

The utilization of mobile technologies can extend the geographical reach and promote the participation of diverse adolescent populations in health research. Our study specifically focuses on adolescents aged 13-19 years, as that is the common age of high school students utilizing our participating school-based health centers (SBHCs). It is important to note that there is variation in the definition of adolescents. For instance, the World Health Organization defines adolescence as between ages 10-19[11], while the American Academy of Pediatrics considers adolescence as between ages 11-21[12]. Almost all adolescents in the United States (US) (95%) have access to smartphones, and 45% said that they are "almost constantly" online[8]. This is true for youth from lower socio-economic and diverse racial/ethnic backgrounds. Specifically, 93% of low-income adolescents, 96% of Hispanic, and 91% of Black adolescents have access to a smartphone [8]. Further, among US smartphone owners, young adults, those with no college education, and those with lower income levels are most likely to use their mobile phone as their main source to access the internet[13]. At the same time, studies

show that youth from diverse racial/ethnic, sexual orientation, gender identity, and low-income backgrounds are often underrepresented in research[14-16]. Thus, using these technologies can potentially expand youth participation, increase the diversity of participants[8,17,18], and reach youth from historically under-resourced communities[18]. A recent study comparing virtual recruitment studies to in-person recruitment for medical research found that virtual studies were able to enroll participants from more geographically diverse regions and recruit higher percentages of females[19]. Online recruitment is more cost-effective and time-efficient than in-person recruitment. In-person recruitment involves greater costs associated with travel to clinic study sites and study staff time spent on recruitment activities[5]. Online surveys can also be translated and accessed in multiple languages, further expanding accessibility for non-English speaking participants. It can also include audio features for groups with lower literacy levels[20]. Online surveys are, therefore, an opportunity to expand youth participant reach for populations who have been historically excluded from health research and, in doing so, they can help reduce inequities in research participation related to gender, race, ethnicity, education, location, age, and language spoken.

Using mobile technology for health research data collection can also improve data quality. Online surveys can increase participants' comfort in completing health surveys, especially those on sensitive topics (*e.g.*, sexual health and behaviors)[18]. Research shows that compared to a trained health educator, adolescents are more comfortable disclosing health information on a computer even when they know it will be shared with their clinician[21]. Additionally, online surveys have been shown to reduce social desirability biases compared to interviewer-administered modes[20,22]. In one study that analyzed social desirability for a sexual health survey, respondents who completed the survey over the internet were more likely than those who responded over the telephone to report more than one sexual partner, indicating that online surveys can decrease social desirability bias[22].

Despite the promise of technology in promoting access to research for diverse populations, barriers remain. While adolescents' use of smartphones has increased for all income levels and races/ethnicities, approximately 5% of adolescents still do not have access[8]. The "digital divide" persists in many groups. In particular, those from rural regions[23] and low-income communities[24] across the US have unequal access to reliable internet. Although recent studies show that mobile phone ownership is becoming more evenly distributed among diverse populations[8], divides in internet access exist among school-aged youth of different household incomes[24]. Thus, the "digital divide" has the potential to create barriers to online recruitment efforts and can perpetuate inequalities in health research for some populations.

Online recruitment methods can also create barriers to obtaining informed consent, risk the inclusion of fraudulent users, and hinder participant retention over time. These barriers have been identified in a national study that used online surveys for sexual and gender minority adolescent health research[16]. Obtaining consent online may make it difficult for some participants to fully understand their rights, risks, and benefits of participating in research. Even when the language is simplified, consent can be complicated. When informed consent is done online, there is no research staff present and readily available to answer questions, provide clarification, and ensure the potential participants' understanding[16]. While potential participants can be encouraged to contact research staff with questions, they are not required to do so. To compensate for this limitation and increase comprehension of the consent and study processes, researchers have used videos, consent quizzes, and interactive follow-up methods[16]. Online surveys are also prone to fraudulent or repeat users, especially when incentives are distributed for survey completion[16,25]. For example, an online study on COVID-19's impact on LGBTQ+ populations resulted in 62% fraudulent survey responses due to the infiltration of bots[25]. Actions such as robust built-in data safety measures, requiring the same data point throughout the survey, and avoiding automatic incentive payments when the survey is complete, can decrease fraudulent users. However, implementing these safeguards is time-consuming for researchers and may decrease participation from authorized participants due to increased survey time and potential time delays for incentive distribution after survey completion[25]. In addition, participant retention over time may also be problematic when online recruitment strategies are used due to a lack of personal contact, and participants' early interest in the study may fade over time, especially without a personal connection to the study[26,27].

Despite these technology-related limitations, there are several advantages to online research methodologies. They can increase research during COVID isolation periods[1,2], reduce research-related personnel and travel costs for researchers and participants[5], and improve the feasibility and efficiency of conducting research across multiple geographic regions, thereby increasing diverse populations of youth access to research[8,17,19]. Due to ever-changing technology landscapes, there is a need for additional research on best practices for online survey recruitment, data collection, and participant retention strategies.

There are only a few papers that describe online study processes used in conducting adolescent sexual and reproductive health (SRH) research; however, these papers are not primarily focused on methodologies. These studies include an online human immunodeficiency virus (HIV) prevention study called YouthNet[27], an online adolescent and young adult HIV study called Just/Us[28], and an adolescent SRH study focused on online social media recruitment called SpeakOut[29]. There are a few gaps in this literature that our methodology paper seeks to address. The papers describing YouthNet[27], Just/Us[28], and SpeakOut[29] are focused on online recruitment and enrollment methods, but do not go into detail about survey program, settings, security, monitoring, and tracking. In addition, our study differs from these studies because it: (1) Uses a hybrid approach of recruiting in-person and data collecting online; and (2) engages with a youth advisory board that informed our research methods. Specifically, we engaged youth input to ensure the inclusivity of genders and improve participant retention. This methodology paper aims to address these gaps and expand the literature on online data collection processes for adolescent health research.

MATERIALS AND METHODS

This methodology paper provides a case study of an online system that we developed to evaluate *Health-E You/Salud iTu*™, an interactive, individually tailored mobile SRH application (app) that is available in English and Spanish. The web-based app is a pre-visit tool that provides a brief risk pregnancy-risk assessment, personalized patient education, and contraceptive decision-making support. The app also shares a confidential summary with the clinician, in real-time, prior to the clinician-patient encounter to improve the delivery of patient-centered contraceptive care. In a cluster randomized control trial (RCT) of 18 SBHCs in Los Angeles County, California, with 1360 Latina participants, use of the app increased knowledge, self-efficacy, and use of effective contraception over a 3- and 6-month follow-up[30]. The app is now being disseminated to SBHCs across the US to evaluate the effectiveness of the app on a broader population of adolescents, using a randomized stepped-wedge design and an online recruitment and follow-up system. This study uses a hybrid approach; recruitment occurs in person at SBHCs, and the consent, data collection, and incentive distribution occurs *via* an online system that is detailed in this methodology paper. This study includes adolescents who were sex assigned as female at birth, who have had sexual intercourse in the past three months, not currently pregnant and who are not currently using a long-acting contraceptive (LARC) device. The participants are between the ages of 13-19 year, the age range of most youth served in our participating SBHCs.

Data collection survey process

The eligibility, baseline and follow-up surveys were programmed into the Qualtrics online survey platform[31]. The eligibility survey took less than 5 minutes to complete, and the baseline and 3-month follow-up surveys took approximately 10 minutes. These surveys can be taken on any device (*e.g.*, smartphone, tablet, or computer) connected to the internet.

Clinic staff were asked to provide all adolescents coming into the participating SBHC with a link to the online eligibility survey. Clinic staff distributed the eligibility survey link *via* business cards that had a QR code. In addition, clinics hung posters that included information about the study along with the survey QR code and bit.ly shortened survey link. This link directed adolescents to information about the study, and it then asked about their interest in participating, assessed eligibility, and obtained informed consent.

Consented participants were then asked to provide their cell phone number, which was saved securely in Qualtrics and used to distribute subsequent survey links through SMS text messages[9]. To link the eligibility, baseline, and follow-up surveys and to protect participants' confidentiality, we created a unique participant identifier (ID) that included the participant's first letter of their first name, the first letter of their last name, birth date, and birth month.

After creating a unique ID, participants were immediately texted a link to the baseline survey prior to the visit with their SBHC clinician. This SMS text was generated and distributed through Qualtrics. We also set up the Qualtrics system to distribute texts at 1 and 2 months after baseline to remind participants about when they would receive the link for the 3-month follow-up survey with the goal of increasing retention rates. In addition, 3 months after baseline, participants received an SMS text with the link to the 3-month follow-up survey. Participants received SMS text reminders to complete the 3-month survey beginning 24 hours after receiving the link and every other week for up to 2 months (for a maximum of three text reminders and two email reminders) as part of our retention efforts.

The National School-Based Health Alliance Youth Advisory Board (YAB) informed the language on the SMS texts and schedule of the SMS reminders to maximize recruitment and retention. The YAB recommended that the name of the principal investigator be included to increase the "friendliness" of the text and decrease the risk of it appearing as spam. They reviewed the language of the messages to ensure that they were gender-inclusive, reduced the length of the text messages, and provided language about the incentives for completing the survey. They also provided input on the look of the cards and posters used at the SBHCs to promote the study.

Electronic gift card incentive system

Participant incentives were also distributed through an online system. Qualtrics was used in conjunction with an electronic gift card (e-gift card) system. For this study, we used Rewards Genius, operated by Tango Card[32]. The Qualtrics/Tango integration was included with our University's Qualtrics license and allowed for the automatic distribution of digital rewards (e-gift cards) to survey respondents. The Rewards Genius system allowed us to select the monetary amount of the gift card for each specific survey, limit the maximum amount of gift cards distributed, and included a setting to prevent the distribution of multiple gift cards to the same email for the same survey. Rewards Genius has a self-serve online portal to track how many incentives have been sent and monitor the incentive budget. At the end of each survey, the participant was asked how they would like to receive their gift card. If they provided their email, the participant immediately received an email from Tango with a link to redeem a gift card of their choice. If a participant did not have (or did not provide) an email, they could request that their gift card be texted to them. For the SMS option, gift cards were sent manually (as there was no automated option available in this system). To do this, the research assistant downloaded survey data from Qualtrics every other week and used Stata to export the participants' cell phone numbers, without a corresponding email, into an Excel sheet. Research staff manually texted each of these participants with a link to a gift card.

Survey settings

Qualtrics has a variety of setting options that are important to consider for each survey. In this study, Qualtrics was set to record incomplete surveys for partial data after 1 week for the eligibility survey and 1 month for the baseline and 3-month follow-up surveys. The eligibility survey was open for 1 week to decrease the chance of an individual using the

QR codes multiple times. The 3-month follow-up survey remained open for 1 month after the initial completion date to increase participant response rates. Each survey included a back button for participants to change or review their responses, skip logic to route participants to different questions based on their prior responses, and a Qualtrics setting to ensure that email and phone numbers were entered correctly.

Data storage and security

Data was securely stored in the Qualtrics database. Qualtrics is General Data Protection Regulation (GDPR) and California Consumer Privacy Act (CCPA) compliant and provides technology for users to be compliant as well[33]. As mentioned previously, to further protect participants' confidentiality, data from the eligibility survey were stored separately from the baseline and follow-up surveys. The baseline and follow-up surveys included the participant's unique ID, so there was no way to identify an individual with their survey responses, if in a rare event, the back-end database was hacked. Rewards Genius and Tango Card also protect data and privacy through GDPR and the CCPA in addition to multi-factor authentication[32]. Only authorized research staff had access to these systems. We also set up a code within Qualtrics that includes reCAPTCHA (Completely Automated Public Turing Test to Tell Computers and Humans Apart) data to identify bots and relevant ID data to prevent duplicate responses, fraudulent users, and the distribution of multiple gift cards to any individual user. The security system in Qualtrics was vital because our online surveys were attached to incentive gift card distribution. Participants or hackers may be motivated to complete the surveys multiple times with inaccurate responses to obtain e-gift cards[33].

Data monitoring

Monitoring participant enrollment, follow-up survey completion, and gift card distribution were critical to the integrity of this study. Data, including the participant variables included in the unique ID and participant contact information from the eligibility, baseline, and 3-mo surveys, were downloaded from Qualtrics by SBHC in each state. The participant's unique ID was used to match the baseline and follow-up surveys using Stata programming. The Stata code identified potential duplicates, participant identification data errors, and participants without emails who need manual (SMS) gift card incentive deliveries. Fraudulent and repeat users were identified during this data monitoring process through duplicate unique IDs, emails, or phone numbers. The code also produced Excel files of unmatched surveys, including participants who were eligible but did not complete a baseline survey and/or participants who completed the baseline but not the 3-month follow-up survey. This monitoring system allowed us to manually send unmatched participants an SMS text reminder with the survey link. As part of data monitoring efforts, enrollment and 3-month survey completion rates were provided to each participating SBHC on a monthly basis. The investigators discussed this data with clinicians and staff champions from each site, along with implementation successes and challenges.

We worked with SBHCs in diverse locations that largely serve youth who are underserved by the broader health care system. To increase the representation and diversity in our sampling, we asked SBHC staff to provide all adolescents coming for care the opportunity to participate in the study and use the app (when in intervention mode). In addition, we used data monitoring to ensure that the online sampling was representative of youth at the SBHCs. For each school year, we compared the demographics of the survey responses with the retention rates. While we encouraged the distribution to all adolescents and had an incentive system to encourage participation, our sample is one of convenience and relied on the youth's willingness to participate.

The statistical methods of this study were reviewed by Lance Pollack, PhD at the University of California San Francisco.

Ethical approval

Informed consent by all participants were obtained through an online consent process. The research protocols and study were approved by ethics review boards at the University of San Francisco.

RESULTS

Participant enrollment and retention

In the academic year between September 2021 and June 2022, 26 SBHCs across seven states: California, Illinois, Massachusetts, Michigan, Minnesota, New York, and Texas agreed to participate in this study. A total of 415 adolescents were screened to determine eligibility. The screening rate was based on participants who at least clicked on the link that the SBHC staff provided them. Of these, 43.9% (n = 182) were eligible based on study inclusion criteria. There were no significant differences between ineligible and eligible participants when comparing age, race/ethnicity, and language spoken at home. Of the 182 eligible participants, there was a 78.0% (n = 142) retention rate of those who were enrolled and completed the baseline survey (Figure 1). Of the enrolled participants, all were female sex assigned at birth (per inclusion criteria), 95.1% (n = 135) were identified as female, 2.8% (n = 4) identified as non-binary, 1.4% (n = 2) as male or transgender male, and 0.7% (n = 1) as gender fluid (Table 1). The mean age was 16.7 (SD +/- 1.1) years. Nearly half (49.3%) of the participants identified as Hispanic/Latin, 15.5% Black/African American, 12.7% Asian, 10.6% White/Caucasian, and 12% multi-racial/ethnic. Many (40.8%) spoke Spanish with their family, either solely or in addition to English.

Of those who were enrolled in the study, there was a 62.0% (n = 88) retention rate of those who completed the 3-month follow-up survey. There were no significant differences in age, race/ethnicity, and languages spoken at home between

Table 1 Descriptive statistics of participants at baseline[a,b,c]

Demographics	*n* (%)
Gender	
Female	135 (95.1)
Male	1 (0.7)
Transgender male	1 (0.7)
Non-binary	4 (2.8)
Gender fluid	1 (0.7)
Sex assigned at birth	
Female	142 (100)
Age group, mean +/- SD	16.7 +/- 1.1
Race/ethnicity	
Asian	18 (12.7)
Black/African/African Amer	22 (15.5)
Hispanic/Latinx/o/a	70 (49.3)
White/Caucasian	15 (10.6)
Multi-racial/ethnic	17 (12)
Speaks Spanish with family	58 (40.8)

[a]*N* = 142 unless otherwise noted.
[b]Outcomes are *n* (%) unless otherwise noted.
[c]Percentages may not add up to 100 due to rounding.

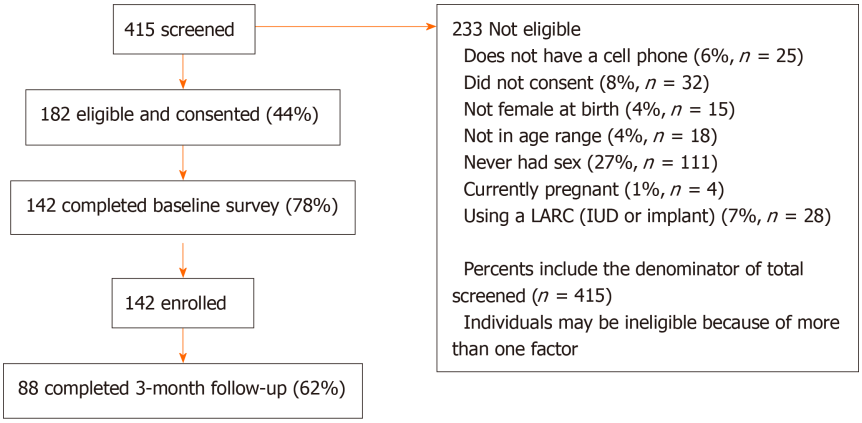

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Figure 1 Participant flow diagram.

those who completed the 3-mo follow-up and those who did not (Table 2). Among the 3-month follow-up survey participants, 95.5% were identified as female with a mean age of 16.8 years (SD +/- 1.04). Nearly half (46.6%) identified as Hispanic/Latin, 11.4% Black/African American, 14.8% Asian, 12.5% White/Caucasian, and 14.8% reported being multi-racial/ethnic.

Challenges

There were a few challenges that resulted with this online data system. As part of ongoing data monitoring efforts, we provided SBHC clinicians and staff monthly data and discussed implementation barriers. Some staff reported that it was difficult to remember to distribute the link because they had other responsibilities, were short-staffed, or they forgot when the adolescent was being seen for a non-reproductive health visit. A total of 21 out of the 26 SBHCs reported being short-staffed or overworked due to ongoing challenges with COVID-19 that increased rates of illness for staff and their family members, exacerbated youth mental health issues, and contributed to burn-out. Additionally, some clinicians and

Table 2 Descriptive statistics of participants at 3-mo follow-up[a,b,c]

Demographics	*n* (%)
Gender	
Female	84 (95.5)
Transgender male	1 (1.1)
Non-binary	3 (3.4)
Sex assigned at birth	
Female	88 (100)
Age group, mean +/- SD	16.8 +/- 1.04
Race/ethnicity	
Asian	13 (14.8)
Black/African/African Amer	10 (11.4)
Hispanic/Latinx/o/a	41 (46.6)
White/Caucasian	11 (12.5)
Multi-racial/ethnic	13 (14.8)
Speaks Spanish with family	34 (38.6)

[a]*N* = 88 unless otherwise noted.
[b]Outcomes are *n* (%) unless otherwise noted.
[c]Percentages may not add up to 100 due to rounding.

staff reported that internet access and connectivity problems were barriers to youth accessing and completing the surveys. There were internet connectivity issues for cellular data at five SBHCs, limiting access for youth to use their phones to complete the surveys. The high school affiliated with two SBHCs, did not allow students to use their cell phones on campus so youth could not access the internet until these sites were able to connect tablets to their clinic Wi-Fi, which involved setting up a secure guest wifi network. As a result, not all potential participants received the eligibility survey link.

Despite protections against duplicate and fraudulent users, there were some duplicate users that we identified and removed, and one individual, not related to the study, hacked the system and obtained multiple e-gift cards. Duplicate users came from SBHCs that provided adolescents with iPads to access the online eligibility survey. Since multiple youth were using the same device, a generic link had to be used to access the online system. Thus, it was not possible to set up Qualtrics to limit the number of times that a survey was completed for respondents using the same device. Duplicates were removed as part of the data monitoring and cleaning process. Additionally, one SBHC posted the survey link on their social media website. An individual, not involved with this SBHC, obtained the survey link to access the survey, identified the study eligibility criteria, and generated multiple, fictitious participant contacts to complete multiple baseline surveys and obtain incentives. The hacker used the system over the weekend and by Monday, when study staff returned to work and discovered the problem through routine data monitoring, the hacker completed 668 surveys and obtained $6680 in gift cards. This was the only time in which this issue occurred. All SBHCs were advised to distribute the link only to individual patients coming to their clinic and avoid posting the link on social media or other clinic websites. There was no breach of any participant data during this incident.

DISCUSSION

This methodological paper provides a case study of the online system used to evaluate the *Health-E You/Salud iTu*™ app. We found that this system enabled us to recruit and retain a diverse study population without having to deploy study personnel to the 26 SBHC sites across seven states. We found no statistically significant differences between eligible and non-eligible participants based on age, race/ethnicity, and language spoken at home. There were also no significant differences between participants who completed the baseline and participants who completed the 3-month follow-up survey based on age, race/ethnicity, and language spoken at home.

Strengths of the online system

A major strength of this online research system was its ability to reach a diverse group of youth at multiple SBHCs across the nation including Northern and Southern California, Illinois, Massachusetts, Michigan, Minnesota, New York, and Texas. In addition to geographic diversity, this study recruited a racially diverse sample size with almost half coming

from Hispanic/Latin backgrounds and the balance comprising relatively equal proportions of Black, Asian, White, and multi-racial/ethnic participants. Additionally, almost half respondents reported that they were Spanish speakers. The online system allowed participants to participate in their preferred language English or Spanish and they could toggle between languages throughout the process. Increasing diversity of participants' region, race, and language spoken is a vital aspect to increasing inclusivity and representation of underrepresented populations in health research.

Online research systems can reduce costs and increase efficiency for researchers. Online research systems allow for increased organization, centrally located documents and materials, and an efficient tracking system to save time for researchers. The study recruitment and surveys were set up online with automatic survey distributions and reminders using Qualtrics settings, which allowed our research staff to have more time to track and communicate with participants individually, meet with clinics more frequently, create and meet with the youth council, and make adaptations to improve the study. Online surveys saved costs on transportation, survey materials, and data collection staff. In this study, these aspects would have been costly due to the number of participating SBHCs across multiple states in the US. However, it should be noted, that there can be research costs when a study uses paid adds to recruit *via* social media or through paid online survey platforms[5] (neither of these were used in this study). Our hybrid approach that included initial in-person contact (by SBHC staff) followed by online data collection and monitoring, cost less than other online studies[27,29,35]. An online HIV study spent $13,000 on banner advertising[27] and a smoking-cessation study spent $172.76 per participant on social media[35]. In contrast, our study spent approximately $32.77/clinic on promotional materials for direct study recruitment.

Online surveys are also an extremely effective way to increase the accuracy of survey responses from adolescent participants as well as their comfort responding to sensitive questions about their SRH. In previous SRH studies, adolescents have reported concerns about clinician judgment, power differential, and a lack of confidentiality[34]. Research also shows that adolescents feel more comfortable answering SRH questions online compared to clinician or researcher interview[21]. In addition, while not examined in the current study, prior research found that social desirability bias occurred when research was conducted in person or on a phone call rather than online[22].

Limitations of the online process

Despite the advantages of online systems, such as those used in the current study, there are important challenges to consider. While asking clinic staff to distribute the link did not seem like it would be burdensome, staff commonly forgot to do so. Clinics reported being short-staffed, overworked, and were focused on other pressing priorities at their clinic and/or with their patients – most of which were related to ongoing challenges associated with the COVID-19 pandemic.

Consistent with prior research[16,25], our study found that online recruitment and follow-up surveys can increase the possibility of duplicate survey responses and invalid survey participants or hackers. By automatically linking online surveys to gift card incentive distributions (participants receive an e-gift card directly after survey completion), hackers can take advantage of incentive systems to target the survey through code that searches the internet for surveys linked to gift cards. To prevent unsolicited participants from finding online surveys, survey links should not be posted online on public platforms. However, restricting access to survey links can also limit broader recruitment through online platforms such as social media sites. To maximize reach and limit fraud, gift cards could be manually distributed *via* text or email after each survey is verified and/or researchers can consider validating the authenticity of the participant through follow-up phone calls prior to study enrollment. However, both of these methods can increase the burden for research staff and create delays in the distribution of participants' gift cards. To limit these duplicate and fraudulent user issues, we implemented robust security systems in Qualtrics (described in the methods section); however, there was still a possibility for error of fraudulent or duplicate users in these security systems. Researchers as well as potential participants need to better understand the risks of online research, such as fraudulent users, duplicates users, and potential data security breaches, especially in the context of rapidly evolving computer-based and online technologies.

While the retention rates in this study are comparable to other online studies focused on SRH, there is a need to improve retention rates in online studies. The recruitment and 3-month retention rates in this study were higher than those of the original cluster RCT (78% *vs* 57% for recruitment rates and 3-month retention rates were 62% *vs* 50%, respectively)[30]. These improvements in the current study may be due to lessons learned from the original trial, additional input from the YAB, and the expanded diversity of the study population. One advantage of this study's online system, compared to the original RCT, was the use of automatic reminders for surveys through Qualtrics. Our retention rates were also greater than that of another online HIV prevention study, which had a 53% retention rate at the 2-month follow-up[27]. This HIV study relied heavily on online recruitment through banner advertisements, which is advantageous for reaching a larger and more diverse study sample; however, using this approach resulted in approximately 20% of potentially fraudulent participants. Our study was able to overcome this issue because, by its very nature, the intervention, use of the *Health-E You* app, is designed to be used in conjunction with a health care visit. While data collection was done *via* our online system, SBHC clinic staff provided the opportunity to use the eligibility link to begin the online system with real patients. In addition, we verified participants by requiring phone numbers to receive future surveys and matched across surveys using the match ID and email addresses. In another online HIV study with adolescents and young adults, retention rates were 69% at the 2 month follow-up and 50% at the 6 month follow-up[28]. While this is more comparable to our study, these rates are lower than those found in other SRH studies conducted in person[28]. In contrast, the retention rates in the current study are lower than those found in a study that recruited adolescents *via* social media[29] whose retention rates ranged from 71% (in the control group) to 79% (intervention). This is likely due to the fact that once deemed eligible *via* the online system, a research assistant conducted a follow-up phone call to verify eligibility and randomize participants to the intervention or control condition. This approach was not possible in our study, since participants were recruited in clinic and the baseline survey had to be completed prior to seeing their clinician. Recruiting *via* social media is advantageous for recruiting a greater number of individuals over a

shorter time period as was demonstrated in the SpeakOut study[29]. In this study, high retention rates can be attributed to the work of research assistants who called each participant to verify their eligibility. This verification process improved the integrity of the data; however, this is a time-consuming and costly approach (in terms of staff time). When we compared our study's retention rates with a smoking cessation study conducted on line, our retention rates were higher [35]. That study had an overall 52% 3-month follow-up retention rate and did not find any significant differences in retention rates between the online methods (including social media, ads, and standard media) *vs* the traditional recruitment methods that they used[35]. Despite these variations in retention rates, some research suggests that the overwhelming majority (82%) of young adults prefer online surveys over mail-in surveys and this preference was greater not only for youth of younger ages, but also for those from higher socio-economic backgrounds[36]. On going efforts to improve retention rates for all participants are needed.

To improve retention rates, researchers have used immediate incentives, continual contact information collection, and consistent reminders[28,29,35,36]. Our study also used these strategies and resulted in comparable or slightly better retention rates than those found in other studies using similar online methods. Thus, it is important to identify and further investigate additional approaches to recruit and increase participant retention when using online methodologies. While the use of online systems for research can increase the reach and diversity of study populations, relatively low retention rates can limit the generalizability of study findings.

Researchers using online systems also need to make special efforts to include participants who do not have internet access. Online surveys require internet access through cellular data, Wi-Fi connection, or ethernet cable connection and this can prevent individuals without such access from participating in research. They may not have cell phones that can access the internet or may have limited data plans with their smartphones. Others may not have household internet access, especially if they live in rural and other underserved areas. Data from the National Center for Education Statistics found that the percentage of households (with youth aged 3 to 18 years old) with home internet access was highest among those who were Asian (99%) and White (97%), and lowest among those who were American Indian/Alaska Native (83%), Pacific Islander (90%), and Black (91%)[37]. Reasons for lack of access included "did not need it/not interested" (50%) and "internet too expensive" (26%)[37]. Additionally, rural US residents also experience lower access to home internet (72%) compared to their suburban (79%) and urban (77%) counterparts[23]. In 2021, the United Nations adopted a resolution on the internet as a human right and encouraged countries to adopt "national internet-related public policies that have at their core the objective of universal access"[38]. However, the US lacks a national policy guaranteeing universal access and internet access disparities remain. Because online survey research systems are dependent on internet access, it is important for future research to explore ways to recruit and retain participants with more equitable rates rather than excluding populations with limited access. This may require hybrid approaches that use a combination of internet and in-person recruitment methods and partnering with community-based organizations to reach and include groups underrepresented in research.

Another limitation of online-only research studies is the lack of in-person interaction. Although the online system can decrease the time that clinics are required to dedicate to the study, it also limits the interpersonal connection that researchers make while in the clinics. To compensate for this limitation, our research team met with the clinic staff every few months *via* Zoom; however, a few clinics were unresponsive over email. In-person interaction could potentially increase clinic staff engagement in the study. The lack of in-person contact with participants, may also contribute to lower follow-up rates as they may feel less of a connection to the researchers and with the study.

Lastly, our study is limited because its findings are not generalizable to all adolescents. Our study participants are female at birth, attend SBHCs, are between the ages of 13-19 years, and not currently pregnant or using a LARC device. However, our online methods are still relevant to the overall literature on adolescent health.

Future implications

This case study of an online system for health research has implications for future research. Ensuring the security of participants' data is a top priority as is maintaining the authenticity of participants and data quality. Although there is increasing information available to the public about data security in settings such as jobs, browsing the internet[39], and social media[40], there is a lack of research describing how to ensure data security in research settings. As shown in our study, added measures are critical to safeguard the distribution of electronic gift cards. Researchers need to be fully aware of these risks and vigilant in protecting and monitoring data security[41]. However, health researchers are often not trained in or aware of all of the details involved with data security and need to partner with experts within and/or outside of their institution to ensure that the best possible security protections are in place, such as separately storing data, securing public Wi-Fi networks, and using data leak prevention and protection systems[42,43]. In this study, we worked closely with Qualtrics representatives and our UCSF Salesforce team. With ever evolving cyber-attacks, new technologies emerge to address this growing threat such as data storage programs and security protected online files[44]. It is vital for future studies to specifically address ways to maximize outreach and recruitment while ensuring the authenticity of the participants and their responses. This involves exploring online and social media recruitment but instituting robust security measures to verify participants such as contact information validation and mobile device authentication [25].

Although this study displayed ways that online systems can reach more racially, geographically, and linguistically (language) diverse populations, there are still disparities in online access through limited Wi-Fi and/or cell service[24]. It is important for studies to continue to identify strategies that include diverse populations through online systems and consider hybrid approaches when online inclusion is not possible. This includes conducting research activities in person with populations that have limited device or internet access. Lastly, there is a need to research the online system limitations related to engagement and the connection between the researcher and participant or clinic staff. It would be helpful for future studies to analyze the extent to which participant engagement is lost in online studies as opposed to in-

person studies. As these limitations are addressed, online systems can be a powerful strategy for increasing the reach and diversity of populations included in health research.

CONCLUSION

Overall, this methodological paper displays the importance of online systems for youth participation in health research and provides examples of methods used to maximize efficiency of these systems. This case study of the *Health-E You/Salud iTu*™ app discusses the use of online systems that helped recruit youth *via* their mobile devices, distribute surveys, monitor participants, and deliver reminders. These systems improved the geographic reach and inclusion of diverse youth participation. Additionally, in an era of COVID-19 remote work, increased use of telehealth, and youth's use of technology, online systems are crucial for health research. Future studies should study how to leverage technology to further improve reach, diversity, and inclusion of underrepresented groups in research.

ARTICLE HIGHLIGHTS

Research background

Online surveys can align with youth's increased use of the internet and can be a mechanism for expanding youth participation in research. The utilization of mobile technologies can extend the geographical reach and promote the participation of diverse adolescent populations in health research. Using mobile technology for health research data collection can also improve data quality. However, the advantages and drawbacks of online systems used for research need to be carefully considered before utilizing such methodologies.

Research motivation

There are few methodology papers that describe online study processes in the same field as our study, adolescent sexual and reproductive health (SRH). These studies that describe online methodologies include an online human immunodeficiency virus (HIV) prevention study called YouthNet, an online adolescent and young adult human immunodeficiency virus study called Just/Us, and an adolescent SRH study focused on online social media recruitment called SpeakOut. However, there is a lack of research on how to specifically involve adolescents in research and the methods used to ensure diversity, keep the adolescents retained, and maintain data security.

Research objectives

The purpose of this study is to describe and discuss the strengths and limitations of an online system developed to recruit adolescent girls for a sexual health research study and follow them for 3 months. It aims to address the gap of methodology papers and expand the literature on online data collection process for adolescent health research.

Research methods

This methodology paper examines the use of an online system to recruit and follow participants to evaluate a mobile SRH application, *Health-E You/Salud iTu*™, for adolescent females attending school-based health centers (SBHCs) across the US. The paper goes into detail regarding the following methodologies for our online study: Data collection and survey processes, the electronic gift card incentive system, survey settings, data storage and security, and data monitoring.

Research results

This online recruitment and retention system enabled participant recruitment at 26 different SBHCs in seven states across the United States. Between September 2021 and June 2022, 415 adolescent girls were screened using the Qualtrics online survey platform, and 182 were eligible to participate. Participants were racially, geographically, and linguistically diverse; most of the participants (89.4%) were non-White, and 40.8% spoke Spanish. Limitations of this system included reliance on internet access (*via* Wi-Fi or cell service), which was not universally available or reliable, and some issues individuals outside the study discovering the survey link and completing multiple surveys.

Research conclusions

Online systems for health research can increase the reach and diversity of study participants, reduce costs for research personnel time and travel, allow for continued study operation when in-person visits are limited (such as during the coronavirus disease 2019 pandemic), and connect youth with research using technology. The methods detailed using online surveys, online gift card distribution, and online data monitoring and tracking are new and add to the lack of methodology papers. However, there are challenges and limitations to online systems, which include limited internet access, intermittent internet connection, data security concerns, and the potential for fraudulent users. These challenges should be considered prior to using online systems for research.

Research perspectives

This case study of an online system for health research has implications for future research. Ensuring the security of participants' data is a top priority as is maintaining the authenticity of participants and data quality and as shown in our

study, added measures are critical to safeguard the distribution of electronic gift cards. It is important for studies to continue to identify strategies that include diverse populations through online systems and consider hybrid approaches when online inclusion is not possible. Lastly, there is a need to research the online system limitations related to engagement and the connection between the researcher and participant or clinic staff.

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FOOTNOTES

Author contributions: Salem M and Tebb KP performed the research; Tebb KP, and Pollack L designed the research study; Pollack L analyzed the data; Salem M, Tebb KP, and Zepeda A wrote the manuscript; all authors have read and approved the final manuscript.

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Basic Study

Comprehensive analysis of cell-extracellular matrix protein Ras suppressor-1 in function and prognosis of gastrointestinal cancers

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Abstract

BACKGROUND

Ras suppressor 1 (RSU1), a highly conserved protein, plays an important role in actin cytoskeleton remodeling and cell-extracellular matrix adhesion. Aberration of RSU1 activity can cause changes in cell adhesion and migration, thereby enhancing tumor proliferation and metastasis. However, the correlation between RSU1 and gastrointestinal cancers (GICs), as well as its prognostic role related to tumor-infiltrating immune cells (TIICs) remains unclear.

AIM

To shows RSU1 plays a potential promoting role in facilitating tumor immune escape in GIC.

METHODS

Differential expression of RSU1 in different tumors and their corresponding normal tissues was evaluated by exploring the Gene Expression Profiling Interactive Analysis (GEPIA) dataset. The correlation between RSU1 expression and prognosis of GIC cancer patients was evaluated by Kaplan-Meier plotter. Then, RSU1-correlated genes were screened and functionally characterized *via* enrichment analysis. The correlation between RSU1 and TIICs was further characterized using the Tumor Immune Estimation Resource (TIMER). In addition, the correlation between RSU1 and immune cell surface molecules was also analyzed by TIMER.

RESULTS
High RSU1 expression was associated with poor overall survival of gastric cancer patients, exhibiting a hazard ratio (HR) = 1.36, first progression HR = 1.53, and post progression survival HR = 1.6. Specifically, high RSU1 Levels were associated with prognosis of gastric cancer in females, T4 and N3 stages, and Her-2-negative subtypes. Regarding immune-infiltrating cells, RSU1 expression level was positively correlated with infiltration of CD4+ T cells, macrophages, neutrophils, and dendritic cells (DCs) in colorectal adenocarcinoma and stomach adenocarcinoma. RSU1 expression was also predicted to be strongly correlated with immune marker sets in M2 macrophage, DCs and T cell exhaustion in GICs.

CONCLUSION
In gastrointestinal cancers, RSU1 is increased in tumor tissues, and predicts poor survival of patients. Increased RSU1 may be involved in promoting macrophage polarization, DC infiltration, and T cell exhaustion, inducing tumor immune escape and the development of tumors in GICs. We suggest that RSU1 is a promising prognostic biomarker reflecting immune infiltration level of GICs, as well as a potential therapeutic target for precision treatment through improving the immune response.

Key Words: Ras suppressor 1; Gastrointestinal cancer; Immune infiltration; Prognosis; Actin cytoskeleton remodeling

Core Tip: Ras suppressor 1 (RSU1), is a highly conserved protein involved in actin cytoskeleton remodeling and cell-extracellular matrix adhesion. The current study provides a comprehensive analysis of RSU1 in gastrointestinal cancer and shows its potential promoting role in facilitating tumor immune escape.

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INTRODUCTION

The International Agency for Research on Cancer has released new data on the global burden of cancer for 2020. China has the world's highest number of new cases and deaths. There were 4.57 million new cancer cases in China in 2020, the top four being lung, colorectal, stomach and breast cancers. At the same time, the top five cancer deaths in China in 2020 were recognized as lung, liver, stomach, esophageal and colorectal cancers[1], with the incidence and mortality of gastrointestinal cancers (GICs) showing a clearly increasing pattern[2]. Currently, the prognosis of GIC patients has been slowly improving with the continuous progress of therapeutic strategies and extensive application of surgery, chemotherapy, biological targeted therapy, immunotherapy and other therapeutic methods[3]. However, poor clinical therapeutic effects remain for a subpopulation of GIC patients, showing the need for more specific and sensitive therapeutic targets for GIC patients. Development of new targeted drugs is a promising method in the treatment of GICs.

On the other hand, immune checkpoint inhibitors have emerged as promising antitumor drugs for multiple tumor types, either as single agents or in combination with chemotherapy[4]. For example, the KEYNOTE-062 and CheckMate-649 phase III clinical trials achieved positive results for immune checkpoint inhibitors in advanced first-line treatment of patients with gastric cancers (GCs)[5,6]. Therefore, clinical guidelines in many countries recommend immunotherapy combined with chemotherapy as the first-line treatment for metastatic GCs[7]. However, it is not clear how to select GIC patients who will benefit most from checkpoint inhibitors, necessitating further investigation for novel biomarkers to predict outcomes and immunotherapeutic response.

Ras suppressor 1 (RSU1) was originally found to suppress RAS-dependent oncogenic transformation, and localizes to human chromosome 10p13[8]. Later, it was found that RSU1 binds with high affinity, *via* its LRR domain, to the LIM5 domain of PINCH1, thereby forming an IPPR complex with ILK-PINCH-Parvin to regulate cell adhesion at sites of focal adhesion[9,10], and participate in physiological and pathological processes of local adhesion and tumor metastasis[11,12]. RSU1 has long been associated with cancers, but its expression in various cancer types or its role in metastasis has been unclear. It has been suggested that RSU1 is involved in the regulation of migration and invasion of breast cancer, liver cancer and brain cancer cells, and has the function of enhancing metastasis in a cell type-dependent manner[11,13-15]. RSU1 could also serve as a therapeutic anti-metastatic target in liver and breast cancer[16]. To evaluate the potential role of RSU1 in GIC, the correlation of RSU1 expression with prognosis in GIC patients with various clinicopathological factors was investigated, as well as the function of RSU1 in the occurrence of GIC and the correlation between RSU1 and immune infiltration.

MATERIALS AND METHODS

The expression pattern of RSU1 in different types of cancers

This platform includes RNA sequencing data from 9736 tumor tissues and 8587 normal tissues from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) databases. The main functions of GEPIA (http://gepia.cancer-pku.cn/) include gene expression analysis, gene correlation analysis, survival analysis, similar gene prediction, and dimension reduction analysis. The expression of RSU1 in tumors and normal tissues was analyzed *via* GEPIA.

The prognostic value of RSU1 in malignancies

Kaplan-Meier plotter (http://kmplot.com/analysis/) contains 10461 cancer samples for assessing the impact of 54675 genes on survival. Patients with cancers were divided into two groups (high- *vs* low-expression) to analyze the poorer overall survival (OS), poorer first progression (FP), progression free survival (PFS), and poorer post-progression survival (PPS) by means of HRs, 95% confidence intervals and log-rank *P* values. To predict the prognostic values of RSU1, GEO datasets were analyzed through the PrognoScan databases (http://dna00.bio.kyutech.ac.jp/PrognoScan/index.html) based on Cox *P* values.

The signaling pathway associated with RSU1

DAVID (https://david.ncifcrf.gov/conversion.jsp) is a biological information database that integrates biological data, using analytical tools, to provide systematic and comprehensive annotation of biological functions for large-scale gene or protein lists, and extract biological information of interesting genes. RSU1-related genes were analyzed, regarding the top 10 highly enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and Gene Ontology (GO) items.

The immune infiltration regulated by RSU1 in GICs

TIMER 2.0 (http://timer.cistrome.org) uses state-of-the-art algorithms to provide more reliable estimates of immune infiltration levels for TCGA or user-provided tumor profiles. TIMER 2.0 provides three modules, Immune Association, Cancer Exploration and Immune Estimation, for investigating associations between immune infiltration and genetic or clinical characteristics. TIMER was applied to analyze the expression of RSU1 in GIC patients and its relationship with 6 types of infiltrating immune cells (B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and DCs). The abundance of T cells, neutrophils, macrophages, and DCs, as well as tumor purity are important factors affecting immune infiltration in tumor samples analyzed by genomics.

ESTIMATE was conducted in the open-source R software to analyze the gene expression profiling of GICs for StromaScore, ImmuneScore and ESTIMATEScore. The datasets were downloaded from the GEO database, GSE17536, which had 177 patients with colorectal cancer (CRC), and GSE62254, which had 300 patients with GC. All patients were divided into two groups, high RSU1 *vs* low RSU1 based on the median RSU1 expression level.

Statistical analysis

The survival results from Kaplan-Meier plotter and GEPIA2 are displayed with HRs and *P* or Cox *P* values based on the log-rank test. Spearman correlation and statistical significance were used to evaluate the correlation of gene expression with immune biomarkers in GICs. Differences with $P < 0.05$ were considered significant.

RESULTS

Expression levels of RSU1 mRNA in different types of human cancers

The expression pattern of RSU1 in different cancers was analyzed by GEPIA based on TCGA and GTEx datasets. It was found that, compared with normal tissues, RSU1 was highly expressed in glioblastoma multiforme (GBM), brain lower grade glioma (LGG), pancreatic adenocarcinoma (PAAD), stomach adenocarcinoma (STAD), and testicular germ cell tumors (TGCT) tissues, whereas a low level of RSU1 was found in kidney chromophobe (KICH) tissues (Figure 1A). However, there was no significant difference in RSU1 expression in colon adenocarcinoma (COAD), although the level of RSU1 in COAD tissues tended to be slightly increased.

Prognostic value of RSU1 in patients with different types of cancer

Further investigation focused on the prognostic role of RSU1 in different types of cancer. Based on the Kaplan-Meier plotter database, survival information was analyzed in patients with GC, breast cancer, ovarian cancer and lung cancer. A high expression level of RSU1 in patients with GC predicted poor OS, with hazard ratios (HR) = 1.36 (1.09-1.7), first progression HR = 1.53 (1.13-2.07) and post-progression survival HR = 1.6 (1.22-2.11) (Figure 2A-C). Regarding breast cancer, the expression level of RSU1 did not affect either the OS or PFS of patients with breast cancer, although significantly poor PPS was found in breast cancer patients with high RSU1 expression (HR = 1.8 (1.26-2.58), Figure 2D-F). In patients with ovarian cancer, the association between RSU1 level and survival was only found in OS [HR = 1.35 (1.09-1.68)], while PFS and PPS were not associated with RSU1 expression (Figure 2G-I). However, a high level of RSU1 predicted good OS in patients with lung cancer, with an HR = 0.56 (0.47-0.66), but no relationship with FP and PPS (Figure 2J-L). The above survival results in different types of cancer suggested that RSU1 may have distinct function in GCs, even in GICs.

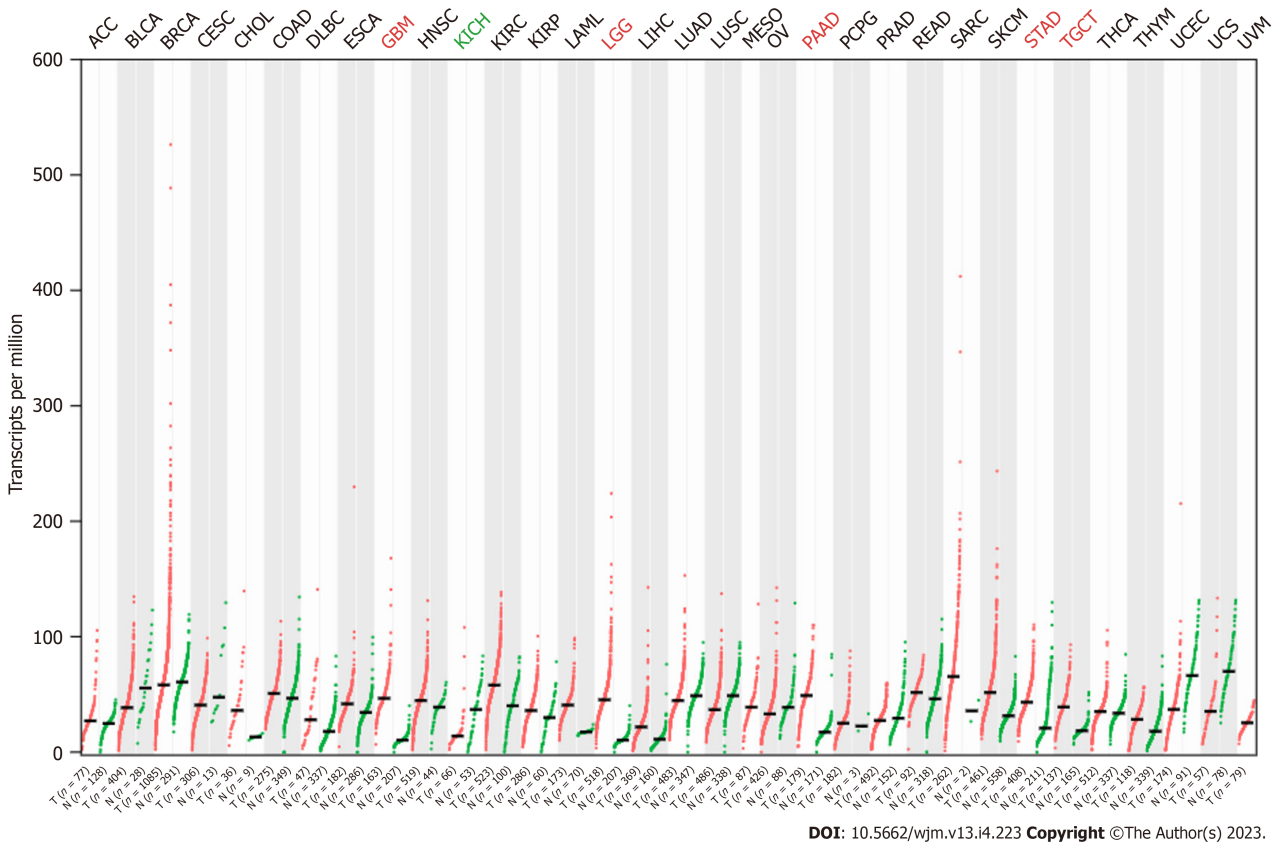

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Figure 1 Expression of Ras suppressor 1 in different tumors. Red dots indicate tumors, and green dots are corresponding normal tissue.

RSU1 is prognostic for GIC

To better understand the relevance and underlying mechanisms of RSU1 expression in GC, the relationship between the RSU1 expression and clinical characteristics of GC patients in the Kaplan-Meier plotter database was analyzed through six GC cohorts (GSE14210, GSE15459, GSE22377, GSE29272, GSE51105, GSE62254). Interestingly, in female patients with GC, the expression level of RSU1 was associated with OS, FP and PPS ($P < 0.05$, Table 1). Among different tumor stage parameters, the expression of RSU1 was correlated with large tumor size (T) and predicted poor survival of GC patients with the highest HR = 4.86. However, with or without lymph node metastasis, high RSU1 expression was associated with poor survival in GC, with HRs ranging from 1.35 to 10.98. Regarding distant metastasis, GC patients with increased RSU1 expression predicted shorter OS, and poor FP and PPS. Even HER2 status can affect the prognostic capability of RSU1, giving an HR = 1.46–1.79 in GC patients with negative HER2 status.

To investigate the prognostic value of RSU1 in other GICs, GEO datasets were recruited for further analysis, as no survival information of CRC was found in Kaplan-Meier Plotter. Interestingly, both in GSE17536 and GSE17537, CRC patients with high RSU1 expression tended to have short OS, disease-free survival (DFS), and disease-specific survival (DSS). However, as the sample sizes were limited, statistical significance was only found in GSE17536 in regard to DSS in CRC patients (HR = 1.86, Figure 3).

Pathway enrichment analysis of RSU1-correlated genes

To investigate the potential signaling pathways involved in RSU1-regulated development of GIC, the top 100 RSU1-related genes were collected and analyzed with the KEGG pathways and GO projects, and mapped onto GO for biological process (BP), cellular component (CC), and molecular function (MF) analysis (Figure 4).

The highest enrichment of BP, CC and MF included actin cytoskeleton organization, focal adhesion, extracellular exosome, protein binding and actin binding (Figure 4A-C). In addition, among the top 10 KEGG pathways, endocytosis, Salmonella infection, bacterial invasion of epithelial cells, and tight junction were significantly enriched for RSU1 and RSU1-related genes (Figure 4D). It is reported that the actin cytoskeleton is essential for maintaining cell shape and promoting movement, and plays a key role in tumor invasion and metastasis[17], suggesting that RSU1 may be linked to the tumorigenesis and progression of cancers.

RSU1 expression is associated with immune infiltration levels in GIC

Tumor immune escape is a major obstacle limiting the efficacy of current immunotherapy. It has been reported that actin cytoskeletal remodeling can protect tumor cells from natural killer-mediated cytotoxicity[18]. Thus, RSU1 could affect immune infiltration in GICs based on its association with actin cytoskeletal remodeling.

Table 1 Correlation of Ras suppressor 1 expression and prognosis in gastric cancer with various clinicopathological factors

	OS (631)			FP (522)			PPS (384)		
	n	HR	*P* value	*n*	HR	*P* value	*n*	HR	*P* value
Sex									
Female	187	1.88 (1.22-2.89)	[c]	179	1.65 (1.09-2.51)	[a]	127	1.99 (1.21-3.25)	[b]
Male	349	1.36 (0.94-1.97)	0.098	341	1.4 (0.98-2.01)	0.064	256	1.52 (1.09-2.14)	[a]
Stage									
I	62	2.84 (0.63-12.88)	0.16	60	2.7 (0.6-12.26)	0.18	31	2.79 (0.53-14.68)	0.21
II	135	1.47 (0.79-2.75)	0.22	131	0.73 (0.4-1.32)	0.29	105	2.01 (1.04-3.9)	[a]
III	197	1.27 (0.87-1.87)	0.22	186	1.51 (1.02-2.22)	[a]	142	1.2 (0.77-1.86)	0.42
IV	140	1.53 (0.95-2.46)	0.078	141	1.17 (0.74-1.84)	0.51	104	1.79 (1.13-2.83)	[a]
T									
T2	241	1.64 (0.98-2.73)	0.055	239	1.42 (0.88-2.29)	0.15	196	1.57 (0.9-2.72)	0.11
T3	204	1.3 (0.92-1.83)	0.14	204	1.36 (0.95-1.94)	0.091	150	1.36 (0.93-1.99)	0.12
T4	38	3.33 (1.12-9.96)	[a]	39	2.12 (0.85-5.3)	0.1	29	4.68 (1.34-16.32)	[b]
N									
N0	74	2.77 (1.19-6.43)	[a]	72	2.69 (1.16-6.23)	[a]	41	10.98 (2.7-44.62)	[c]
N1-3	422	1.54 (1.18-2.01)	[b]	423	1.35 (1.04-1.74)	[a]	337	1.64 (1.22-2.19)	[c]
M									
M0	444	1.72 (1.2-2.47)	[b]	443	1.63 (1.16-2.31)	[b]	342	1.77 (1.31-2.4)	[c]
M1	56	1.84 (1.02-3.29)	[a]	56	1.44 (0.79-2.6)	0.23	56	2.09 (0.98-4.45)	0.052
HER2 status									
Negative	429	1.46 (1.12-1.91)	[b]	429	1.55 (1.06-2.26)	[a]	283	1.79 (1.28-2.5)	[c]
Positive	202	1.41 (0.95-2.09)	0.086	166	1.46 (0.9-2.38)	0.13	101	1.46 (0.89-2.4)	0.14
Treatment									
Surgery alone	380	1.44 (1.07-1.93)	[a]	375	1.36 (0.97-1.9)	0.071	277	1.82 (1.31-2.52)	[c]
5-FU-based adjuvant	34	1.77 (0.69-4.52)	0.23	34	1.8 (0.77-4.25)	0.17	21	0.39 (0.13-1.18)	0.085
Other adjuvant	76	2.65 (1.09-6.4)	[a]	80	3.46 (1.03-11.67)	[a]	74	2.5 (0.98-6.41)	[a]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
5-FU: 5-fluorouracil; FS: First progression; HR: Hazard ratio; OS: Overall survival; PPS: Post-progression survival.

To explore the potential function of RSU1 in GICs, two datasets related to GICs were downloaded and analyzed through ESTIMATE in R software. It is found that along with the increased RSU1 expression level, the StromaScore and ESTIMATEScore were elevated gradually with $P < 0.05$ in CRC and GC (Figure 5A and C). After dividing the patients into high RSU1 *vs* low RSU1 groups, similar results were found in StromaScore and ESTIMATEScore. In the group with high RSU1 levels, StromaScore and ESTIMATEScore were significantly higher compared with the low RSU1 group (Figure 5B and D).

The relationship between RSU1 expression and immune infiltration levels in GIC was explored, revealing that in COAD, RSU1 expression was not significantly correlated with tumor purity (r = -0.089, P = 7.37e-02), CD8+ T cells (r = -0.1, P = 9.74e-02) or B cells (r = -0.03, P = 6.16e-01), but was positively correlated with the infiltration levels of CD4+ T cells (r = 0.36, P = 7.73e-10), macrophages (r = 0.304, P = 2.69e-07), neutrophils (r = 0.12, P = 4.66e-02) and DCs (r = 0.237, P = 7.21e-05) (n = 458) (Figure 6A). Interestingly, in STAD, RSU1 expression was found to be associated with the changed immune infiltration, which was positively correlated with infiltration levels of CD8+ T cells (r = 0.41, P = 8.50e-17), CD4+ T cells (r = 0.235, P = 3.66e-06), macrophages (r = 0.46, P = 2.78e-21), neutrophils (r = 0.309, P = 8.33e-10), and DCs (r = 0.372, P = 6.43e-14) (n = 415), but not for tumor purity (r = -0.062, P = 2.29e-01) and B cells (r = 0.057, P = 2.70e-01) (Figure 6B).

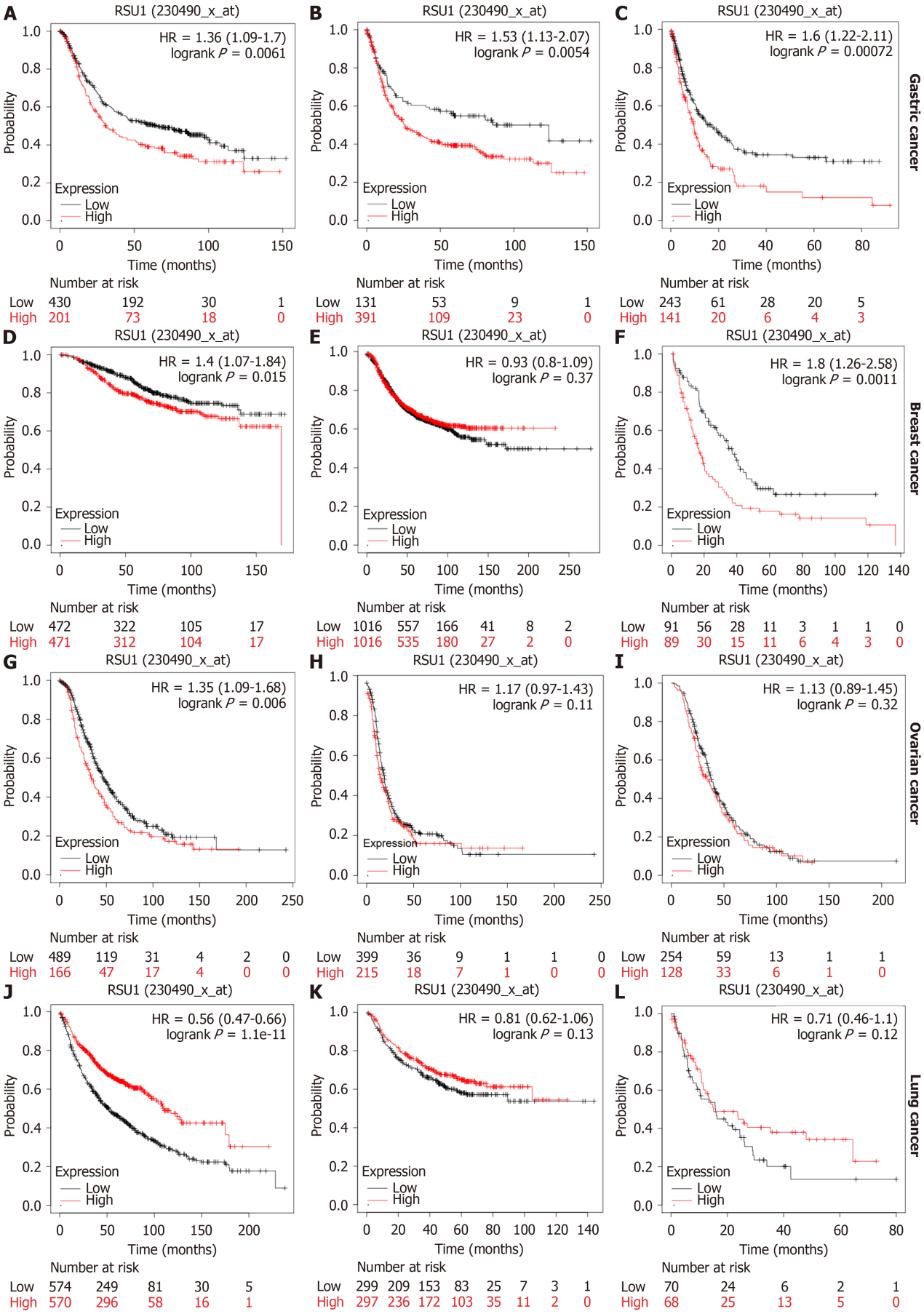

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Figure 2 The prognostic value of Ras suppressor 1 in different tumors. A: Overall survival (OS) in gastric cancers (GC); B: First progression (FP) in

GC; C: Post-progression survival (PPS) in GC; D: OS in breast cancer (BC); E: PFS in BC; F: PPS in BC; G: OS in ovarian cancer (OC); H: PFS in OC; I: PPS in OC; J: OS in lung cancer (LC); K: FP in LC; L: PPS in LC.

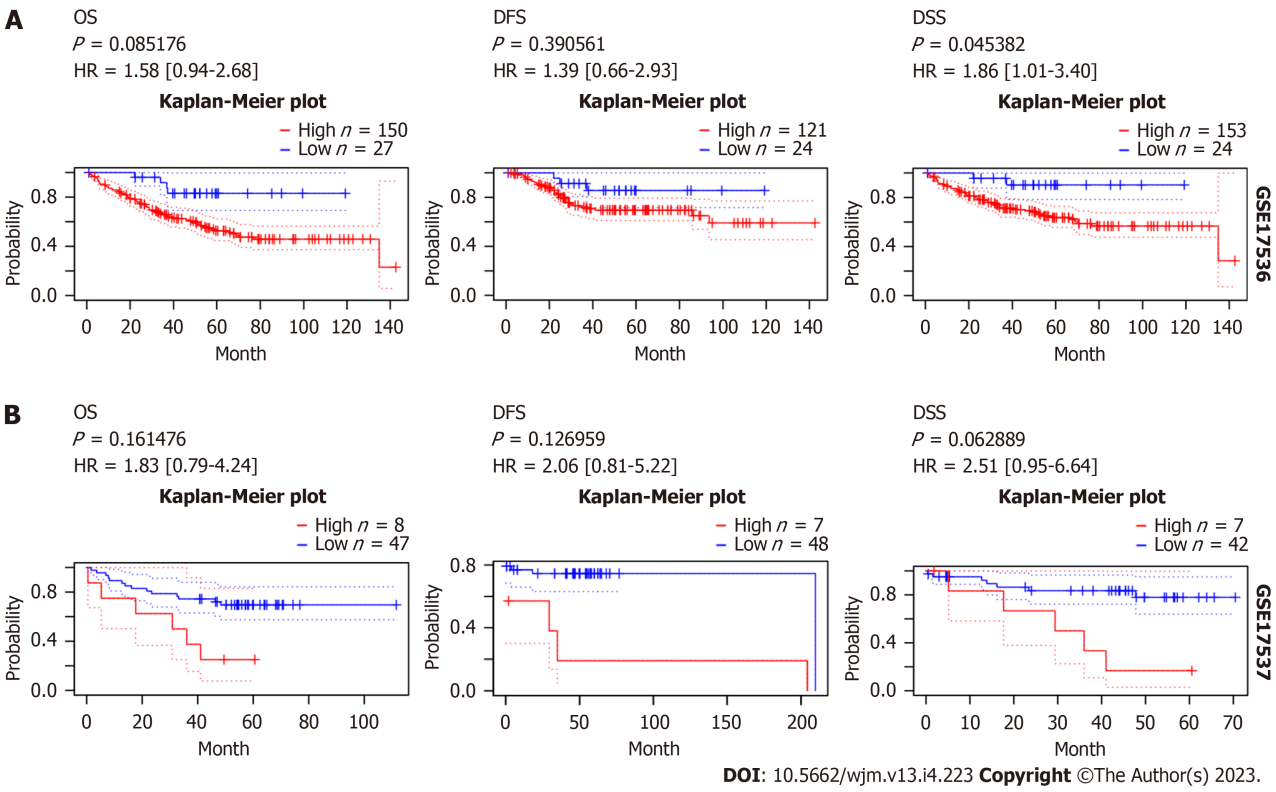

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Figure 3 The prognostic value of Ras suppressor 1 in patients with colorectal cancer. A: Overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS) in GSE17536; B: OS, DFS and DSS in GSE17537.

The clinical trials or vaccine therapies based on immune checkpoint blockade against GBM have not been successful, mainly due to its highly immunosuppressive environment and multiple resistance mechanisms[19]. To compare these findings, GBM was analyzed as control and found that except for macrophage and DC infiltration, expression of RSU1 was not associated with most immune cell infiltration ($P > 0.05$) (Figure 6C). These findings indicate that RSU1 may play a specific role in immune infiltration in the development of GIC, especially through regulating the infiltration of CD4+ T cells, macrophages and DCs.

Correlation between RSU1 level and immune cell biomarkers in GIC

As a relationship between RSU1 Level and immune infiltration was found, biomarkers of different immune cells were characterized to explore the potential function and mechanism of RSU1-related immune infiltration in GIC. The immune cells recruited included CD8+ T cells, T cells, B cells, monocytes, Tumor-associated macrophage (TAMs), M1 and M2 macrophages, neutrophils, natural killer (NK) cells, and DCs, as well as functionally different T cells, such as Th1, Th2, Tfh, Th17, Treg, and exhausted T cells (Table 2). After adjustment for purity, RSU1 expression levels were significantly correlated with 33 out of 57 immune cell biomarkers in COAD, and 48 out of 57 in STAD (Table 2).

Interestingly, the expression levels of biomarkers in most monocyte, TAM, and M2 macrophage marker groups were strongly correlated with RSU1 expression in GIC. It has been reported that the polarization of macrophages from M1 (anti-tumor macrophages) to M2 (pro-tumor macrophages) triggers apoptosis of CD8 T cells, and restricts T cell receptor clustering, all of which contribute to immune escape and promote tumor progression[20]. Specifically, the chemokines of TAMs (CCL-2 and IL10), and M2 (CD163, VSIG4, and MS4A4A) were positively correlated with RSU1 expression in GICs ($P < 0.001$), suggesting a potential role of RSU1 in modulating macrophage polarization in GICs.

High expression of RSU1 was also associated with high infiltration of DCs in GIC, based on its positive association with DC markers, such as HLA-DRA, HLA-DPA1, BDCA-1, BDCA-4 and CD11c ($P < 0.05$). For T cells with different functions in GIC, RSU1 was positively correlated with FOXP3, CCR8, and STAT5B in Treg cells, and associated with CTLA and TIM-3 in T cell exhaustion, indicating the potential role of RSU1 in regulating Treg and T cell exhaustion.

For comparison, GBM was also analyzed for the relationship between RSU1 level and immune cell biomarkers. Only 12 out of 57 immune cell biomarkers were found to be associated with high RSU1 expression in GBM, those being CD115 in monocytes, CD68 in TAMs, COX2 in M1 macrophages, CD11B and CCR7 in neutrophils, BDCA-4 and CD11c in DCs, STAT6 in Th2 T cells, BCL6 in Tfh T cells, STAT3 in Th17 T cells, and STAT5B and TGFβ in Tregs. These findings confirm a potential role of RSU1 in immune escape in GIC through regulating macrophage polarization, DC infiltration and T cell

Table 2 Correlation between Ras suppressor 1 level and immune cell biomarkers in gastrointestinal cancers

Immune cell	Biomarker	COAD				STAD				GBM			
		None		Purity		None		Purity		None		Purity	
		Cor	*P* value	Cor	*P* value	Cor	*P* value	Cor	*P* value	Cor	*P* value	Cor	*P* value
CD8+ T cell	CD8A	0.052	2.64E-01	0.008	8.73E-01	0.306	c	0.305	c	-0.056	4.90E-01	-0.026	7.62E-01
	CD8B	-0.043	3.60E-01	-0.076	1.25E-01	0.158	b	0.151	b	-0.157	5.30E-02	-0.124	1.50E-01
T cell	CD3D	0.034	4.72E-01	-0.009	8.63E-01	0.23	c	0.228	c	-0.140	8.37E-02	-0.114	1.86E-01
	CD3E	0.123	b	0.099	a	0.248	c	0.245	c	-0.042	6.06E-01	0.007	9.38E-01
	CD2	0.176	c	0.168	c	0.304	c	0.307	c	-0.074	3.61E-01	-0.034	6.96E-01
B cell	CD19	0.116	a	0.099	a	0.183	c	0.161	b	0.019	8.14E-01	-0.047	5.86E-01
	CD79A	0.197	c	0.18	c	0.18	c	0.155	b	0.093	2.55E-01	0.133	1.21E-01
Monocyte	CD86	0.255	c	0.258	c	0.361	c	0.375	c	0.024	7.72E-01	0.104	2.28E-01
	CD115 (CSF1R)	0.189	c	0.176	c	0.439	c	0.44	c	0.200	a	0.302	c
TAM	CCL2	0.352	c	0.337	c	0.348	c	0.355	c	0.034	6.74E-01	0.083	3.35E-01
	CD68	0.096	a	0.094	5.76E-02	0.17	c	0.169	c	0.169	a	0.275	b
	IL10	0.21	c	0.204	c	0.384	c	0.406	c	-0.043	5.98E-01	0.036	6.78E-01
M1 Macrophage	INOS (NOS2)	-0.196	c	-0.196	c	0.035	4.75E-01	0.061	2.36E-01	0.049	5.50E-01	0.082	3.39E-01
	IRF5	0.216	c	0.219	c	0.108	a	0.093	7.03E-02	0.040	6.26E-01	0.094	2.74E-01
	COX2 (PTGS2)	0.084	7.40E-02	0.039	4.31E-01	0.186	c	0.183	c	0.198	a	0.254	b
M2 Macrophage	CD163	0.187	c	0.168	c	0.395	c	0.397	c	0.155	5.51E-02	0.213	a
	VSIG4	0.18	c	0.158	b	0.401	c	0.421	c	0.018	8.25E-01	0.101	2.39E-01
	MS4A4A	0.221	c	0.204	c	0.421	c	0.431	c	0.060	4.58E-01	0.166	5.21E-02
Neutrophils	CD66B (CEACAM8)	-0.024	6.15E-01	-0.013	7.98E-01	0.029	5.57E-01	0.034	5.08E-01	0.033	6.87E-01	0.044	6.11E-01
	CD11B (ITGAM)	0.136	b	0.13	b	0.392	c	0.392	c	0.233	b	0.319	c
	CCR7	0.17	c	0.16	b	0.322	c	0.325	c	0.226	b	0.254	b
Natural killer cell	KIR2DL1	-0.024	6.08E-01	-0.057	2.51E-01	0.143	b	0.145	b	-0.025	7.62E-01	-0.027	7.52E-01
	KIR2DL3	-0.076	1.06E-01	-0.091	6.78E-02	0.094	5.45E-02	0.083	1.07E-01	-0.022	7.88E-01	-0.052	5.48E-01
	KIR2DL4	-0.072	1.23E-01	-0.11	a	0.005	9.25E-01	0.003	9.61E-01	-0.009	9.11E-01	0.009	9.13E-01
	KIR3DL1	-0.049	2.92E-01	-0.073	1.40E-01	0.142	b	0.127	a	0.042	6.06E-01	0.018	8.34E-01
	KIR3DL2	-0.01	8.31E-01	-0.063	2.04E-01	0.146	b	0.147	b	-0.086	2.93E-01	-0.060	4.86E-01
	KIR3DL3	-0.086	6.63E-02	-0.093	6.04E-02	-0.078	1.12E-01	-0.064	2.16E-01	-0.118	1.48E-01	-0.107	2.12E-01
	KIR2DS4	-0.015	7.48E-01	-0.026	5.99E-01	0.051	3.03E-01	0.044	3.95E-01	-0.001	9.88E-01	0.003	9.72E-01
Dendritic cell	HLA-DPB1	0.051	2.73E-01	0.024	6.27E-01	0.287	c	0.291	c	0.032	6.91E-01	0.108	2.08E-01
	HLA-DQB1	0.056	2.29E-01	0.037	4.55E-01	0.152	b	0.153	b	0.152	6.11E-02	0.234	b
	HLA-DRA	0.125	b	0.103	a	0.268	c	0.27	c	-0.049	5.51E-01	0.014	8.73E-01
	HLA-DPA1	0.16	c	0.142	b	0.255	c	0.256	c	0.032	6.91E-01	0.108	2.08E-01
	BDCA-1 (CD1C)	0.29	c	0.291	c	0.303	c	0.302	c	-0.030	7.10E-01	0.025	7.70E-01
	BDCA-4 (NRP1)	0.348	c	0.37	c	0.523	c	0.52	c	0.376	c	0.462	c
	CD11c (ITGAX)	0.156	c	0.15	b	0.341	c	0.348	c	0.081	3.19E-01	0.099	2.49E-01
Th1	T-bet (TBX21)	0.069	1.39E-01	0.06	2.27E-01	0.266	c	0.264	c	0.237	b	0.258	b
	STAT4	0.159	c	0.148	b	0.301	c	0.294	c	-0.091	2.63E-01	-0.043	6.18E-01
	STAT1	0.197	c	0.182	c	0.189	c	0.177	c	0.078	3.38E-01	0.075	3.84E-01
	IFN-γ (IFNG)	0.023	6.28E-01	0.009	8.53E-01	0.098	a	0.091	7.73E-02	0.120	1.40E-01	0.130	1.30E-01

	TNF-α (TNF)	0.118	[a]	0.098	[a]	0.104	[a]	0.071	1.67E-01	0.022	7.83E-01	0.026	7.67E-01
Th2	GATA3	0.176	[c]	0.183	[c]	0.305	[c]	0.304	[c]	0.125	1.24E-01	0.143	9.67E-02
	STAT6	0.006	8.92E-01	0.01	8.44E-01	0.224	[c]	0.219	[c]	0.289	[c]	0.353	[c]
	STAT5A	0.155	[c]	0.172	[c]	0.431	[c]	0.426	[c]	0.071	3.81E-01	0.104	2.24E-01
	IL13	0.124	[b]	0.099	[a]	0.151	[b]	0.153	[b]	0.021	7.93E-01	0.029	7.39E-01
Tfh	BCL6	0.145	[b]	0.143	[b]	0.388	[c]	0.367	[c]	0.238	[b]	0.232	[b]
	IL21	0.074	1.13E-01	0.06	2.31E-01	0.133	[b]	0.12	[a]	0.023	7.73E-01	-0.026	7.67E-01
Th17	STAT3	0.318	[c]	0.327	[c]	0.426	[c]	0.411	[c]	0.404	[c]	0.394	[c]
	IL17A	0.055	2.42E-01	0.057	2.51E-01	-0.124	[a]	-0.133	[b]	-0.077	3.42E-01	-0.082	3.42E-01
Treg	FOXP3	0.218	[c]	0.214	[c]	0.224	[c]	0.223	[c]	0.065	4.24E-01	0.073	3.98E-01
	CCR8	0.317	[c]	0.327	[c]	0.341	[c]	0.336	[c]	0.052	5.26E-01	0.082	3.38E-01
	STAT5B	0.401	[c]	0.413	[c]	0.499	[c]	0.491	[c]	0.218	[b]	0.179	[a]
	TGFβ (TGFB1)	0.114	[a]	0.106	3.28E-02	0.418	[c]	0.406	[c]	0.325	[c]	0.387	[c]
T cell (exhausted)	PD1 (PDCD1)	-0.016	7.28E-01	-0.05	3.16E-01	0.205	[c]	0.202	[c]	0.085	2.96E-01	0.132	1.23E-01
	CTLA4	0.1	[a]	0.092	6.43E-02	0.17	[c]	0.164	[b]	0.030	7.12E-01	0.060	4.89E-01
	LAG3	-0.001	9.91E-01	-0.041	4.04E-01	0.202	[c]	0.196	[c]	0.116	1.52E-01	0.126	1.42E-01
	TIM-3 (HAVCR2)	0.223	[c]	0.22	[c]	0.38	[c]	0.391	[c]	0.046	5.76E-01	0.106	2.16E-01
	GZMB	0.028	5.53E-01	0.007	8.89E-01	0.134	[b]	0.132	[b]	-0.009	9.15E-01	0.043	6.20E-01

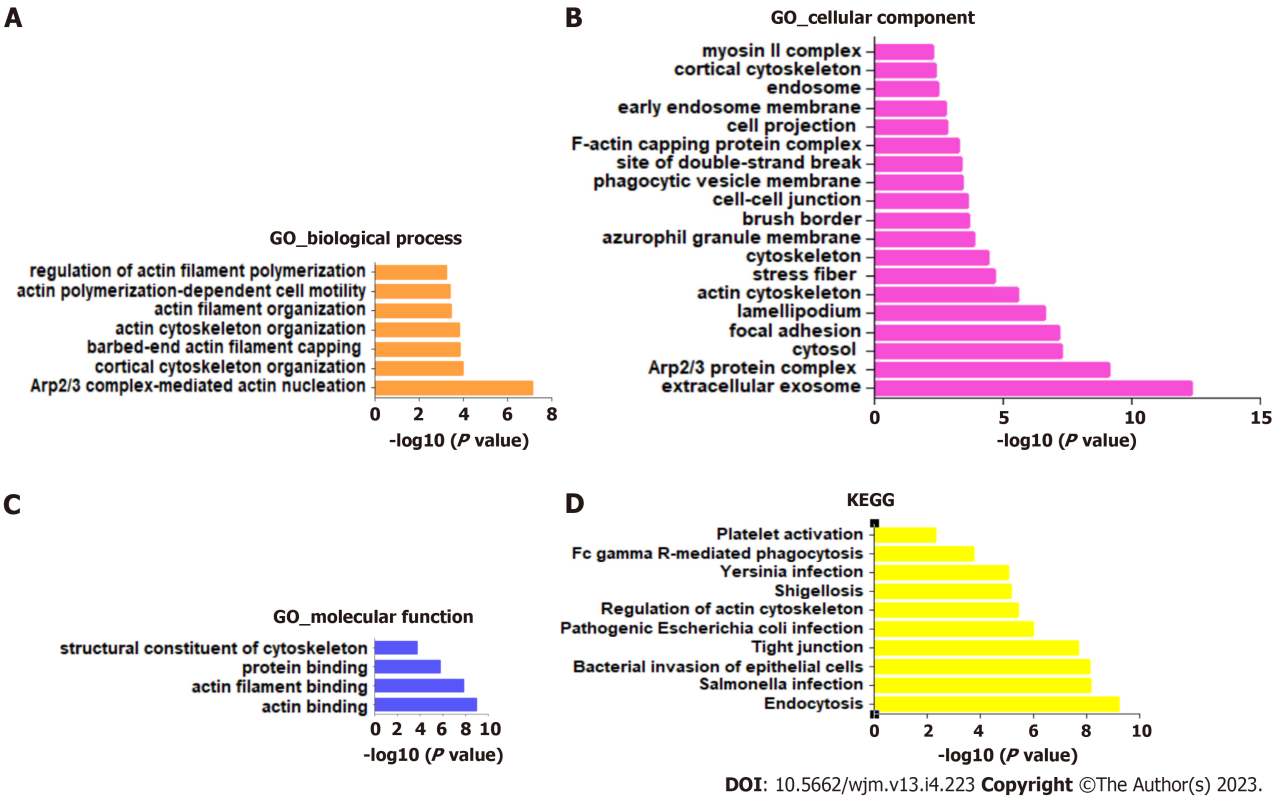
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
COAD: Colon adenocarcinoma; STAD: Stomach adenocarcinoma; GBM: Glioblastoma multiforme.

exhaustion, resulting in promotion of tumor progression.

DISCUSSION

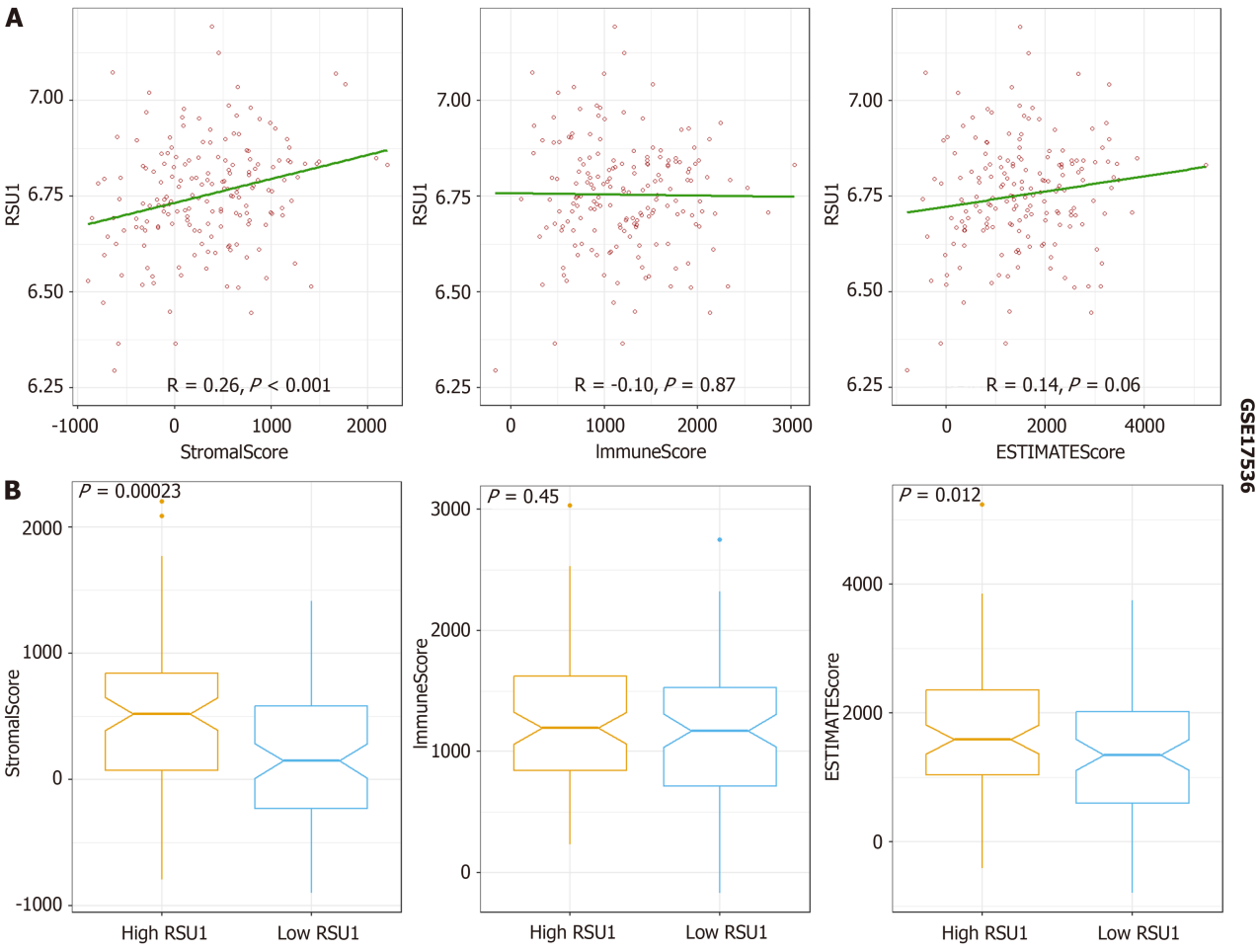
The actin cytoskeleton mediates many essential biological functions in all eukaryotic cells. In addition to providing the structural framework necessary to determine cell shape and polarity, the actin cytoskeleton, especially its dynamics, is also closely related to cell movement, division, adhesion, and phagocytosis[21]. The actin cytoskeleton also mediates many pathological functions, such as playing a key role in tumor cell invasion and metastasis[22,23]. Among diverse different regulating factors, RSU1 participates in actin cytoskeletal remodeling, which is essential for the development of cancers. Current research reported the potential role of RSU1 in regulating immune escape in GICs through mediating the actin cytoskeleton.

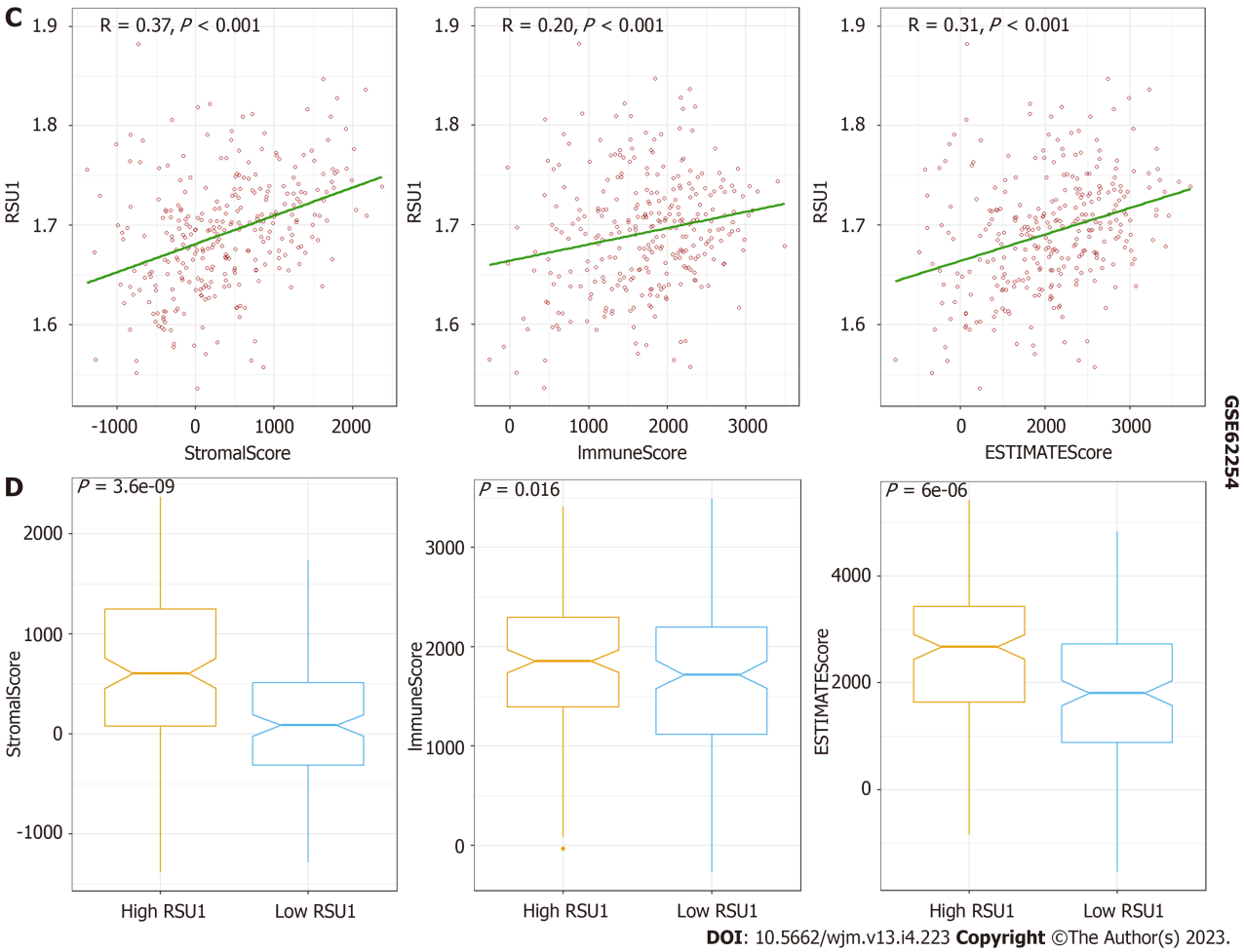
It is found that RSU1 is involved in tumor progression in various cancer cell lines *in vitro*, but *in vivo* studies of the role of RSU1 in cancer is still missing. In this study, the expression pattern of RSU1 in different cancers was examined. Although at the mRNA level, RUS1 Level is associated only with GBM, LGG, PAAD, STAD, and TGCT, in patients with GICs, the high level of RSU1 is predicted to promote the development of gastric and colorectal cancers. In breast cancer studies, Vasaturo *et al*[24] demonstrated that overexpression of RSU1 in Michigan Cancer Foundation-7 (MCF-7) breast cancer cells induced p21 activation and reduced cancer cell proliferation by inhibiting cyclin-dependent kinase, suggesting that RSU1 acts as a tumor suppressor gene in breast cancer, but another study revealed that RSU1 is upregulated at both mRNA and protein levels in more aggressive and highly aggressive MDA-MB-231 breast cancer cells compared to non-invasive MCF-7 breast cancer cells[25]. Consistent with the above study, Christou *et al*[26] reported that high RSU1 expression is associated with poor breast cancer survival. In hepatocellular carcinoma, RSU1 expression has also been found to be elevated in more aggressive HepG2 hepatocellular carcinoma cells compared to non-metastatic Alexander cells[13], and RSU1 promotes invasion of hepatocellular carcinoma, similar to breast cancer cells. In glioblastoma, the more aggressive cells (A172 and U87-MG) also exhibit increased expression of RSU1 compared to less aggressive glioma cell lines (H4 and SW1088)[11]. In aggressive liver, breast cancer and brain cells, RSU1 is upregulated, and the blocking of its expression efficiently inhibits cell migration and invasion. Based on the previous reports and current study, the oncogenic role of RSU1 has emerged in different types of malignancies, especially in GICs. Here, we report a study supporting the role of RSU1 in GC. RSU1 mRNA expression is significantly higher in STAD tissues compared with adjacent normal tissues, and RSU1 expression is associated with poor prognosis of GC patients in the Kaplan-Meier plotter databases. Also, high RSU1 expression is associated with poorer OS, poorer FP, and poorer PPS in GC. However,



DOI: 10.5662/wjm.v13.i4.223

Figure 4 Pathway enrichment analysis of Ras suppressor 1-related genes. A: Biological process; B: Cellular component; C: Molecular function; D: Kyoto Encyclopedia of Genes and Genomes.





DOI: 10.5662/wjm.v13.i4.223

Figure 5 ESTIMATE analyses of Ras suppressor 1 with StromaScore, ImmuneScore and ESTIMATEScore. A and B: Correlation with Ras suppressor 1 (RSU1) level in colorectal cancer; C and D: Correlation with RSU1 level in GC.

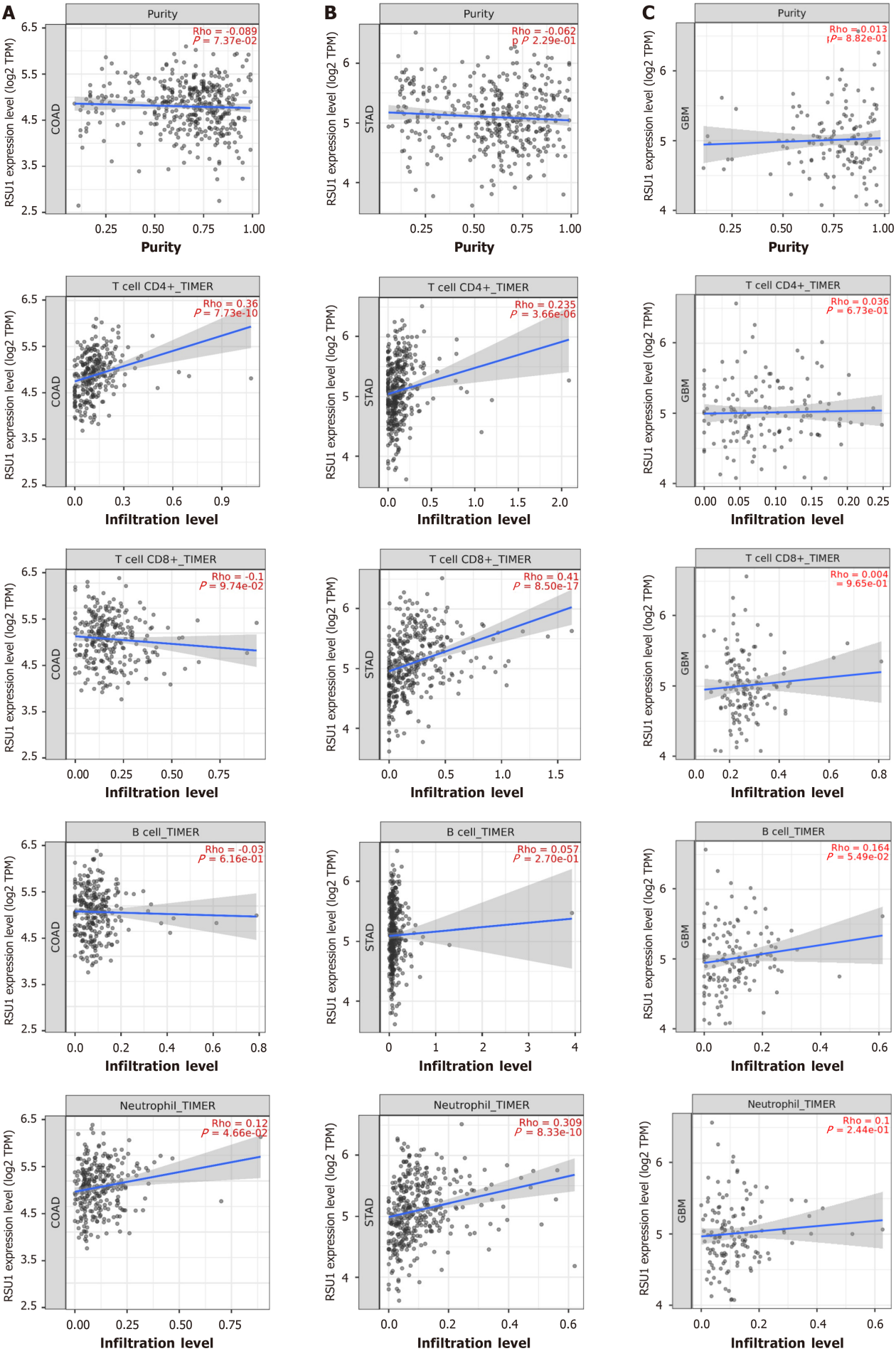
the underlying mechanism is unclear.

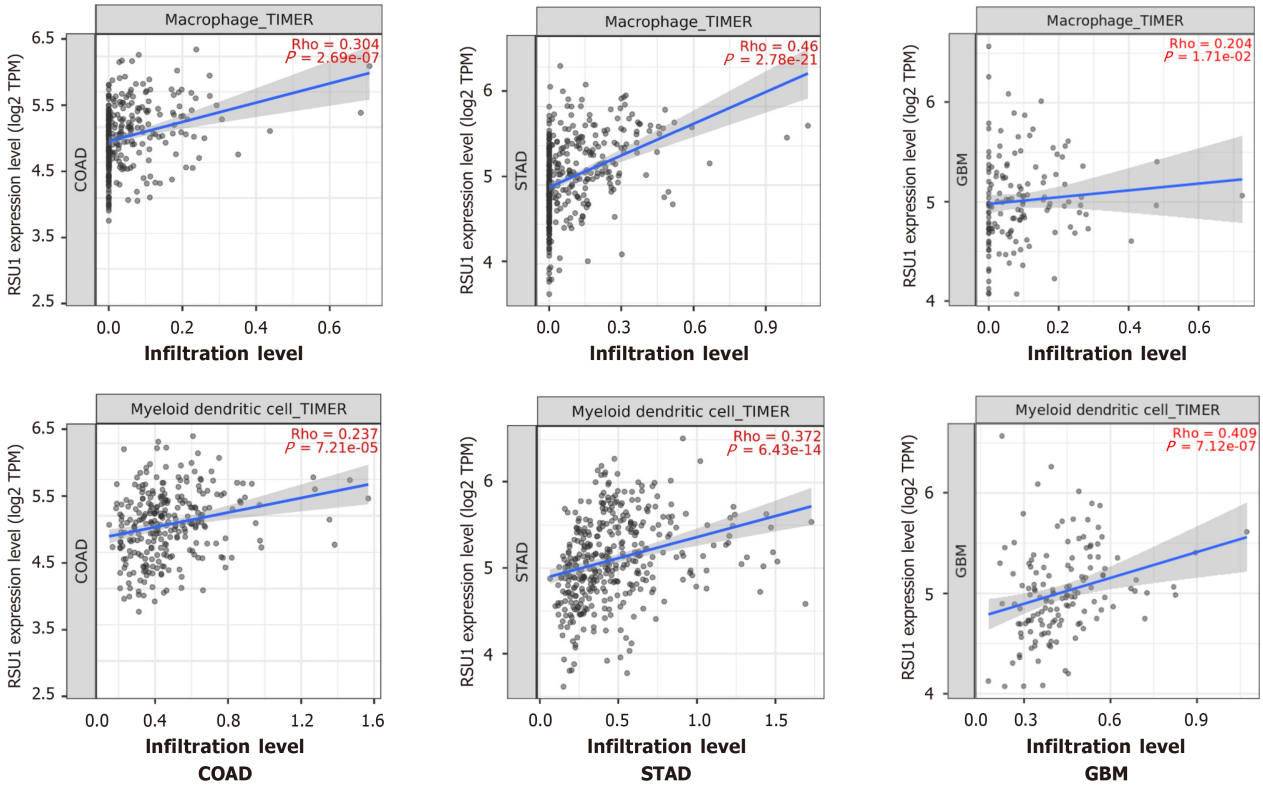
Recent studies have shown that actin cytoskeletal remodeling is also closely related to the function of various immune cells (including T cells, B cells, and macrophages), which are involved in the formation of immune synapses and the development and maturation of T cells[27,28]. Actin cytoskeletal remodeling is also involved in the function of B cells and chemotaxis and phagocytosis in macrophages, through B cell antigen presentation by regulating BCR signaling[29,30]. Interestingly, actin is increased in resistant tumor cells, and the actin response is related to the protection of cancer cells against NK cell attack[18]. However, the regulatory function of tumor cell RSU1 on immune cells has not been studied yet. To elaborate the relationship between RSU1 and different immune cells, we found RSU1 expression is positively correlated with infiltration levels of CD4+ T cells, macrophages, neutrophils, and DCs in STAD. RSU1 plays a crucial role in immune escape of STAD microenvironments through macrophage polarization, DC infiltration, and T cell exhaustion, resulting in promotion of tumor progression.

The results of two clinical studies, CheckMate-649 and KEYNOTE-062, predicted that the response to immunotherapy cannot be judged solely by traditional indications, such as PD-L1 or tumor mutational burden. Since then, a large number of tumor patients with PD-L1 negative or low TMB have produced unusually long-lasting responses. Therefore, the development of new markers to predict immunotherapeutic response needs further investigation. PD-1, PD-L1 and CTLA4 are the main targets of immunotherapy. The present study shows that RSU1 is positively correlated with the expression of PD1 and CTLA4 in GC, and therefore RUS1 may be a potential prognostic factor for predicting the efficacy of immunotherapy.

CONCLUSION

In conclusion, our study provides insights into the potential role of RSU1 in tumor immunology and its prognostic value. RSU1 is associated with prognosis and TIICs in patients with different types of cancer, especially COAD and STAD, including CD4+ T cells, macrophages, neutrophils, and DCs. Higher RSU1 expression is associated with poor prognosis of GC patients and RSU1 plays a crucial role in immune escape of STAD microenvironments through macrophage polarization, DCs infiltration, and T cell exhaustion, and promotes tumor progression. RSU1 mRNA level is correlated


A
B
C
Purity
Rho = -0.089
P = 7.37e-02
Rho = -0.062
P = 2.29e-01
Rho = 0.013
P = 8.82e-01
COAD
STAD
GBM
RSU1 expression level (log2 TPM)
Purity
T cell CD4+_TIMER
Rho = 0.36
P = 7.73e-10
Rho = 0.235
P = 3.66e-06
Rho = 0.036
P = 6.73e-01
Infiltration level
T cell CD8+_TIMER
Rho = -0.1
P = 9.74e-02
Rho = 0.41
P = 8.50e-17
Rho = 0.004
P = 9.65e-01
B cell_TIMER
Rho = -0.03
P = 6.16e-01
Rho = 0.057
P = 2.70e-01
Rho = 0.164
P = 5.49e-02
Neutrophil_TIMER
Rho = 0.12
P = 4.66e-02
Rho = 0.309
P = 8.33e-10
Rho = 0.1
P = 2.44e-01



DOI: 10.5662/wjm.v13.i4.223

Figure 6 Correlation between Ras suppressor 1 expression and immune infiltration levels in COAD, STAD and GBM using TIMER2.0. A: COAD; B: STAD; C: GBM.

with prognosis and immune infiltration level in GIC, suggesting that RSU1 can be used as a biomarker of prognosis.

ARTICLE HIGHLIGHTS

Research background

At present, gastrointestinal cancers (GICs) in clinical immunotherapy effect is not significant, this study found that Ras suppressor 1 (RSU1) participation in the immune escape process may affect the efficacy of immunotherapy, providing a new target for improving the efficacy of immunotherapy.

Research motivation

The main topic of this study is to explore the role of RSU1 in GICs. Currently, GICs have no significant effect on immunotherapy, and this study found that RSU1 can affect the efficacy of immunotherapy through immune escape, providing a way to improve the efficacy of immunotherapy.

Research objectives

RSU1 is a promising prognostic biomarker reflecting the level of GICs immunoinfiltration and a potential therapeutic target by improving the immune response. At present, this study needs clinical data for verification.

Research methods

We evaluated differential expression of RSU1 in different tumors and their corresponding normal tissues by exploring Gene Expression Profiling Interactive Analysis datasets. The prognostic relationship between RSU1 expression and GICs patients was evaluated using Kaplan-Meier plotter and PrognoScan. Then, RSU1 related genes were screened and functional enrichment was performed by DAVID. Tumor Immune Estimation Resource (TIMER) was used to further characterize the correlation between RSU1 and tumor-infiltrating immune cells. In addition, the correlation between RSU1 and immune cell surface molecules was analyzed by TIMER.

Research results

Our study reveals the potential role of RSU1 in tumor immunology and its prognostic value. RSU1 is involved in immune escape of tumor microenvironment through macrophage polarization, dendritic cells infiltration, T cell depletion and other pathways to promote tumor progression. RSU1 can be used as a prognostic biomarker to provide therapeutic target

for improving the efficacy of immunotherapy.

Research conclusions

The new theories that this study proposes is RSU1 plays a crucial role in immune escape and thus the efficacy of immunotherapy in gastrointestinal cancers. The new methods that this study proposed is the immune status was expressed by analyzing the expression of immune-related factors in the online database.

Research perspectives

This is the first comprehensive analysis of the potential role and prognostic value of the RSU1 in diverse gastrointestinal cancers. However, the current research is limited, and future studies need to further explore the molecular mechanism of RSU1 in regulating the oncogenesis and development of GICs.

FOOTNOTES

Author contributions: Xu Y and Liu J contributed to the study conception and design. Material preparation, data collection and analysis were performed by Xu Y, Hou YY, Wu Z, Fang ZX, and Wu HT; The first draft of the manuscript was written by Xu Y and all authors commented on previous versions of the manuscript; As the corresponding author, Liu J is the general person in charge of the project, responsible for the project funding, design, writing and checking of the article; All authors read and approved the final manuscript.

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Institutional review board statement: In current manuscript, NO-animal experiment was conducted, or NO-Human Participants was involved. So, we did not apply the approval form or document from the committee. Meanwhile, the ARRIVE guidelines were not appropriate for this article.

Conflict-of-interest statement: No conflict of interest is claimed by any author.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

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P-Editor: Xu ZH

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Retrospective Cohort Study

Role of the phase angle in the prognosis of the cirrhotic patient: 15 years of follow-up

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Abstract

BACKGROUND

In 2019, cirrhosis accounted for 2.4% of global deaths. The projection for 2030 is an increase in this index. In recent years, hospitalization costs have escalated by 36% for compensated cirrhosis and 24% for decompensated cirrhosis. Therefore, it is necessary to identify a tool capable of predicting the mortality of these patients according to their clinical condition and consequently extending their survival time. Different studies have shown that the phase angle (PA) can be a feasible method in clinical practice, with the potential to guide assertive patient management in the therapeutic of chronic liver disease.

AIM

To evaluate the prognostic role of PA in cirrhotic patients over a 15-year follow-up period.

METHODS

Retrospective cohort study with 129 cirrhotic patients of both sexes over 18 years old. Diagnosis of cirrhosis by liver biopsy. The first year of data collection was 2007, and data regarding outcomes was collected in 2023. Data were gathered from medical records, such as esophageal varices (EV), EV bleeding, ascites,

spontaneous bacterial peritonitis (SBP), encephalopathy, laboratory findings and PA. The cut-off value for the PA was 5.4°, a value described in 2012 by Fernandes *et al* for 129 patients evaluated in this study and the cut-off points for the Brazilian population presented in percentiles (P), as described by Mattiello *et al*. The mortality was assessed using the PA percentile through Kaplan-Meier curves and multivariate binary logistic regression models.

RESULTS

Patients were divided into two groups according to the PA 5.4th (PA > 5.4°, n = 40; PA ≤ 5.4°, n = 89) PA percentile (< P50, n = 56; ≥ P50 n = 73). The percentile classification was more accurate in identifying long-term deaths than the 5.4° PA. Patients with < P50 had a higher number of relevant complications such as ascites, SBP, liver encephalopathy and HCC. PA is strongly correlated with serum albumin (P < 0.001), International Normalized Ratio (P = 0.01), total bilirubin (P = 0.02) and direct bilirubin (P = 0.003). PA is correlated with survival time (P < 0.001) and length of stay (P = 0.02). Logistic regression analysis shows that an increase of 1° in PA enlarges the cirrhotic patient's chance of survival by 17.7%.

CONCLUSION

PA is a good predictor of morbidity and mortality for cirrhotic patients. The PA by percentile showed greater sensitivity in predicting mortality compared to the cut-off point of 5.4°.

Key Words: Liver cirrhosis; Phase angle; Prognosis; Liver transplantation; Electrical bioimpedance

Core Tip: Cirrhosis is characterized by the destruction of hepatic cells, resulting in metabolic alterations that compromise the body's homeostasis. This has a detrimental effect on the patient's clinical condition, negatively impacting their prognosis. Identifying a parameter capable of predicting relevant events is essential for a more assertive approach, reducing mortality and promoting higher life quality. This study aimed to assess the prognostic role of Phase Angle (PA) in cirrhotic patients. One hundred and twenty-nine patients were included, concluding that PA is a promising tool in predicting the clinical condition of chronic liver disease.

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INTRODUCTION

In 2019, cirrhosis was associated with 2.4% of global deaths. The main etiology of cirrhosis during that period was hepatitis C virus infection, followed by alcohol-related liver disease. However, with advancements in the management of viral hepatitis and the increase in obesity levels and alcohol consumption, the epidemiology of cirrhosis is changing, leading to a growing number of cases associated with Metabolic Associated Steatotic Liver Disease (MASLD) and alcohol, an epidemiological situation that results in a reduced mortality rate for other etiologies[1]. It is estimated that mortality from advanced chronic liver disease will more than double between 2016 and 2030[2].

Cirrhosis has a peculiar pathophysiological characteristic, an increase in the body's energy demand, which results in increased depletion of muscle and hepatic glycogen, increased degradation and protein needs, increased lipoperoxidation due to oxidative stress, and activation of the pro-inflammatory cascade, favoring disease progression and development of complications[3].

This disruption of body homeostasis in cirrhosis, regardless of etiology, leads to cellular damage in terms of integrity and functionality, resulting from parenchymal rearrangement, which causes vascular alterations, portal hypertension, and hepatocellular dysfunction. This pathophysiological characteristic substantially impacts the prognosis of cirrhotic patients[4].

Systematically monitoring the progression of chronic liver disease is a complex task for many healthcare services, as it has numerous limitations, such as being an invasive and costly method and discrepancies in the collected data among professionals. Therefore, there is an urgent need to explore new tools, such as a temporal prognostic index of chronic liver disease based on the natural history of the disease.

Currently, it is possible to assess cellular structure through phase angle (PA). PA is derived from the relationship between resistance and reactance, reflecting the conductivity of electric current through body cells. The value of PA expressed in degrees, is measured by the bioelectrical impedance analysis device[5].

Several studies refer to PA as a prognostic indicator because it can measure damage to cellular integrity and functionality resulting from diseases, compromised nutritional status, and/or hydration status. Thus, it is widely used as a guiding parameter in managing various diseases[6-10].

Therefore, we conducted a cohort study of cirrhotic patients with different etiologies to capture longitudinal trajectories over 15 years. We analyzed the association between PA and the two main outcomes, death and liver transplantation. Additionally, we evaluated the correlation of PA with laboratory parameters of liver function, survival curves of the study population according to PA values, and associations of PA with the main complications of cirrhosis, such as ascites, encephalopathy, spontaneous bacterial peritonitis (SBP), and bleeding esophageal varices.

This study suggests that the segmented and systematic use of PA in routine evaluation of cirrhotic patients can provide important information about the patient's health condition at the time of assessment, enabling early and effective therapeutic intervention to extend the survival time of cirrhotic patients while improving their quality of life.

MATERIALS AND METHODS

Study population

A retrospective cohort study was conducted, enrolling cirrhotic patients of both sexes, over 18 years old, treated at the gastroenterology clinic of a hospital complex in Porto Alegre, Brazil. The diagnosis of cirrhosis was established through histological analysis of liver biopsy, imaging tests, and biological markers. Patients with intestinal malabsorption, acquired immunodeficiency syndrome, chronic kidney failure, those on enteral diet, upper limb neuromuscular alterations, chronic pancreatitis, chronic diarrhea, and mental and/or cognitive disorders were excluded from the study. For survival analysis, patients who underwent transplantation during the follow-up were included until the moment of transplantation. This study was conducted in accordance with the Helsinki Declaration and was approved by the ethics and research committee of the Federal University of Health Sciences of Porto Alegre, RS, Brazil, under the number 5203619. All participants signed the Informed Consent Form in advance.

Data collection

Data collection in the first year occurred in January 2007, and data regarding the outcomes were gathered in January 2023. Demographic data such as age and sex were collected. The clinical data on patient outcomes included the number of hospitalizations, ascites, paracentesis, encephalopathy, VE, SBP, and hepatocellular carcinoma (HCC). The staging of cirrhosis was assessed through the Child-Pugh and Model for End-Stage Liver Disease (MELD) scores.

The laboratory tests taken into consideration were those performed up to three months before or after the evaluation, which included: Albumin, aspartate aminotransferase (AST or TGO), alanine aminotransferase (ALT or TGP), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP or FA), bilirubin levels, and International Normalized Ratio (INR). The duration of hospitalization was calculated based on the admission date and discharge date.

Phase angle analysis

The PA data was collected using tetrapolar electrical bioimpedance from the Biodynamics 450 brand. For the test, participants were instructed to remove all metal objects that could interfere with the examination. The patients were positioned in a supine position with the palms of their hands facing down and their arms along their bodies; electrodes were placed on the middle finger and wrist of the right hand and the ankle and middle finger of the right foot. The PA was established using the following formula: PA = tangent arc (Xc/R) × 180/π.

The PA was categorized according to two references for analysis of the outcomes of death and transplantation: Fernandes[7], which establishes the cut-off point for PA at 5.4°. Thus, a PA score of 5.4 points indicates a suboptimal outcome for all statistical evaluations of the study. The additional reference used was Mattiello[11], through their epidemiological study, which establishes cut-off points of PA for the Brazilian population by percentiles (p) p5, p25, p50, p75, p95. The PA value by percentile is distributed considering the age and sex of the studied sample. A PA in the range of the p50 represents the average normality; hence, a p below 50 (< P50) represents a poor prognosis.

Statistical analysis

A general description of the data gathered is provided through simple and relative frequencies. Data normality was assessed using the Shapiro-Wilk test, and the data were compared using the student's t-test for independent samples. Pearson's correlation was used to evaluate potential interactions between different variables. Survival analysis was performed using the Kalan-Meier method, using PA values. Binary logistic regression was also performed to assess the predictive potential of specific variables with the patient's outcome. Significant values were considered when $P < 0.05$. All data were analyzed using the statistical program Statistical Package for Social Sciences version 22.0.

RESULTS

The study assessed 129 cirrhotic patients with an average age of 56.32 (SD 56.32 ± 11.25), with a predominance of male sex (56.6%). The prevailing etiology was hepatitis C virus (43.40%). Other patient characteristics included in the study are described in Table 1.

The clinical condition of the patients was determined by the Child-Pugh score, where 65.89% were classified as A, 25.59% as B, and 8.52% as C. The MELD score showed an average score of 10.70 (SD 10.70 ± 4.70).

Table 1 Characterization of the sample, *n* (%)

Variáveis	Total, *n* = 129
Age (yr), mean ±SD	56.32 ± 11.25
Gender	
Male	73 (56.6)
Female	56 (43.4)
Weight (kg), mean ± SD	74.46 ± 14.69
Height (m), mean ± SD	164.43 ± 8.97
Phase angle, mean ± SD	6.62 ± 2.95
Etiology Cirrhosis	
Alcohol	31 (24)
Autoimmune	5 (3.90)
Nash	5 (3.90)
Others	16 (12.5)
Virus C	56 (43.40)
Virus C+ alcohol	12 (9.30)
Virus B	4 (3.10)
Meld, mean ± SD	10.98 ± 4.69
Classification Child-Turcotte-Pugh	
Child A	85 (65.89)
Child B	33 (25.59)
Child C	11 (8.52)

NASH: Non-alcoholic steatohepatitis

Table 2 Clinical outcomes according to phase angle classifications, *n* (%)

Variable	*n* = 129	< 5.4, *n* = 89	> 5.4, *n* = 40	< 50, *n* = 56	> 50, *n* = 73	mean ± SD, PA
Deaths from the 1st year to the 5th year (1-60 mo)	41	17 (41.46)	24 (58.53)	22 (53.65)	18 (46.35)	5.81 ± 1.87
Deaths from the 6th to the 10th year (61-120 mo)	19	7 (36.84)	12 (63.15)	10 (52.63)	9 (47.36)	6.63 ± 3.21
Deaths from the 11th to the 15th year (121-180 mo)	6	1 (16.67)	5 (83.33)	2 (33.34)	4 (66.66)	6.65 ± 1.90
Alive not transplanted	45	6 (13.33)	39 (86.66)	11 (24.44)	34 (75.55)	7.04 ± 3.07
Alive transplanted	10					8.62 ± 5.48
Dead transplanted	8	4 (50)	4 (50)	6 (75)	2 (25)	5.75 ± 1.01
Deaths from the 1st year to the 5th year (1-60 mo)	3	1 (33.33)	2 (66.67)	1 (33.33)	2 (66.67)	6.57 ± 1
Deaths from the 6th to the 10th year (61-120 mo)	4	2 (50)	2 (50)	4 (100)	-	5.28 ± 0.56
Deaths from the 11th to the 15th year (121-180 mo)	1	1 (100)	0	1 (100)	-	5.19 ± 0

Results expressed by mean ± SD, median ± SD or *n* (%).

The mortality rate of the non-transplanted patients (*n* = 111) over the 15-year period showed that 66 died (59.45%), and among these, 41 (62.12%) died within the first to fifth year, 19 (28.78%) from the sixth to the tenth year, and 6 (9.09%) from the eleventh to the fifteenth year. Of the 41 who died in the first five years, 41.46% had a PA < 5.4° and 53.65% had a percentile < P50. Of the 19 who died between the sixth and tenth year, 36.84% had PA< 5.4, and 52.63% had < P50. The 6 patients who died in the last 5 years of the study, 16.66% had PA < 5.4 and 33.33% had < P50 (Table 2).

Table 3 Clinical outcomes according to phase angle classifications, %

Variables	Total, *n* = 129	< P50, *n* = 56	> P50, *n* = 73
Deaths	57.4	71.40	46.60
SPB	18.6	23.2	15
Ascites	57	66.1	50.70
Paracentesis	30.20	32.10	28.80
EV	75	82.10	69.90
Varicose veins bleeding	10	10.71	10.95
Encephalopathy	34.9	46.40	26
HCC	8.50	10.70	6.80

SPB: Spontaneous bacterial peritonitis; EV: Esophageal varices; HCC: Hepatocellular carcinoma.

Table 4 Biomarkers according to percentil classification

Variable	*P* < 50, *n* = 56	*P* > 50, *n* = 73	*P* value
GOT (mg/dL) mean ± Dp	128 ± 428	71 ± 47	0.27
GPT (mg/dL) mean ± Dp	79 ± 227	58 ± 42	0.46
GGT (mg/dL) mean ± Dp	102 ± 80	94 ± 103	0.69
ALP (mg/dL) mean ± Dp	117.4 ± 55.1	101.4 ± 54.6	0.13
Albumin (g/dL) mean ± Dp	3.6 ± 1.9	3.9 ± 0.6	0.34
Total Bilirubin (mg/dL) mean ± Dp	2.4 ± 2.6	1.7 ± 1.2	**0.02**[a]
Direct Bilirubin (mg/dL) mean ± SD	1 ± 1.1	0.7 ± 0.5	**0.02**[a]
Indirect bilirubin (mg/dL) mean ± SD	1.3 ± 1.5	0.9 ± 0.9	0.10
Urea (mg/dL) mean ± SD	36 ± 16	36 ± 13	0.79
Creatinine (mg/dL) mean ± SD	1 ± 0.3	1 ± 0.2	0.64
Sodium (mg/dL) mean ± SD	137 ± 4	139 ± 4	**0.03**[a]
Potassium (mg/dL) mean ± SD	4.6 ± 2	4.9 ± 2.7	0.32
INR mean ± SD	1.36 ± 0.38	1.45 ± 0.51	**0.02**[a]

[a]T test for independent samples.
GOT: Oxaloacetic Transaminase; GPT: Pyruvic Transaminase; ALP: Alkaline phosphatase; INR: International normalized ratio.

Over the 15 years, 18 patients underwent liver transplantation, and 8 (44.44%) died. Of these, 4 (50%) died in the first six years and the remaining 50% between the seventh and fifteenth year. Of the patients who died between the first and sixth year, 2 (50%) had P50 and a PA 5.40, and those who died between the seventh and fifteenth years, 4 (100%) had P50, and 50% had a PA 5.40.

The average age of the transplanted patients was 51 (SD 51 ± 11) years, 61.11% were male. Among the main causes of transplantation, we cite C virus (27.77%) and C virus + alcohol (16.66%). The leading cause of death of the transplanted patients was post-transplant infection (37.5%). When analyzing the cause of death according to the percentile, infection was the predominant cause (50%) in the < P50 group, while in the >P50 group, the unknown cause and pulmonary cause had the same distribution (50%).

Upon analyzing the clinical outcomes, 57.40% of the patients died due to cirrhosis. Among them, 71.4% had a PA in the $P < 50$. As for cirrhosis complications, 57% of the patients had ascites, 34% developed encephalopathy, and 75% had esophageal varices (EV), of which 10.9% presented with upper gastrointestinal bleeding (Table 3).

Patients classified between the P25 and P50 had a higher occurrence of EV; however, those classified between the P5 and P25 had a higher occurrence of variceal bleeding as well as encephalopathy.

The serum values of total bilirubin and direct bilirubin were significantly higher in the $P < 50$ group ($P = 0.02$) in addition, this same group had significantly lower levels of sodium ($P = 0.03$) and INR ($P = 0.02$) as shown in Table 4.

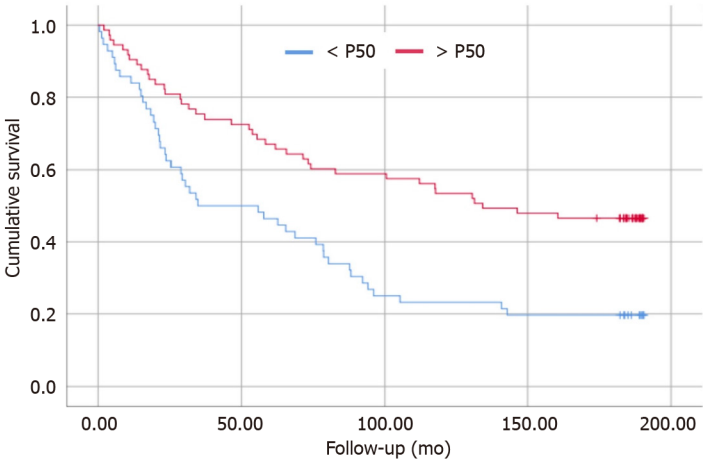

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Figure 1 Survival curves.

Upon verifying the relationship between the PA and the duration of hospitalization, the interval in days between hospitalizations, and the survival time, it was observed that the phase angle is significantly correlated with survival time (R^2 = 0.242; P = 0.006), and the length of hospital stay (Rho = -0.201; P = 0.02).

The survival curve is a point that deserves attention regarding the PA values reflecting the staging of cirrhosis. Patients with PA < P50 presented higher mortality when compared to patients in the > P50 group (Figure 1). Through logistic regression, for each 1° increase in PA, the patient increases their chance of survival by 17.7%.

DISCUSSION

The natural history of cirrhotic patients indicates an average survival duration of approximately 10 years. However, depending on their clinical conditions, some patients may exhibit distinctive cirrhosis complications that negatively impact morbidity and mortality[12-14].

Early diagnosis or treatment of these complications prolongs survival time, improves the quality of life for cirrhotic patients, and reduces the mortality rate of patients on the waitlist for liver transplantation.

Accordingly, this study evaluated 129 cirrhotic patients over a 15-year follow-up to identify a non-invasive, practical, observer-independent, and easily reproducible parameter capable of predicting cellular impairment in the patho-physiological evolution of cirrhosis.

The demographic characteristics of the population in this study align with the findings of Belarmino's study, which followed 134 cirrhotic patients with an average age of 54.3 (SD 54.3 ± 10.10), predominantly male[4]. Similar demographic findings were noted in Ruiz *et al*'s cohort[15], which assessed 136 cirrhotic patients, again predominantly male, with an average age of 54.5 (SD 54.5 ± 10.0). However, it is noteworthy that the population of this study presented compensated cirrhosis, as opposed to the findings by Belarmino *et al*[4], where only 18% were classified as Child-Pugh A, 55% as B, and 27% as C, and the average MELD score was 14.11 (SD14.11 ± 4,95). Ruiz *et al*'s study included a homogeneous sample according to the Child-Pugh classification, with 34.1% B, 33.3% C, and a MELD score of 14 (14 ± 6)[15].

Regarding mortality, the increased percentage of deaths is related to a reduction in PA in degrees and percentile. These findings align with Belarmino *et al*[4] study, which identified that patients with PA less than 4.9°, even with compensated cirrhosis, had a higher mortality rate. A similar mortality outcome associated with PA was observed in Saueressig *et al*[16] study, evaluating 97 hospitalized cirrhotic patients with decompensated disease throughout 11.2 mo (2.4-21). However, it is worth highlighting that the same study established 5.52° as the cut-off point for PA, resembling the 5.4° value utilized in this study, but with divergent disease staging characteristics as per the Child-Pugh score, being 9.3% A, 60.8% B, and 29.9% C. This strengthens the hypothesis that PA reflects systemic cellular damage, not solely linked to the parameters used for score calculations.

Regarding liver transplantation, the etiological presence of hepatitis C virus was observed, recalling that data collection began in 2007. Until 2014, hepatitis C cirrhosis was the leading cause of liver transplantation. However, a study conducted between 2014 and 2019, including 51329 patients listed for transplantation, demonstrated a change in this scenario due to an increased incidence of MASLD and alcoholic cirrhosis, justified by rising obesity levels and an increase in alcoholic individuals[17].

Serrano *et al*[18] study, evaluating the outcome of 15998 liver transplants over 10 years, sustains the findings of this study, showing an exponential increase in the mortality rate. On the other hand, the authors observed a difference in survival between men and women, as in the first year, male mortality was higher, which did not occur in subsequent years. This difference in findings between the two studies can be justified by the size of the population studied by Serrano *et al*[18].

Nitski *et al*[19] evaluated 42146 Liver transplant recipients from the Scientific Registry of Transplant Recipients in the US (UHN) and data from the University Health Network (UHN) in Canada, with average follow-ups of 8 and 5 years, respectively, and found that among the leading causes of death in post-liver transplant patients were various types of cancer, infection, organ rejection, and cardiovascular causes, including stroke. These findings align with the results found in this study, which shows a predominance of deaths due to infection followed by HCC and stroke. Patients who died due to infection had < P50, demonstrating the potential of PA as a predictive value of cellular impairment related to the inflammatory process[20,21].

Ascites, encephalopathy, and EV are commonly observed complications in the cirrhosis picture. Román *et al*[22], evaluating 100 cirrhotic patients, described that 63% of these had ascites, 12% had encephalopathy, and 31% had EV, unlike the findings of this study, which showed a prevalence of encephalopathy and EV. The difference in disease staging could explain the difference between the studies, as in Román *et al*'s study, 81% of patients were classified as Child-Pugh A[23].

Shi *et al*[24] evaluated 248 cirrhotic patients over 4 years, with the variables analyzed including serum levels of AST, GGT, AP, bilirubin, albumin, and PA. The authors presented a statistically significant correlation of patients with PA < 5.1° (the cut-off point for this patient sample) with increased levels of albumin, total and direct bilirubin, which corroborates this study.

Hospitalization costs for cirrhotic patients grew by 30.2% from 2008 to 2014. Concurrently, there was a 36% increase in hospitalizations of compensated cirrhotic patients and a 24% gain in those of decompensated patients. Hospitalizations of patients with decompensated cirrhosis represented 58.6% of the total hospitalizations of cirrhotic patients in 2014. The main operators of rising costs are the costlier procedures, escalating from 15% to 152%, and the presence of clinical complications[25].

Román *et al*[22] observed that PA is also related to the occurrence of clinically relevant events. The same was observed in this study, where a significant correlation was found between PA, the number of hospitalizations (P = 0.01), length of hospital stay (P = 0.003), and mortality (P = 0.001).

The survival curve presented by various studies[7,26-29] evaluating PA in cirrhotic patients reinforces the results found in this study, demonstrating that a reduction in PA, regardless of the cut-off point, is associated with a growth in morbidity and mortality of cirrhotic patients.

Among the study's limitations, we mention the manual recording of collected data in the patient's medical record, which makes detailing some information impracticable, such as the degree of cirrhosis complications. However, the outcome of the 129 patients included in the study was described.

CONCLUSION

This study is a pioneer on PA as a predictor of mortality in cirrhotic patients, with PA values per percentile for the Brazilian population. The PA by percentile showed greater sensitivity in predicting mortality compared to the cut-off point of 5.4°.

The PA, measured through electrical bioimpedance, can be measured in a segmented way, where the patient can be evaluated daily. In more specific cases, such as in the case of ascites, the measurement of the PA can be performed before and after the paracentesis, informing the cellular condition after a procedure. Thus, the PA becomes a guiding tool in the clinical management of cirrhotic patients by significantly reducing the number of events due to complications characteristic of chronic liver disease. The use of PA can bring as positive outcomes: a lower number and length of hospitalizations, improved quality of life, better results in liver transplantation and, consequently, increased survival time.

ARTICLE HIGHLIGHTS

Research background

The number of new cases of cirrhotic patients is growing worldwide and, as a consequence, an increase in the demand for specialized care to treat the disease *per se* and the complications inherent in cirrhosis, in addition to the increase in patients on the waiting list for orthotopic transplantation of liver. Given this scenario, it is necessary to identify a tool to predict the mortality of these patients linked to their clinical condition. Within this perspective, the phase angle (PA) becomes a good alternative because it is a viable method in clinical practice, with the potential to guide the clinical management of the patient and extend their survival time and better quality of life.

Research motivation

Identifying a tool capable of predicting mortality and severity of chronic liver disease in real time as a clinical practice brings numerous benefits to this population and to the professionals who treat them.

Research objectives

To the best of our knowledge, no study has evaluated the role of PA as a predictor of mortality in cirrhotic patients with a 15-year follow-up.

Research methods

Retrospective cohort study with 129 cirrhotic patients of both genders aged over 18 years. Diagnosis of cirrhosis by liver biopsy. The cut-off value for the PA was 5.4°, a value described in 2012 by Fernandes *et al* for 129 patients evaluated in this study and the cut-off points for the Brazilian population presented in percentiles (P), as described by Mattiello *et al*. Mortality was assessed using the PA percentile using Kaplan-Meier curves and multivariate binary logistic regression models.

Research results

The percentile ranking was more accurate in identifying long-term deaths than the 5.4th PA. Patients with < P50 had a higher number of relevant complications, such as ascites, SBP, liver encephalopathy and HCC. PA is strongly correlated with serum albumin ($P < 0.001$), INR ($P = 0.01$), total bilirubin ($P = 0.02$) and direct bilirubin ($p = 0.003$). PA is correlated with survival time ($P < 0.001$) and length of stay ($P = 0.02$). Logistic regression analysis shows that a 1° increase in PA increases the chance of survival of cirrhotic patients by 17.7%.

Research conclusions

PA is a good predictor of morbidity and mortality for cirrhotic patients.

Research perspectives

Identifying clinical factors that enhance a poor prognosis for cirrhotic patients, such as ascites, encephalopathy, length of stay, is relevant. With this information, it is possible to act early in the clinical management of these patients and increase the effectiveness of the therapeutic response, with consequent improvement in the prognosis and quality of life of this population.

FOOTNOTES

Author contributions: Pinto LP contributed to the methodological development and material support, collected data, interpreted results, conducted data analysis, wrote and revised the manuscript; Marroni AC contributed to the conception and critical review of the manuscript; Czermainski J collected data and interpreted the results; Dahlem MLF contributed to the methodological development and material support; Carteri R conducted data analysis and interpreted the results; Fernandes SA designed the research project, collaborated in writing, and critically reviewed the manuscript; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Association of carbon monoxide poisonings and carboxyhemoglobin levels with COVID-19 and clinical severity

Abuzer Coskun, Burak Demirci, Kenan Ahmet Turkdogan

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19), which recently spread throughout the entire world, is still a significant health issue. Additionally, the most common cause of risky poisoning in emergency services is carbon monoxide (CO) poisoning. Both disorders seem to merit more research as they have an impact on all bodily systems *via* the lungs.

AIM

To determine how arterial blood gas and carboxyhemoglobin (COHb) levels affect the clinical and prognostic results of individuals requiring emergency treatment who have both COVID-19 and CO poisoning.

METHODS

Between January 2018 and December 2021, 479 CO-poisoning patients participated in this single-center, retrospective study. Patients were primarily divided into two groups for analysis: Pre-pandemic and pandemic periods. Additionally, the pandemic era was divided into categories based on the presence of COVID-19 and, if present, the clinical severity of the infection. The hospital information system was used to extract patient demographic, clinical, arterial blood gas, COVID-19 polymerase chain reaction, and other laboratory data.

RESULTS

The mean age of the 479 patients was 54.93 ± 11.51 years, and 187 (39%) were female. 226 (47%) patients were in the pandemic group and 143 (30%) of them had a history of COVID-19. While the mean potential of hydrogen (pH) in arterial blood gas of all patients was 7.28 ± 0.15, it was 7.35 ± 0.10 in the pre-pandemic group and 7.05 ± 0.16 in the severe group during the pandemic period ($P < 0.001$).

COHb was 23.98 ± 4.19% in the outpatients and 45.26% ± 3.19% in the mortality group ($P < 0.001$). Partial arterial oxygen pressure (PaO_2) was 89.63 ± 7.62 mmHg in the pre-pandemic group, and 79.50 ± 7.18 mmHg in the severe group during the pandemic period ($P < 0.001$). Despite the fact that mortality occurred in 35 (7%) of all cases, pandemic cases accounted for 30 of these deaths (85.7%) ($P < 0.001$). The association between COHb, troponin, lactate, partial arterial pressure of carbon dioxide, HCO_3, calcium, glucose, age, pH, PaO_2, potassium, sodium, and base excess levels in the pre-pandemic and pandemic groups was statistically significant in univariate linear analysis.

CONCLUSION

Air exchange barrier disruption caused by COVID-19 may have pulmonary consequences. In patients with a history of pandemic COVID-19, clinical results and survival are considerably unfavorable in cases of CO poisoning.

Key Words: Emergency department; Coronavirus disease 2019; Carbon monoxide; Mortality; Carboxyhemoglobin; Intoxication; Poisoning

Core Tip: This retrospective study included 479 patients with a mean age of 54 years. The association of both coronavirus disease 2019 and carbon monoxide poisoning in the emergency department has not been described in the literature. This study includes meticulous work on this association carried out in the emergency room. The clinical, hospitalization, complication and mortality rates were evaluated.

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INTRODUCTION

Carbon monoxide (CO) is an odorless, tasteless, nonirritating gas produced by the incomplete combustion of carbon compounds. It has been reported as one of the most prevalent causes of death, accounting for 31% of toxic poisonings[1]. CO is the third leading cause of accidental gas inhalation-related death in the United States[2]. This gas is readily absorbed and unaltered by the lungs. 90% is bound to hemoglobin (Hb), 10% to myoglobin, and 10% to cytochrome C-oxidase after absorption. Less than 1% is dissolved in plasma, and less than 1% is oxidized to carbon dioxide[3]. CO binds with high affinity to Hb in the blood to form carboxyhemoglobin (COHb). Exposure to CO levels as low as 10 ppm can result in approximately 2% COHb[4]. CO is 250 times more attractive than oxygen to Hb. CO competes with oxygen for binding to Hb, reducing oxygen transport capacity[5,6]. CO prevents oxidative phosphorylation by inhibiting mitochondrial respiration *via* heme a3 binding. As a result, it causes hypoxia in many organs[7].

Signs of lung injury in coronavirus disease 2019 (COVID-19) can range from minimal to severe acute respiratory distress syndrome (ARDS)[8]. Silent hypoxemia is the most important factor in COVID-19 patients. This term refers to arterial hypoxemia in patients who are conscious and alert but have no significant dyspnea. In certain instances, there is profound hypoxemia with pulse oximetry values of 70% and partial arterial oxygen pressure (PaO_2) values of 40 mmHg [9]. Associated with the phenomenon of silent hypoxemia are parenchymal compliance, hypoxic pulmonary vascularity, ventilation control, and dyspnea. The causes of hypoxemia directly initiate inflammation *via* viral infection and secondary immune response. Disease progression can result in diffuse alveolar damage, exudative-proliferative stages, hyaline membrane structure damage, edema, atypical pneumocyte hyperplasia, alveolar hemorrhage, endothelial cell damage, micro-thrombosis, dilatation, and characteristic ARDS features, including hypoxemia due to capillary occlusion[10,11]. Vascular findings, which also occur in many other organs, have led to the belief that COVID-19 patients experience lung injury and significant hypoxia[12]. Although CO poisoning and COVID-19 cause hypoxia *via* distinct mechanisms, it is evident that they interact to reduce lung diffusion capacity. Mo *et al*[13] examined the conventional lung capacity of mild, moderate, and severe COVID-19 survivors 20–30 d after the onset of symptoms. Despite relatively normal spirometry, patients had a 50% reduction in lung diffusion CO capacity (DLCO) and a 25% reduction in DLCO/alveolar volume. In his study, Nusair[14] found that low DLCO is primarily attributable to decreased alveolar volume, and not residual interstitial or pulmonary vascular abnormalities caused by COVID-19.

In the present study, we aimed to determine the cumulative increasing mortality rates, the effects of high COHb levels, and serum lactate levels in COVID-19 patients who were exposed to CO poisoning during the pre-pandemic and pandemic periods.

MATERIALS AND METHODS

Study design and population

This cross-sectional cohort analysis comprised 479 patients over the age of 18 years with CO poisoning who attended the emergency department between January 2018 and December 2021. All CO poisonings were caused by heating system malfunctions or accidents. Our hospital's registration system includes patient diagnoses, admission dates, contact information, and demographic, clinical, and laboratory data. Furthermore, pre-pandemic and pandemic CO poisoning cases, pandemic COVID-19 cases, patient polymerase chain reaction (PCR) records, and data from patients who presented to our hospital with CO poisoning are all incorporated in our system.

When categorizing the patients, two groups were included: Pre-pandemic and pandemic. Patients between January 2018 and December 2019 were classified as pre-pandemic, whereas those between January 2020 and December 2021 were classified as pandemic. Patients in the pre-pandemic group were chosen by evaluating individuals who presented to the emergency clinic due to CO poisoning and had a COHb value greater than 10%. Both non-COVID-19 CO poisoning cases and cases with COVID-19, or those with positive PCR results and exposure to CO poisoning, were included in the pandemic group, as long as the COHb value was greater than 10%. The study comprised patients whose arterial blood gas, serum lactate, troponin I value, and CO exposure periods were known and recorded at the time of admission to the emergency department.

Patients with a coma score of less than 10, prior cerebrovascular disease, significant psychiatric illness or drug use, a history of infectious disease other than COVID-19, and pregnant patients were excluded from the study. Furthermore, individuals less than 18 years old with unknown arterial blood gas, troponin I, serum lactate levels, or CO exposure duration were excluded from the study.

Cases exposed to acute CO poisoning during the pre-pandemic and pandemic eras were divided into two groups. The pandemic period was also divided into two parts: Non-COVID-19 and COVID-19. Those who tested positive or had COVID-19 were also evaluated according to their clinical condition, which was divided into three categories: Mild, moderate, and severe[15]. Four groups were constructed based on the clinical history of the patients: Outpatient follow-up, hospitalization, intensive care unit (ICU), and mortality. All patients who died in the emergency department or in the critical care unit died during the acute period. The approximate CO inhalation time was used for determining the CO exposure time.

Laboratory analysis

The patients' COHb levels were assessed by arterial blood gas analyses performed using ABL 835 Flex Radiometer laboratory instruments, Blood Gas system (Aknlab, Istanbul, Turkey). Arterial blood gas data were examined in 5-10 min, and individuals with a COHb value of 10% or higher were classified as having CO poisoning and participated in the study. As clinical results were not detected, COHb values ranging from 1% to 10% were excluded from the study. Depending on their clinical status, all patients with COHb levels above 15% received hyperbaric oxygen therapy for 1-3 sessions. Serum lactate levels were also measured during arterial blood gas analysis, and values between 0.5 and 1.6 mmol/L over the reference range were considered significant. Troponin I STAT Elecsys and Cobas e 411 Hitachi (Roche, Swaziland) analyzers were used to measure Troponin I levels. Troponin I results were analyzed between 45-60 min and levels above 0.05 ng/mL were considered significant.

Statistical analysis

The SPSS 20.0 software package (SPSS Inc., Chicago, IL, United States) was used to analyze the data in this study. The normal distribution of the variables was examined using a one-sample Kolmogorov-Smirnov test. As the variables did not have a normal distribution, the Kruskal-Wallis-H test was used to compare the groups. The associations between nominal variable groups were investigated using Chi-square analysis. Spearman's correlation analysis was used to determine the correlation between groups. Furthermore, linear regression was employed to identify univariate and multivariate variable analyses. Univariate analysis was used to determine the association between patient groups and factors. Univariate analysis factors that were statistically significant were used in the multivariate linear regression risk model. The sensitivity and specificity of the COHb, troponin, and lactate mortality values were evaluated using a Receiver Operating Characteristic curve. $P < 0.05$ was declared statistically significant for interpreting the results.

RESULTS

The mean age of the 479 patients was 54.93 ± 11.51 years, 187 (39%) were female, and the age range was 23-78 years. The mean age in the pre-pandemic group was 50.56 ± 11.24 years, and was 60.76 ± 8.44 years in the pandemic group ($P < 0.001$). The relationship between the pre-pandemic/pandemic period and gender was not statistically significant. The duration of exposure to CO poisoning in all patients was 4.31 ± 1.74 h, and there was no significant difference between the groups ($P = 0.201$). When the arterial blood gases of all patients were evaluated, the mean potential of hydrogen (pH) was 7.28 ± 0.15, while it was 7.35 ± 0.10 in the pre-pandemic group and 7.05 ± 0.16 in the severe group during the pandemic period ($P < 0.001$). In addition, while the partial arterial pressure of carbon dioxide ($PaCO_2$) was 43.32 ± 6.81 mmHg in the pre-pandemic group, it increased to 57.76 ± 4.49 mmHg in the pandemic group ($P < 0.001$). Likewise, while PaO_2 was 89.63 ± 7.62 mmHg in the pre-pandemic group, this value decreased to 79.50 ± 7.18 mmHg in the severe group ($P < 0.001$). Mean potassium level was 4.20 ± 0.71 mmol/L ($P < 0.001$), sodium was 138.04 ± 4.52 mmol/L ($P = 0.239$), and calcium was 1.16 ± 0.26 mmol/L ($P = 0.020$). It was observed that the glucose level, which was 120.49 ± 20.98 mg/dL in

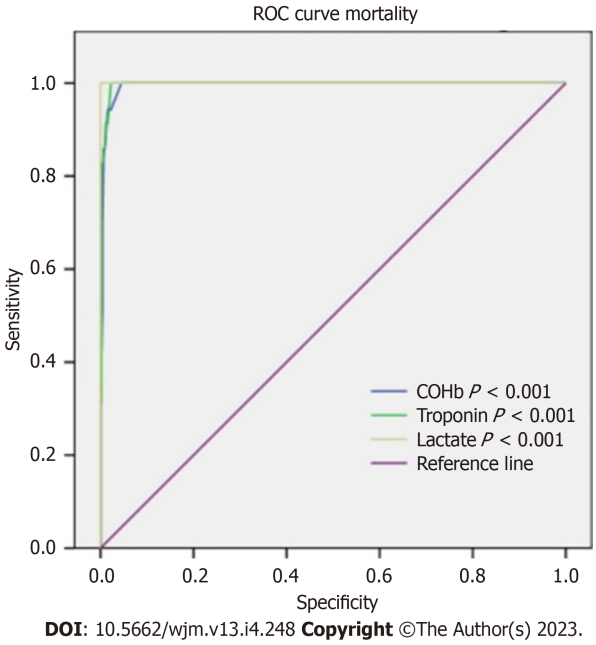

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Figure 1 Receiver operating characteristic curve for mortality. ROC: Receiver operating characteristic.

the pre-pandemic group, increased to 154.50 ± 15.73 mg/dL in the pandemic group (P < 0.001). In addition, while bicarbonate (HCO_3) was 20.31 ± 5.46 mmol/L in the pre-pandemic group, it decreased to 9.92 ± 3.73 mmol/L, which was the lowest level in the pandemic group. The mean base deficit was 7.09 ± 5.56 mmol/L (P < 0.001). While lactate was in the normal range at 1.89 ± 1.24 mmol/L in the pre-pandemic group, it increased to 6.33 ± 1.76 mmol/L in the pandemic group (P < 0.001). COHb value was 26.19% ± 6.68% in the pre-pandemic group and 41.08% ± 7.55% in the pandemic group (P < 0.001). Troponin I value was 0.11 ± 0.25 ng/mL in the pre-pandemic group and 1.09 ± 0.50 ng/mL in the pandemic group (P < 0.001) (Table 1).

In the analysis according to the survival status of the patients, the mean age of the outpatients was 50.27 ± 10.67 years, while the mean age of the patients who died was 66.63 ± 6.95 years (P < 0.001). There was no significant relationship between survival and gender. The duration of exposure to CO poisoning was determined as 5.14 ± 1.78 h in the mortality group (P < 0.001). In addition, COHb was 23.98% ± 4.19% in the outpatients and 45.26% ± 3.19% in the mortality group (P < 0.001). Troponin I was found to be increased at 1.35 ± 0.36 ng/mL and lactate at 8.14 ± 0.63 mmol/L in the mortality group (P < 0.001). In addition, in the analysis of the patient groups by survival, it was seen that 10 (4%) patients in the pre-pandemic group were in the ICU and 5 (2%) of these patients were in the mortality group. Fifty-nine (26.1%) of 226 patients in the pandemic group were followed in the ICU, and 30 (13.3%) died (P < 0.001) (Table 2).

In the univariate linear analysis, COHb, troponin, lactate, $PaCO_2$, HCO_3, calcium, glucose, age, pH, PaO_2, potassium, sodium, and base excess levels were found to be statistically significant in the pre-pandemic and pandemic groups. On the other hand, in multivariate linear regression analysis, COHb, troponin, lactate, $PaCO_2$, HCO_3, calcium, and glucose values were found to be prognostic signs in the pre-pandemic and pandemic groups (Table 3).

Changes in COHb, lactate, and troponin due to CO poisoning are shown in Figure 1 based on the receiver operating characteristic curve analysis. Based on this analysis, the optimal cut-off values (sensitivity and specificity), the area under the curve, and the 95% confidence interval of COHb, lactate, and troponin were found to be over 45% to predict the evolution of the pre-pandemic and pandemic groups (P < 0.001). In addition, in the correlation analysis of the variables for patient groups and survival, a medium-strong positive relationship was found between age, exposure time, COHb, troponin, lactate, $PaCO_2$, glucose, and base excess, and a strong negative relationship with HCO_3, pH, and PaO_2 (Tables 4 and 5).

DISCUSSION

CO intoxication and COVID-19 are both serious disorders that impact the respiratory system, impairing oxygenation and causing hypoxia. There are numerous studies on CO poisoning and COVID-19 in the literature. However, in our search of the literature, we did not discover any studies in which both diseases coexisted. This encouraged us to explore the morbidity and mortality effects of CO poisoning in patients with current or previous COVID-19. We found that the mortality rate during the pandemic period, including hyperbaric oxygen, mechanical ventilation, and all ICU treatments, was 6.4 times greater in COVID-19 patients with a COHb value of 10% or higher than the mortality rate before the pandemic.

Although the pathophysiological basis of CO poisoning is not clear, recent studies suggest that different mechanisms play a role in the toxicity caused by CO[16-18]. CO combines with respiratory pigments, enzymes, and proteins

Table 1 Basal and laboratory findings of the patients

			Disease periods					
				Pandemic (*n* = 226)				
		All patients (*n* = 479), mean ± SD	Pre-pandemic, (*n* = 253), mean ± SD	Non-COVID-19 (*n* = 83), mean ± SD	Mild COVID-19 (*n* = 60), mean ± SD	Moderate COVID-19 (*n* = 45), mean ± SD	Severe COVID-19 (*n* = 38), mean ± SD	*P* value
Baseline characteristics								
Age (year)		54.93 ± 11.51	50.56 ± 11.24	56.87 ± 10.29	57.32 ± 9.58	65.98 ± 6.70	62.87 ± 7.50	**< 0.001**
Gender	Female	187 (39)	98 (38.7)	38 (45.8)	24 (40)	16 (35.6)	11 (28.9)	0.3461
	Male	292 (61)	155 (61.3)	45 (54.2)	36 (60)	29 (64.4)	27 (71.1)	
Exposure time (h)		4.31 ± 1.74	4.09 ± 1.86	4.84 ± 1.98	4.25 ± 1.26	4.69 ± 1.24	4.24 ± 1.23	0.201
Laboratory findings								
Arterial blood gas	pH (7.35-7.45)	7.28 ± 0.15	7.35 ± 0.10	7.29 ± 0.12	7.23 ± 0.12	7.14 ± 0.16	7.05 ± 0.16	**< 0.001**
	$PaCO_2$ (mmHg) (32-45)	47.07 ± 8.34	43.32 ± 6.81	46.04 ± 7.90	51.10 ± 6.34	55.67 ± 4.93	57.76 ± 4.49	**< 0.001**
	PaO_2 (mmHg) (80-100)	86.92 ± 8.01	89.63 ± 7.62	87.10 ± 6.44	83.01 ± 7.40	82.81 ± 6.50	79.50 ± 7.18	**< 0.001**
	K+ (mmol/L) (3.4-4.5)	4.20 ± 0.71	4.00 ± 0.58	4.01 ± 0.55	4.34 ± 0.78	4.64 ± 0.64	5.25 ± 0.63	**< 0.001**
	Na+ (mmol/L) (135-149)	138.04 ± 4.52	138.52 ± 4.70	137.35 ± 4.33	137.98 ± 4.22	17.13 ± 4.23	137.48 ± 4.33	0.239
	Ca++ (mmol/L) (1.15-.29)	1.16 ± 0.26	1.18 ± 0.25	1.19 ± 0.26	1.11 ± 0.20	1.07 ± 0.29	1.06 ± 0.37	**0.02**
	Cl- (mmol/L) (98-106)	99.90 ± 8.27	99.97 ± 7.14	100.01 ± 5.72	100.01 ± 12.69	99.98 ± 10.19	98.92 ± 9.05	0.944
	BS (mg/Dl) (70-105)	129.59 ± 24.66	120.49 ± 20.98	129.35 ± 21.89	132.75 ± 24.18	155.91 ± 21.58	154.50 ± 15.73	**< 0.001**
	HCO_3 (mmol/L) (22-26)	17.68 ± 6.18	20.31 ± 5.46	17.91 ± 5.49	15.13 ± 4.59	12.47 ± 4.62	9.92 ± 3.73	**< 0.001**
	BE (mmol/L) (-3.0-3.0)	7.09 ± 5.56	4.76 ± 4.68	6.76 ± 4.85	9.22 ± 4.43	11.79 ± 4.48	14.41 ± 3.58	**< 0.001**
	Lactate (mmol/L) (0.5-1.6)	2.85 ± 1.99	1.89 ± 1.24	2.60 ± 1.57	3.54 ± 1.44	4.87 ± 1.92	6.33 ± 1.76	**< 0.001**
	COHb (%) (0.5-1.5)	29.68 ± 7.85	26.19 ± 6.68	27.63 ± 5.37	34.25 ± 5.00	37.35 ± 5.38	41.08 ± 7.55	**< 0.001**
Troponin I (ng/mL) (0.0-0.05)		0.40 ± 1.91	0.11 ± 0.25	0.20 ± 0.28	0.42 ± 0.35	0.82 ± 0.31	1.09 ± 0.50	**< 0.001**

[1]Chi-Square test.

Other *P* values were calculated by the Kruskal-Wallis H test. Bold values indicate significance at $P < 0.05$. SD: Standard Deviation; COVID-19: Coronavirus disease 2019; pH: Potential of Hydrogen; $PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Partial arterial oxygen pressure; K^+: Potassium; Na^+: Sodium; Ca^{++}: Calcium; Cl^-: Chloride; BS: Blood sugar; HCO_3: Bicarbonate; BE: Base Excess; COHb: Carboxyhemoglobin.

(myoglobin, Hb, cytochrome a3, and cytochrome P450). It is thought to act as a result of binding with cytochrome oxidase enzymes, such as cytochrome-a3, which is the terminal enzyme in the electron transport chain. Hypoxia and decreased blood flow cause CO to bind and inhibit cytochrome C oxidase and impair cellular respiration at the mitochondrial level [19,20]. CO, at toxic levels, activates platelets by increasing the frequency of thrombosis. It then stimulates neutrophils, leading to myeloperoxidase release, generation of reactive oxygen species, and inflammation[21]. As a result of these, aerobic respiration is affected, adenosine triphosphate production is disrupted, and if progression of this process is not prevented, lactic acidosis accumulates in the cells and death occurs when the cells begin anaerobic respiration. In

Table 2 Analysis of patient survival, baseline values and variables (mean ± SD)

Survival			Outpatient (*n* = 258)	Hospitalization (*n* = 117)	ICU (*n* = 69)	Mortality (*n* = 35)	*P* value
Baseline characteristics							
Age (yr)			50.27 ± 10.67	47.76 ± 11.05	61.61 ± 7.56		**< 0.001**
Gender		Female	107 (41.5)	47 (40.2)	21 (30.4)	12 (34.3)	0.128[1]
		Male	151 (58.5)	70 (59.8)	48 (69.6)	23 (65.7)	
Exposure time (h)			3.90 ± 1.62	4.45 ± 1.68	5.19 ± 1.79	5.14 ± 1.78	**< 0.001**
COHb (%)			23.98 ± 4.19	3238 ± 2.81	38.49 ± 2.99	45.26 ± 3.19	**< 0.001**
Troponin I (ng/mL)			0.04 ± 0.09	0.33 ± 0.27	0.77 ± 0.21	1.35 ± 0.36	**< 0.001**
Lactate (mmol/L)			1.42 ± 0.39	3.54 ± 0.95	4.34 ± 0.68	8.14 ± 0.63	**< 0.001**
Patient groups	Pre-pandemic		198 (76.7)	40 (34.2)	10 (14.5)	5 (14.3)	**< 0.001**[1]
	Pandemic	Non-COVID-19	50 (19.4)	26 (22.2)	5 (7.2)	2 (5.7)	
		Mild	8 (3.1)	28 (23.9)	21 (30.4)	3 (8.6)	
		Moderate	2 (0.8)	16 (13.7)	17 (24.6)	10 (28.6)	
		Severe	0	7 (6)	16 (23.2)	15 (42.9)	

[1]Chi-Square test.

Other *P* values were calculated by the Kruskal-Wallis H test. Bold values indicate significance at $P < 0.05$. SD: Standard deviation; COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; COHb: Carboxyhemoglobin.

autopsies, the lungs in CO poisonings are swollen, edematous, light red, contain multiple foci of subpleural hemorrhage, and abundant foamy, bloody edematous fluid has been observed in lung sections[22]. As there were forensic cases due to CO poisoning in our study, the autopsy reports of these cases showed swollen and edematous lungs, brown in COVID-19 cases and smokers, and light red in other cases. In addition, bloody and foamy edema fluid was present, especially in COVID-19 patients.

COVID-19 may present with clinical manifestations ranging from mild upper respiratory tract symptoms to interstitial pneumonia[23]. They are specifically targeting COVID-19 and type II alveolar cells[24]. In those who survive COVID-19, gas exchange abnormalities may develop due to abnormal alveolar injury healing, loss of pulmonary vascular bed, or both[25]. It is known that loss of pulmonary vasoregulation causes hypoxia. In patients with COVID-19 pneumonia, especially in the early stages, hypoxemia is more severe than would be predicted based on anatomical shunts[26,27]. This is because the primary change in pulmonary perfusion results in deep ventilation/perfusion inequalities[28]. Gattinoni *et al*[28] demonstrated by computed tomography (CT) that early-phase lungs (Type L/Type I) are characterized by low elasticity, collectibility, and ventilation/perfusion ratio. COVID-19 has been documented to exhibit microvascular thrombosis. Pulmonary microvascular thrombosis, characterized by subsegmental vascular enlargement and elevated D-Dimer levels near areas of opacities on thorax CT, has been consistently reported and has been linked to increased mortality[29,30].

Although the recovery period for COVID-19 varies according to the severity of the disease, recovery can take a few weeks to a few months. It is not yet known how much damage will occur in which organ after the disease. In the early period of recovery, more than half of COVID-19 patients have impaired diffusion capacity, decreased respiratory muscle strength, and abnormalities in lung imaging. Severe cases are associated with greater reductions in total lung capacity, CO diffusion capacity, and the six-minute walk test[31]. Four months after COVID-19, severe cases had a lower PaO_2 than mild/moderate cases. During acute COVID-19, various measures of pulmonary function at follow-up were negatively correlated with mechanical ventilation duration, CO diffusion capacity, and total lung capacity in subjects requiring mechanical ventilation[32]. CO diffusing capacity dysfunction has been demonstrated in COVID patients at discharge and one month later. According to their study, abnormalities in CO diffusing capacity were noted in 47.2% and 52.6% of patients, respectively. Significant differences in impaired diffusion capacity have been reported between different severe COVID-19 groups[13,33].

Both our study and studies in the literature showed that while COVID-19 itself causes a decrease in lung diffusion capacity, CO poisoning also contributes to this. Thus, both conditions cause a significant decrease in the lung diffusion capacity of CO and an increase in the mortality rate. Recent studies, similar to our study, have shown that approximately half of discharged patients have residual abnormalities on chest CT scans[34]. These studies have shown that approximately three-quarters of COVID-19 patients develop pulmonary dysfunction during early convalescence, the most common being impaired diffusion capacity and decreased forced expiratory volume/forced vital capacity ratio. More than half of COVID-19 patients appear to have CO lung diffusion capacity abnormalities and impaired intra-alveolar diffusion pathways. Impaired CO lung diffusion capacity is the most common abnormality, even in severe acute respiratory syndrome survivors, ranging from 15.5% to 43.6%[35-39]. Mild to moderate cases are more likely to have CO

Table 3 Univariate and multivariate analysis of variables in patient groups

Patient groups	Univariate				Multivariate			
	R square	β	*t*	*P* value	R square	β	*t*	*P* value
COHb (%)	0.452	0.672	19.837	**< 0.001**	0.589	0.166	2.287	**0.023**
Troponin (ng/mL)	0.485	0.696	21.197	**< 0.001**		0.258	3.457	**0.001**
Lactate (mmol/L)	0.468	0.684	20.501	**< 0.001**		0.241	2.462	**0.014**
$PaCO_2$ (mmHg)	0.364	0.604	16.535	**< 0.001**		0.338	6.040	**< 0.001**
Bicarbonate (mmol/L)	0.309	-0.556	-14.659	**< 0.001**		0.259	2.306	**0.022**
Calcium (mmol/L)	0.028	-0.168	-3.723	**< 0.001**		0.072	2.141	**0.033**
Glucose (mg/dL)	0.243	0.494	12.420	**< 0.001**		0.166	3.532	**< 0.001**
Age (year)	0.187	0.433	10.483	**< 0.001**				
pH	0.386	-0.621	-17.319	**< 0.001**				
PaO_2 (mmHg)	0.178	-0.422	-10.164	**< 0.001**				
Potassium (mmol/L)	0.233	0.482	12.031	**< 0.001**				
Sodium (mmol/L)	0.009	-0.095	-2.083	**0.038**				
Base excess (mmol/L)	0.317	0.563	14.480	**< 0.001**				

Bold values indicate significance at $P < 0.05$. COHb: Carboxyhemoglobin; $PaCO_2$: Partial pressure of carbon dioxide; pH: Potential of hydrogen; PaO_2: Partial arterial oxygen pressure.

Table 4 Receiver operating characteristic curve of mortality

	Sensitivity (%)	Specificity (%)	AUC	95%CI	*P* value
COHb (%)	98.4	97.1	0.989	0.980-0.999	< 0.001
Troponin (ng/mL)	98.6	97.8	0.996	0.993-1.000	< 0.001
Lactate (mmol/L)	99.5	98.9	1.000	1.000-1.000	< 0.001

COHb: Carboxyhemoglobin; AUC: Area under the curve; CI: Confidence interval.

lung diffusion capacity abnormalities compared with severe patients[40].

Recently, it was reported that concentrations of particles smaller than particulate matter 2.5 (PM2.5), CO and ozone produced by wildfires are associated with increases in COVID-19 cases and deaths in various parts of California[41,42]. Environmental pollution of PM2.5, CO and ozone can act as a carrier of infection, impair immunity, make humans more susceptible to pathogens, and is an aggravating pathogenic factor for disease[43]. It has been reported that there is a relationship between the severity of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and air pollution. Among the mechanisms by which air pollution may facilitate SARS-CoV-2 infection is a possible link between upregulation of the angiotensin-converting enzyme receptor by air pollution and host susceptibility to more severe COVID-19. In addition, CO is a highly toxic gas that can damage the lungs[44]. These mechanisms, consistent with our study, support the hypothesis that CO, one of the most important environmental pollutant particles, causes an increase in SARS-CoV-2 cases and deaths.

According to this information, we can say that COVID-19 causes a decrease in diffusion capacity and lung functions with subsequent deterioration in alveolar structure. Although CO diffusion capacity was not measured in our study, pH, $PaCO_2$, and PaO_2 levels in arterial blood gas were evaluated. While blood gas parameters were close to normal in the pre-pandemic group, respiratory acidosis, hypercarbia, and low PaO_2 levels were found in the pandemic group.

In this study, as expected, the COHb and pH values were similar in those who did not have a history of COVID-19 in the pre-pandemic period and during the pandemic period. However, both increased levels of COHb and more acidic pH values were observed in proportion to the severity of the disease in the group of patients who were positive and had COVID-19. Both ICU admission and mortality were observed to be higher in CO poisoning during the pandemic period. Both COHb levels and survival status were strongly correlated with patients' status during or before the pandemic. Considering the pathophysiology of COVID and CO poisoning in the light of the above information, we think that the diffusion mechanism of COHb is impaired and its levels increase more easily due to the influence of the pulmonary airways and alveolar structure in patients with a history of COVID, which causes the patients' clinical worsening.

Table 5 Spearman's rho correlation analysis of variables in patient and survival groups

Spearman's rho	Patients		Survival	
	R	*P* value	R	*P* value
Age (year)	0.441	< 0.001	0.480	< 0.001
Exposure time (hour)	0.148	< 0.001	0.290	< 0.001
COHb (%)	0.609	< 0.001	0.873	< 0.001
Troponin (ng/mL)	0.608	< 0.001	0.807	< 0.001
Lactate (mmol/L)	0.643	< 0.001	0.880	< 0.001
pH	-0.595	< 0.001	-0.857	< 0.001
$PaCO_2$ (mmHg)	0.571	< 0.001	0.801	< 0.001
PaO_2 (mmHg)	-0.495	< 0.001	-0.747	< 0.001
Glucose (mg/dL)	0.467	< 0.001	0.432	< 0.001
Bicarbonate (mmol/L)	-0.536	< 0.001	-0.834	< 0.001
Base excess (mmol/L)	0.541	< 0.001	0.839	< 0.001

COHb: Carboxyhemoglobin; pH: Potential of hydrogen; $PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Partial arterial oxygen pressure.

It should be mentioned that pH, $PaCO_2$, PaO_2, blood sugar, HCO_3, base deficit, lactate, COHb and troponin I values in arterial blood gas parameters of patients show that mortality will be high if CO poisoning is present with COVID-19. It was observed that the mortality rate was 6.4 times higher than the normal population if the high ICU rate was accompanied by high blood sugar, COHb, troponin I and lactate levels in patients aged 60 years and above. In the uni-multivariate analysis, these parameters can have a predictive value in the presence of both CO and COVID-19. In addition, it was determined that these parameters were also correlated with mortality and both the sensitivity and specificity values were above 95%.

This study has some limitations. The most important of these was that this was a retrospective single-center study. In addition, not knowing exactly how much CO the patients were exposed to and for how long was due to difficulties in accessing file data, and arterial blood gas results can be counted among other limitations.

CONCLUSION

CO poisoning has been associated with more severe clinical and biochemical abnormalities, as well as a higher rate of mortality, in individuals with a history of COVID-19. We anticipate that this will have important consequences for the future diagnosis and treatment of COVID-19, as CO levels may be abnormal in comparison to healthy persons and can also be higher in mechanically ventilated patients. Furthermore, we believe that relying on pulse oximeters to determine oxygen saturation is unreasonable, and that doctors should produce more precise data using technologies that can discern levels in the lungs, arteries, and the mean of all tissues. In terms of practicality, this is the simplest arterial blood gas measurement. CO alterations may occur as a result of lung structural disorder during external poisonings, as well as COVID pathology, which can elevate CO levels. Further investigations are required to clarify these issues.

ARTICLE HIGHLIGHTS

Research background

There is a need for new techniques to assess risk in patients with both coronavirus disease 2019 (COVID-19) and carbon monoxide (CO) poisoning, and techniques to aid rapid diagnosis.

Research motivation

The impact of emergency room patients with COVID-19 and CO poisoning on clinical status, morbidity and morbidity is worth investigating.

Research objectives

We aim to determine whether patients with COVID-19 and CO poisoning, as the primary outcome, are definite risk factors for short-term emergency hospitalization and whether there is long-term morbidity and mortality during hospitalization as a secondary outcome.

Research methods

This single-center retrospective study was conducted between January 2018 and December 2021, and included 479 CO poisoning patients. The patients were divided according to the pandemic period and the pre-pandemic period. In addition, the pandemic period was classified according to the presence of COVID-19 and its clinical severity. Patients' demographic, clinical, arterial blood gas, COVID-19 polymerase chain reaction, and other laboratory data were extracted from the hospital information system.

Research results

The mean age of the 479 patients was 54.93 ± 11.51 years, and 187 (39%) were female. 226 (47%) patients were included in the pandemic group and 143 (30%) of them had a history of COVID-19. The mean potential of hydrogen (pH) in arterial blood gas of all patients was 7.28 ± 0.15, was 7.35 ± 0.10 in the pre-pandemic group, and was 7.05 ± 0.16 in the severe group during the pandemic period ($P < 0.001$). Carboxyhemoglobin (COHb) was 23.98% ± 4.19% in the outpatients and 45.26% ± 3.19% in the mortality group ($P < 0.001$). Partial arterial oxygen pressure (PaO_2) was 89.63 ± 7.62 mmHg in the pre-pandemic group, and 79.50 ± 7.18 mmHg in the severe group during the pandemic ($P < 0.001$). While 35 (7%) of all cases died, 30 (85.7%) of those that died were in the pandemic group ($P < 0.001$). In the univariate linear analysis, the relationship between COHb, troponin, lactate, partial arterial pressure of carbon dioxide, bicarbonate, calcium, glucose, age, pH, PaO_2, potassium, sodium, and base excess levels was statistically significant with the pre-pandemic and pandemic groups. In the receiver operating characteristic curve analysis, changes in COHb, lactate, and troponin due to CO poisoning were determined. Based on this analysis, the optimum cut-off values (sensitivity and specificity), the area under the curve, and the 95% confidence interval for COHb, lactate, and troponin were found to be above 45% in predicting the evolution of the pre-pandemic and pandemic groups ($P < 0.001$).

Research conclusions

In cases with a history of COVID-19, CO poisoning was observed with more severe clinical and laboratory findings and more frequent mortality. We believe this will have critical implications for the diagnosis and treatment of COVID-19 in the future, as CO levels may be abnormal compared to healthy subjects and can be higher in mechanically ventilated patients.

Research perspectives

CO poisoning in the pre-pandemic period appears to be milder than in the pandemic period. However, it was determined that mortality due to CO poisoning during the pandemic period was much higher in COVID-19 patients with a moderate and severe clinical course.

FOOTNOTES

Author contributions: Coskun A and Demirci B contributed to study design, concept, writing the manuscript, and revising the final form; Coskun A and Turkdogan KA contributed to data collection and manuscript revision; All authors contributed to writing and discussion management; All authors contributed to data management and manuscript revision, data collection, interpretation of data, and revising the manuscript; Coskun A contributed to data collection and revision; Turkdogan KA contributed to data collection; Demirci B contributed to critical revision; Turkdogan KA contributed to statistical analysis; Coskun A suggested the idea, as a chair of the department provided general support and substantial contribution to concept and design, and acquisition of data; All authors read and approved the final manuscript.

Institutional review board statement: All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the last Declaration of Helsinki (2013), and the protocol was approved by the Ethics Committee of Project identification (Decision No: 136).

Conflict-of-interest statement: The authors report there are no competing interests to declare.

Data sharing statement: Informed Consent Form belonging to the research titled "Clinical Relation of Carboxyhemoglobin Levels in Carbon Monoxide Poisonings with COVID-19", which I conducted, was uploaded to the approved system on April 22, 2022.

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ORIGINAL ARTICLE

Observational Study

External validation of the Moroccan Arabic version of the European Organization for Research and Treatment of Cancer colorectal (CR29) module: Monocentric study

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Abstract

BACKGROUND

Quality of life (QoL) outcomes are a focal endpoint of cancer treatment strategies.

AIM

To externally validate the Moroccan Arabic version of the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ) for colorectal cancer (CRC) patients (CR29).

METHODS

Both Moroccan Arabic modules of QLQ-CR29 and QLQ-C30 were administered to Moroccan CRC. Psychometric properties were retested by measuring Cronbach's alpha coefficient for reliability and Intraclass correlation coefficient (ICC) to examine test-retest reproducibility. The multitrait-scaling analysis was performed to demonstrate the validity of the instrument and known-groups comparison was used to test the score's ability to discriminate between different groups of patients.

RESULTS

In total, 221 patients were included in our study and 34 patients completed the questionnaire twice. The Urinary Frequency scale and Stool Frequency scale had good internal consistency with alpha Cronbach coefficients of 0.79 and 0.83 respectively, while the same coefficients were moderately lower for the Blood and Mucus in Stool scale (0.61) and the Body Image scale (0.67). The ICCs ranged from

0.88 to 1 indicating good to excellent reproducibility. In multitrait scaling analyses, the criterion for item convergent and divergent validity was satisfactory. The known-group comparison showed statistically significant differences between patients according to age, gender, stoma status, tumor location, and radiotherapy.

CONCLUSION

The Moroccan Arabic version of the EORTC QLQ-CR29 is a valid and reliable tool that can be used safely for research and clinical purposes in Moroccan CRC patients.

Key Words: Rectal neoplasm; Colorectal cancer; Health-related quality of life; Patient reported outcome measures; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CR29; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30

Core Tip: Patient related outcomes such as quality of life (QoL) are a focal endpoint of cancer treatments strategies. Many QoL Questionnaire (QLQ) are not trully validated. We aim to externally validate the Moroccan Arabic version of the European Organization for Research and Treatment of Cancer QLQ CR29 on larger and more heterogenous population in order to affirm its validity and reliability in arabic colorectal cancer patients.

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INTRODUCTION

Colorectal cancer (CRC) is a global challenge[1]. However, even with an increasing incidence, the implementation of screening programmes and the large array of advanced treatment modalities has significantly reduced mortality[2,3]. Nonetheless, CRC survivors suffer impaired physical and bowel functions, as well as psychological symptoms such as anxiety, sleep disruption, and depression[4]. All together, these symptoms negatively reflect on the quality of life (QoL)[5] and makes looking beyond oncological outcomes of great importance.

Health-related QoL (HRQL) is an abstract and multidimensional concept[6] which can be assessed by the European Organization for Research and Treatment of Cancer (EORTC) questionnaires. Core measurement tools examine issues common to different cancer sites and can be used as a stand-alone questionnaire or in combination with disease specific modules[7]. The EORTC QoL Questionnaire (QLQ) CR29 questionnaire specific to CRC and its psychometric properties have been tested in several languages and contexts[8-16].

Recently, The QLQ-CR29 has just been only translated for Moroccan Arabic dialect[17]. However this adaptation was performed on a very limited sample size of 120 patients under the usual requests of the EORTC organization. The aim of this study is to externally validate this version and assess its psychometric properties on larger Moroccan CRC patients.

MATERIALS AND METHODS

Description of the instruments

We followed the STROBE directive guidelines write the manuscripts[18]. The participants completed a general information section including sociodemographic and clinical data, alongside both the Moroccan Arabic module of EORTC QLQ-CR29[18], and the validated Moroccan Arabic version of the QLQ-C30 (version 3.0)[19].

The EORTC QLQ-C30

The EORTC QLQ-C30 includes five functional subscales (*i.e.*, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), three symptom subscales (*i.e.*, fatigue, nausea and vomiting, and pain), a global QoL subscale, and six single symptom items (*i.e.*, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The scoring of items is on a 1 to 7 and 1 to 4 Likert scales for the global health status/QoL and the other scales. High scores represent better functioning and worse symptoms[20,21].

The EORTC QLQ-CR29

The morocan arabic module of EORTC QLQ-CR29[17], is a colon and rectum site-specific QoL module with 29 items

consisting of 4 multi-item scales (body image, urinary frequency, blood and mucus in stool, and stool frequency) and 17 functional/symptomatic single-items (sexual interest, urinary incontinence, dysuria, abdominal pain, buttock pain, bloating, dry mouth, hair loss, taste, flatulence, fecal incontinence, sore skin, embarrassment, stoma care problem, impotence or dyspareunia). Among these items, only body image, anxiety, weight, and sexual interest are functional scales.

The eighteenth item (Q18) is an indicator of colostomy/ileostomy construction, while the following items are separately arranged for patients with a stoma (Q19-Q25) and without (Q19-Q25) according to symptoms of stool frequency, flatulence, fecal incontinence, sore skin and embarrassment while item 25 is specific for stoma care. Sexual interest, impotence and dyspareunia items are categorized according to gender with the corresponding questions being Q26-Q27 and Q28-Q29 for male and female respondents respectively. All questionnaire items ask about the past week except the ones on sexuality, which request the patients to evaluate the past four weeks. As regards the scoring, the multi-item scales and single items are scored using a 1 to 4 point Likert scale ("not at all", "a little", "quite a bit", "very much") with the highest score representing the best functional status or the worst symptom[22].

Study population and data collection

Patients were prospectively recruited from the national oncology institute during the period between November 2019 and January 2020[23,24]. Patients aged over 18 years old, with pathologically confirmed colon and/or rectum cancer and who underwent surgery at least 6 mo prior to the enrollment in the study were included. Patients were excluded if they were unable to understand the questionnaire, had cognitive and/or medical complications that hindered the interview completion and those who submitted an incomplete questionnaire. Participants were either approached during follow up visits or contacted *via* telephone. Patient's characteristics were reported according to age, gender, stoma status, cancer location (colon *vs* rectum), neoadjuvant radiochemotherapy and adjuvant chemotherapy.

As the sample size determination for psychometric validation studies lacks clear recommendations[25], we determined the required sample by allocating a number of observations 5 to 10 times greater than the variables[26]. Accordingly, the sample needed size ranged between 150 and 300 participants in order to externally validate this version.

Statistical analysis

The scores for the QLQ-CR29 and the QLQ-C30 questionnaires were linearly converted into 0 to 100 point scores according to the standard EORTC guidelines[20]. Descriptive statistics were generated through mean, median, standard deviation, and floor and ceiling effects, while age was categorized in 3 groups: < 40 years ; 41- 65 years and > 65 years.

In order to proceed to the external validation of the Moroccan Arabic module of de QLQ-CR29 we followed the identical steps of a first validation in a totally different population. There are two different levels of reliability, namely internal consistency and reproducibility. Internal consistency reliability was determined using Cronbach's alpha coefficient with a score greater than 0.7 considered acceptable, above 0.8 was good and higher than 0.9 was considered excellent.

A random subgroup of patients was selected to retake the QLQ CR-29 questionnaire after 7 to 14 d from the first interview in order to examine the test-retest reliability. The results of the two measurements were assessed using the Intraclass correlation coefficient (ICC) and an ICC score of 0.7 or higher was considered acceptable.

We tested the construct validity of the EORTC QLQ-CR29 using multitrait scaling analysis[27]. Convergent validity was examined by correlating each item with its own scale with an item-scale correlation of ≥ 0.40 equivalent to high correlation. Divergent validity on the other hand was tested by demonstrating that the item correlated higher with its own scale than with the others.

Concurrent validity was examined by comparing the scores of the QLQ-CR29 and the QLQ-C30 using Pearson's correlation.

Clinical validity was assessed using known group comparison through the Mann Whitney U test to examine the QLQ-CR29' ability to differentiate clinically distinct patients. Subgroups were categorized according to: Age (< 65 years *vs* ≥ 65 years), gender (male *vs* female), stoma status (permanent *vs* no stoma), tumor site (colon *vs* rectal) and neoadjuvant radiotherapy (no *vs* yes). All statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago,IL, United States). Statistically significant results were defined with a $P < 0.05$.

RESULTS

Patients characteristics

The sociodemographic and clinical characteristics of the patients enrolled in the study are detailed in Table 1. In total, 221 of 250 (88,4%) patients completed the questionnaire among which 123 were males and 98 were females. The mean age of our patients was 55.6 ±12.7years. Seventy-eight (35.9%) participants had colonic cancer and 138 (64.1%) had rectal cancer of wich 89 (64%) received neoadjuvant chemoradiotherapy, while 50 patients had a stoma (22,6%). Missing items were only associated with sexual problems with a miss rate of 9% for males and 23% for females.

Table 2 summarizes the distribution of the EORTC QLQ CR-29 and QLQ-C30 scores. The mean score for the different dimensions of the QLQ CR-29 ranged from 16.44 to 75.56 with the items "Hair loss" and "Weight" scoring the lowest and highest respectively. The percentage of respondents at floor was high (> 50%) in 12 areas while the percentage of respondents at ceiling was high (> 50%) in 1 item. The range of scores was broad in 21 dimensions except for the bag change it ranged from 0 to 83.

Table 1 Patients clinical and demographic characteristics

Variables	Description
Age, mean ± SD	55.65 ± 12.87
Sex	
Female	98 (44.5%)
Male	123 (55.5%)
Tumor location	
Colon	78 (35%)
Rectum	139 (62%)
Neoadjuvant chemoradiotherapy	
No	107 (54,6%)
Yes	89 (45,5%)
Definitive stoma	
No	50 (22.6%)
Yes	171 (77.4%)
Adjuvant chemotherapy[a]	
Yes	91 (70%)
No	39 (30%)

[a]Missing data in this variable.

Reliability

The internal consistency of the EORTC QLQ-CR29 reached the 0.7 criterion showing good consistency for the urinary frequency scale (0.79) and stool frequency scale (0.83), while for the blood and mucus (0.615) and the body image (0.672) scales the alpha Cronbach coefficient was slightly below the criterion (0.7). The Cronbach's alpha coefficient was higher for patients without stoma compared to those with stoma, except for the body image scale (0.64 with *vs* 0.69 without) which indicates higher reliability for patients without a stoma. More details are shown in Table 3.

Thirty four patients took the Arabic version of the QLQ-CR29 and for each item, the ICCs ranged from 0.889 to 0.999 indicating good to excellent reproducibility.

Construct validity

All items exceeded the 0.40 criterion for item-scale convergent validity. Similarly, items correlated better with their own scales than with others which shows good divergent validity. Details of the multitrait scaling analysis are shown in Table 3.

Concurrent validity

Correlations between the scales of the QLQ-CR29 and QLQ-C30 were low ($r < 0.40$). However, some areas with more related content showed higher correlations ($r > 0.40$), namely body image and social functioning. The abdominal pain scale also had a good correlation with the QLQ-C30 pain scale and stoma care problems were correlated to the global QoL scale. In addition, most functional scales of the QLQ-CR29 were positively correlated with functional scales of the QLQ-C30 and negatively correlated with symptom scales of the QLQ-C30, while most symptom scales of the QLQ-CR29 were positively correlated with symptom scales of the QLQ-C30 and negatively correlated with functional scales of the QLQ-C30 as detailed in Table 4.

Clinical validity

The EORTC QLQ-CR29 allowed the distinction between patients based on differences between known groups (Tables 5 and 6).

Differences in the scores of patients with stoma were noted as they presented significantly more anxiety and body image issues. Males with stoma reported higher symptom scores for the "impotence" scale.

The participants with rectal cancer had worse QoL than those with colon cancer and male patients with rectal cancer had significantly higher symptom scores for flatulence, fecal incontinence, sore skin around the anus, stool frequency, defecation problems, and sexual dysfunction.

In addition, patients who received neoadjuvant radiotherapy had significantly higher symptom scores and more problems related to blood and mucus, buttock pain, bloating, stoma care problems, flatulence, fecal incontinence, sore skin, stool frequency, embarrassment and defecation problems.

Table 2 Quality of life scores according to European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and Quality of Life Questionnaire-CR29 structure and reliability

Scaling/single-item name	*n*	Item No.	Mean	SD	Floor	Ceiling	Range	ICC
EORTC QLQ-CR29								
All patients	221							
Urinary frequency		31.32	39.89	33.46	26.2	10.9	0-100	0.961
Blood & mucus in stool		38.39	24.73	29.02	43.4	4.1	0-100	0.969
(F) Body image		45-47	77.82	24.83	1.8	38	0-100	0.950
Defecation/stoma problems		49–54	-	-	-	-	-	
Urinary incontinence		33	20.96	32.22	64.7	7.2	0-100	0.982
Dysuria		34	20.66	31.30	63.3	6.8	0-100	0.950
Abdominal pain		35	30.61	34.12	48	8.6	0-100	0.922
Buttock pain		36	27.14	34.62	55.7	9	0-100	0.921
Bloated feeling		37	28.80	33.77	50.2	8.6	0-100	0.945
Dry mouth		40	24.58	34.14	60.2	8.6	0-100	0.979
Hair loss		41	16.44	29.57	71.5	5.9	0-100	0.968
Trouble with taste		42	20.51	32.89	67.0	8.1	0-100	0.975
(F) Anxiety		43	64.67	37.60	16.7	43.4	0-100	0.951
(F) Weight		44	75.56	32.66	8.1	56.6	0-100	0.960
Patients with stoma	50							
Flatulence		49s	41.49	33.00	28.6	10.2	0-100	0.908
Leakage		50 s	42.17	36.49	32.7	16.3	0-100	0.889
Sore skin around stoma		51s	42.85	38.49	34.5	20.4	0-100	0.965
Bags change		52.53 s	18.36	22.62	49	2	0-83	0.969
Embarrassed		54s	45.56	43.09	41.8	29.1	0-100	0.956
Stoma care pb		55s	40.08	41.47	46.8	21.5	0-100	0.912
Stoma pb		49-54s	37.41	20.18	4.1	4.1	0-100	0.999
Patients without stoma	172							
Flatulence		49	30.62	37.01	52.9	12.8	0-100	0.980
Faecal incontinence		50	26.16	37.38	61.6	14.0	0-100	0.970
Sore skin around anus		51	20.34	31.72	64.5	7.6	0-100	0.979
Stool frequency		52.53	29.65	32.33	38.4	7.6	0-100	0.977
Embarrassment		54	31.20	38.51	54.7	15.1	0-100	0.975
Defecation pb		49-54	28.79	25.84	16.1	0.7	0-100	0.969
Male	123							
Sexual functioning		56	42.85	37.81	33	20.5	0-100	0.928
Impotence		57	38.18	38.79	40.9	20	0-100	0.966
Female	98							
Sexual functioning		58	67.06	36.76	11.9	48.8	0-100	0.933
Dyspareunia		59	26.58	35.75	58.3	10.7	0-100	0.985
C30	221							
Physical function		1 - 5	73.64	23.85	0.9	23.9	0-100	-
Role function		6.7	62.92	37.00	13.3	39.0	0-100	-

Emotional function	21-24	67.24	30.77	4.1	30.7	0-100	-
Cognitive function	20. 25	83.94	23.45	0.5	58.3	0-100	-
Social function	26 . 27	79.58	28.93	3.7	57.3	0-100	-
Fatigue	10.12.18	30.98	29.17	27.1	2.8	0-100	-
Nausea and vomiting	14.15	7.79	17.16	78.0	0.5	0-83	-
Pain	9.19	24.31	29.72	46.8	3.7	0-100	-
Dyspnoea	8	21.10	30.59	62.4	4.6	0-100	-
Insomnia	11	27.67	35.25	56.4	9.2	0-100	-
Appetite loss	13	20.48	30.99	63.3	6.4	0-100	-
Constipation	16	27.52	33.97	53.8	1.4	0-100	-
Diarrhea	17	27.67	34.67	53.2	10.6	0-100	-
Financial difficulties	28	51.22	40.61	30.7	30.7	0-100	-

EORTC: European Organization for Research and Treatment of Cancer; QLQ: Quality of Life Questionnaire.

Table 3 Convergent and discriminant validity of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CR29

QLQ-CR29 scales	Total sample (*n* = 221)			Patients without stoma (*n* = 50)			Patients with stoma (*n* = 171)		
	Convergent	Discriminant	α	Convergent	Discriminant	α	Convergent	Discriminant	α
Urinary frequency	0.905-0.907	-0.00-0.25	0.795	0.83-0.84	-0.00-0.21	0.66	0.91-0.92	-0.12-0.25	0.82
Blood or mucus in stool	0.74-0.89	-0.27-0.35	0.615	0.62-0.96	-0.44-0.35	0.581	0.79-0.87	-0.20-0.30	0.65
Body image	-0.66-0.75	-0.00-0.36	0.672	-0.51-0.89	-0.20-0.39	0.690	-0.63-0.72	-0.07-0.19	0.64
Stool frequency	0.83-0.96	-0.30-0.39	0.835[1]	0.83-0.96	-0.31-0.39	0.804	-0.85-0.91	-0.14-0.34	0.87

[1]Mean of cronbach's alpha coefficient for patients without and with stoma.
Multitrait scaling analysis' summary of the results; ranges for convergent and discriminant validity of each multiitem scale and their internal consistency using cronbach's alpha. QLQ: Quality of Life Questionnaire.

Furthermore, the QLQ-CR29 showed differences between age groups with younger patients found to suffer more from defecation problems, stool frequency and embarrassment.

DISCUSSION

HRQL in CRC is an important component in both day to day practice and clinical research, therefore the proper assessment of patients' HRQOL is crucial[28]. This study showed that the Arabic version of the EORTC QLQ-CR29 questionnaire has good internal consistency, test-retest reliability and validity and is therefore valid and reliable to assess the QoL of Moroccan CRC patients.

The internal consistency of the Arabic EORTC QLQ CR-29 demonstrated satisfactory results for the urinary frequency scale and stool frequency scale, with higher reliability scores for patients without a stoma which is similar to the Chinese validation[14]. As regards the blood and mucus and the body image scales, the alpha Cronbach coefficients were acceptable which was the case in other similar studies[12,29]. On the other hand, as suggested by Arraras *et al*[12], some differences may be due to the fact that the EORTC original validation was conducted on an international sample with high variance, while the Spanish validation concerned a more homogenous sample which may impact the alpha Cronbach coefficient.

The ICCs of our study were all greater than 0.8, thus indicating good to excellent reproducibility for both single item and multi-item scales. The Reliability coefficients were higher in our study than those reported by the Dutch validation [10] and mostly similar to those in the original psychometric validation study[8]. As such, the Moroccan Arabic translation of the QLQ CR-29 is a stable instrument.

The multitrait analysis confirmed the structure of all scales, which proves that the Moroccan Arabic translation of the QLQ-CR29 has a valid construct.

Table 4 Correlation between the Quality of Life Questionnaire-CR29 and the Quality of Life Questionnaire-C30

	EORTC QLQ C30														
CR-29	Functional scales						Symptom scales								
Scales/Single items	QoL	PF	RF	EF	CF	SF	FA	NV	PA	DY	SL	AP	CO	DI	FI
Functional scales															
Body image	0.294[2]	0.279[2]	0.370[2]	0.214[2]	0.244[2]	0.403[2]	-0.298[2]	-0.256[2]	-0.161[1]	-0.250[2]	-0.151[1]	-0.278[2]	-0.221[2]	-0.003	-0.079
Anxiety	0.297[2]	0.314[2]	0.264[2]	0.315[2]	0.273[2]	0.285[2]	-0.294[2]	-0.160[1]	-0.210[2]	-0.169[1]	-0.138[1]	-0.117	-0.029	-0.008	-0.167[1]
Sexual function: Male	-0.121	-0.133	-0.058	-0.011	-0.034	-0.111	0.009	-0.010	0.084	0.089	0.124	0.109	0.049	0.049	0.018
Sexual function: Female	-0.299[2]	-0.192	-0.115	-0.079	-0.256[1]	0.040	0.082	-0.033	0.221[1]	-0.001	0.230[1]	0.040	0.017	0.112	0.033
Symptom scales															
Urinary frequency	-0.137[1]	-0.247[2]	-0.201[2]	-0.237[2]	-0.089	0.029	0.244[2]	0.070	0.218[2]	0.230[2]	0.176[2]	0.165[1]	0.042	0.221[2]	0.122
Blood and mucus in stool	-0.241[2]	-0.283[2]	-0.269[2]	-0.190[2]	-0.110	-0.123	0.359[2]	0.215[2]	0.349[2]	0.190[2]	0.277[2]	0.268[2]	0.152[1]	0.302[2]	0.256[2]
Urinary incontinence	-0.009	-0.128	-0.060	-0.237[2]	-0.152[1]	-0.050	0.102	0.014	0.108	0.150[1]	0.195[2]	0.030	0.135[1]	0.032	0.044
Dysuria	-0.017	-0.103	-0.161[1]	-0.069	-0.065	-0.047	0.153[1]	0.012	0.172[1]	0.058	0.133[1]	0.086	0.091	0.100	0.025
Abdominal pain	-0.138[1]	-0.161[1]	-0.099	-0.125	-0.099	-0.055	0.232[2]	0.143[1]	0.443[2]	0.140[1]	0.254[2]	0.122	0.168[1]	0.107	-0.039
Buttock pain	-0.212[2]	-0.265[2]	-0.270[2]	-0.103	-0.098	-0.074	0.363[2]	0.149[1]	0.469[2]	0.194[2]	0.253[2]	0.190[2]	0.025	0.149[1]	0.280[2]
Bloated feeling	-0.206[2]	-0.213[2]	-0.138[1]	-0.213[2]	-0.145[1]	-0.084	0.292[2]	0.171[1]	0.377[2]	0.256[2]	0.380[2]	0.058	0.253[2]	0.040	0.073
Dry mouth	-0.309[2]	-0.341[2]	-0.257[2]	-0.266[2]	-0.283[2]	-0.125	0.340[2]	0.390[2]	0.205[2]	0.202[2]	0.141[1]	0.329[2]	0.211[2]	0.145[1]	0.113
Hair loss	-0.036	-0.195[2]	-0.133[1]	-0.337[2]	-0.242[2]	-0.131	0.183[2]	0.217[2]	0.084	0.080	0.141[1]	0.182[2]	0.200[2]	0.135[1]	0.033
Trouble with taste	-0.099	-0.247[2]	-0.236[2]	-0.134[1]	-0.173[1]	-0.125	0.243[2]	0.343[2]	0.036	0.202[2]	0.010	0.271[2]	0.173[1]	0.101	0.072
Weight	0.176[2]	0.280[2]	0.291[2]	0.157[1]	0.121	0.179[2]	-0.238[2]	-0.128	-0.081	-0.060	-0.143[1]	-0.165[1]	-0.169[1]	-0.083	-0.017
Flatulences	0.124	-0.023	0.139	-0.126	-0.180	-0.260	0.077	0.056	-0.062	0.262	0.042	0.065	0.131	0.147	0.117
Leakage	0.083	0.142	0.046	-0.271	-0.128	-0.146	0.033	0.059	-0.023	0.114	-0.004	0.093	0.029	0.127	0.240
Sore skin around stoma	-0.041	-0.190	0.025	-0.600[2]	-0.402[2]	-0.330[1]	0.295[1]	0.261	0.297[1]	0.247	0.380[2]	0.073	0.172	0.002	0.133
Bags changes	-0.085	-0.169	0.002	-0.404[2]	-0.025	-0.273	0.228	-0.018	0.155	0.218	0.344[1]	0.192	-0.003	0.019	-0.098
Embarrassment	-0.407[2]	-0.312[2]	-0.394[2]	-0.272[1]	-0.150	-0.164	0.476[2]	0.155	0.419[2]	0.325[2]	0.353[2]	0.156	-0.079	0.030	0.361[2]
Stoma care problems	-0.502[2]	-0.391[2]	-0.458[2]	-0.277[1]	-0.182	-0.228[1]	0.529[2]	0.239[1]	0.587[2]	0.328[2]	0.468[2]	0.239[1]	0.093	-0.064	0.343[2]

Stoma problems	-0.077	-0.142	-0.009	-0.580[2]	-0.277	-0.364[1]	0.336[1]	0.108	0.181	0.264	0.301[1]	0.138	0.104	0.179	0.139
Flatulences	-0.160[1]	-0.151[1]	-0.034	-0.149	-0.137	-0.112	0.144	0.032	0.177[1]	0.269[2]	0.173[1]	-0.003	0.008	0.252[2]	0.200[2]
Faecal incontinence	-0.036	-0.081	-0.040	-0.142	-0.122	-0.117	0.153[1]	0.084	0.190[1]	0.141	0.111	-0.017	-0.140	0.403[2]	0.203[2]
Sore skin around anus	-0.081	-0.012	-0.045	-0.057	-0.047	-0.102	0.049	0.113	0.086	0.121	0.027	0.027	-0.006	0.149	0.195[1]
Stool frequency	0.002	-0.019	-0.024	-0.071	0.002	0.024	0.083	-0.044	0.259[2]	0.092	0.123	0.004	-0.035	0.452[2]	0.189[1]
Embarrassment	-0.101	-0.133	-0.135	-0.207[2]	-0.167[1]	-0.208[2]	0.178[1]	0.141	0.149	0.276[2]	0.152[1]	0.062	0.146	0.224[2]	0.203[2]
Defecation	-0.111	-0.116	-0.038	-0.202[1]	-0.159	-0.173[1]	0.190[1]	0.157	0.280[2]	0.316[2]	0.181[1]	0.040	0.106	0.379[2]	0.290[2]
Impotence	0.019	-0.065	-0.149	-0.104	-0.170	-0.218[1]	0.075	0.243[1]	-0.104	0.313[2]	0.065	0.308[2]	0.175	0.008	0.064
Dyspareunia	-0.083	-0.096	-0.118	-0.174	-0.243[1]	-0.345[2]	0.108	0.025	0.260[1]	0.163	0.162	0.156	0.045	0.157	0.236[1]

[1]$P < 0.05$.

[2]$P < 0.01$.

EORTC: European Organization for Research and Treatment of Cancer; QLQ: Quality of Life Questionnaire; QoL: Quality of life; PF: Physical functioning; RF: Role functioning; EF: Emotional functioning CF: Cognitive functioning; SF: Social functioning; FA: Fatigue; NV: Nausea/vomiting; PA: Pain; DY: Dyspnea; SL: Insomnia; AP: Appetite loss; CO: Constipation; DI: Diarrhea; FI: Financial problems.

In the assessment of concurrent validity, correlations between the scales of the QLQ-C30 and the QLQ CR-29 were mostly low (< 0.4) indicating that the two questionnaires measure different concepts. Few areas with related content had higher correlation scores which was expected given the similar concepts of these particular scales. Nonetheless, the results show that the two questionnaires are independent.

In terms of clinical validity, we found less significant differences related to stoma status than the original study[8]. Moreover, patients with colon cancer had a better function and fewer symptoms, including sexual interest in males and stool frequency as opposed to rectal cancer. Interestingly, patients with rectal cancer and a stoma experienced more embarrassment with borderline significance ($P = 0.053$). When comparing age groups, younger patients reported worse symptoms than older patients[30]. Similar results were reported by the Dutch and Spanish Validation studies[10,12]. In addition, the particularities of the Moroccan population may be contributing to elderly patients' display of better resilience, QoL satisfaction, relatively better acceptance and the aforementioned results. Consequently, the QLQ-CR29 was found to discriminate between age groups.

A higher missing data rate was registered for sexual dimensions compared to others as patients were more reticent about answering sex-related questions which makes their interpretation more difficult. Similar observations were made in the Chinese and Iranian studies, which hindered discussions regarding sexual activity and even ostomy[14,16]. Nonetheless, providing explanations to patients when answering the questionnaire was noted to help. In our context, this issue may be explained by the cultural and religious particularities of the Moroccan population where sexual practices are taboo[31]. More studies addressing this problem should be conducted to determine the reliability and validity of the CR-29 in evaluating the sexual aspects of QoL for patients according to cultural contexts.

This study has some limitations, one of which is the limited sample size of patients. However, the minimum sample size was set at one hundred and fifty patients according to EORTC organization and other EORTC QLQ-CR29 validations were performed on a smaller population such as El Alami's research[18]. Self-administration was not possible due to the high level of illiteracy in our context; consequently, patients received the help of one of the investigators who was in

Table 5 Known-group comparisons

	Stoma status			Colon *vs* Rectum			Neoadjuvant radiochemotherapy		
CR-29 scales/single items	Yes (n = 50)	No (n = 171)	P value	Colon (n = 78)	Rectum (n = 139)	P value	Yes (n = 89)	No (n = 107)	P value
Urinary frequency	35.6 (41.1)	41.1 (34.6)	0.412	35.4 (31.2)	42.2 (34.8)	0.215	45.5 (33.9)	35.0 (32.2)	0.031
Blood and mucus in stool	27.6 (28.8)	23.8 (29.1)	0.247	20.2 (26.8)	27.4 (30.2)	0.086	29.9 (30.3)	19.3 (27.1)	0.004
Body image	66.6 (27.5)	81.1 (23.0)	0.000	77.4 (24.8)	77.7 (25.0)	0.938	77.6 (24.1)	78.9 (24.5)	0.625
Urinary incontinence	24.0 (35.0)	20.0 (31.4)	0.451	18.3 (28.7)	21.5 (33.0)	0.788	20.2 (32.0)	21.4 (32.1)	0.592
Dysuria	21.3 (29.1)	20.4 (31.9)	0.469	18.8 (30.6)	22.3 (31.9)	0.120	23.2 (32.3)	18.3 (29.7)	0.299
Abdominal pain	28.0 (32.5)	31.3 (34.6)	0.590	28.6 (34.2)	32.1 (34.3)	0.440	34.4 (34.6)	26.7 (33.4)	0.095
Buttock pain	28.6 (33.6)	26.7 (34.9)	0.563	17.0 (30.26	32.3 (36.1)	0.001	38.5 (36.2)	14.3 (27.5)	0.000
Bloated feeling	30.6 (33.5)	28.2 (33.9)	0.545	27.7 (32.4)	29.0 (34.2)	0.892	35.2 (35.6)	23.6 (31.7)	0.017
Dry mouth	30.0 (36.4)	23.0 (33.4)	0.183	20.5 (29.0)	26.6 (36.5)	0.477	30.7 (38.3)	19.0 (28.9)	0.055
Hair loss	17.3 (28.7)	16.1 (29.1)	0.608	10.6 (24.9)	19.4 (31.5)	0.027	18.7 (30.1)	14.6 (28.6)	0.222
Trouble with taste	27.3 (36.0)	18.5 (31.7)	0.069	13.2 (27.5)	24.4 (35.1)	0.016	20.5 (31.1)	17.7 (31.8)	0.375
Anxiety	52.6 (40.4)	67.8 (36.1)	0.016	63.2 (37.8)	65.4 (37.0)	0.658	65.9 (36.5)	63.5 (38.4)	0.725
Weight	69.3 (38.6)	77.3 (30.6)	0.305	79.4 (30.4)	73.8 (33.2)	0.194	75.6 (30.4)	76.3 (33.9)	0.492
Flatulence				45.8 (31.9)	39.3 (32.7)	0.601	35.0 (34.1)	45.6 (33.7)	0.361
Leakage				45.8 (31.9)	40.4 (38.8)	0.558	42.1 (39.8)	45.6 (31.8)	0.705
Sore skin around stoma				39.5 (32.7)	44.4 (41.3)	0.748	50.8 (43.5)	43.8 (33.4)	0.598
Bags changes				21.8 (27.0)	16.6 (20.4)	0.584	17.5 (19.6)	26.3 (27.3)	0.351
Embarrassment				64.5 (28.46)	40.7 (44.9)	0.056	56.3 (46.3)	36.9 (39.8)	0.055
Stoma care problems				37.5 (38.2)	40.7 (42.5)	0.804	54.0 (42.1)	23.4 (36.7)	0.003
Stoma problems				39.9 (17.1)	36.1 (21.6)	0.499	37.1 (23.4)	41.8 (16.4)	0.387
Flatulences				21.5 (33.6)	34.5 (37.3)	0.017	43.8 (39.1)	19.6 (31.8)	0.000
Faecal incontinence				16.12 (30.6)	31.4 (39.5)	0.009	35.7 (41.0)	17.0 (31.5)	0.001
Sore skin around anus				11.8 (24.2)	25.1 (34.6)	0.012	29.5 (36.1)	13.6 (26.0)	0.002
Stool frequency				19.3 (26.8)	35.8 (34.2)	0.002	37.6 (36.1)	21.5 (26.8)	0.008
Embarrassment				23.1 (35.4)	34.9 (39.1)	0.053	40.4 (39.2)	23.4 (35.7)	0.004
Defecation pb				18.8 (21.5)	36.5 (36.5)	0.000	37.8 (27.4)	19.5 (21.0)	0.000
(F) Sexual function: Male	54.1 (39.1)	39.7 (37.1)	0.162	32.4 (32.4)	48.1 (39.4)	0.047	46.3 (39.4)	36.0 (32.8)	0.211
Impotence	47.2 (39.2)	35.6 (38.5)	0.021	31.5 (34.6)	41.6 (40.6)	0.248	43.9 (39.2)	33.3 (36.8)	0.167
Sexual function: Female	56.8 (38.6)	69.6 (36.1)	0.064	65.4 (33.3)	66.6 (39.6)	0.770	69.4 (35.9)	70.0 (35.2)	0.928
Dyspareunia	33.3 (39.1)	24.8 (34.9)	0.156	20.23 (33.1)	29.4 (37.1)	0.240	26.8 (32.6)	23.3 (35.5)	0.459

charge of reading the questions and different options for the answer. Furthermore, although the use of confirmatory factor analysis may be an option, multitrait scaling analysis is the most frequently used method for the EORTC tools' transcultural validations[21]. Notwithstanding the foregoing, this study clearly validate the Moroccan Arabic validation of the EORTC QLQ-CR29 questionnaire which will allow the correct evaluation of HRQOL of CRC patients.

CONCLUSION

To summarize, the psychometric properties of the Moroccan Arabic version of the EORTC QLQ CR-29 show that it's a reliable and valid instrument to measure the QoL of CRC patients and could be used to complement the EORTC QLQ-C30 in assessing HRQOL. Conducting more transcultural validations and standardizing patient-reported outcome questionnaires, especially in the field of oncology, will allow us to broadly assess cancer therapy outcomes and weigh the benefits against the QoL impact.

Table 6 Known-group comparisons, *P* < 0.0001

	Gender			Age			
CR-29 scales/single Items	Male (*n* = 123)	Female (*n* = 98)	*P* value	≤ 40 (*n* = 26)	41-65 (*n* = 144)	≥ 66 (*n* = 45)	*P* value
Urinary frequency	39.7 (33.1)	40.1 (34.1)	0.862	28.2 (30.4)	42.4 (33.3)	38.1 (34.1)	0.115
Blood and mucus in stool	24.6 (27.8)	24.8 (30.5)	0.794	25.6 (29.5)	26.7 (29.4)	19.2 (27.5)	0.183
Body image	77.4 (25.0)	78.3 (24.7)	0.777	74.3 (23.2)	76.6 (26.1)	80.7 (21.8)	0.481
Urinary incontinence	19.5 (31.9)	22.7 (32.6)	0.385	19.2 (28.5)	19.6 (32.3)	26.6 (33.0)	0.273
Dysuria	23.3 (32.2)	17.3 (29.9)	0.101	23.0 (36.2)	20.8 (31.5)	20.7 (29.5)	0.978
Abdominal pain	27.6 (33.5)	34.3 (34.6)	0.172	32.0 (34.6)	31.9 (35.2)	26.6 (29.8)	0.772
Buttock pain	28.1 (34.9)	25.8 (34.3)	0.478	32.0 (34.6)	27.7 (36.1)	22.2 (30.1)	0.500
Bloated feeling	27.3 (32.8)	30.6 (35.0)	0.495	26.9 (32.6)	31.9 (35.0)	22.9 (30.8)	0.293
Dry mouth	17.3 (28.7)	33.6 (38.1)	0.001	23.0 (33.6)	24.7 (33.8)	25.1 (36.3)	0.967
Hair loss	8.6 (21.7)	26.2 (34.9)	0.000	12.8 (28.4)	19.6 (32.3)	10.3 (19.8)	0.228
Trouble with taste	16.8 (31.4)	25.1 (34.2)	0.040	30.7 (38.7)	20.6 (33.4)	14.8 (27.1)	0.282
Anxiety	69.6 (34.9)	57.8 (39.9)	0.032	65.3 (38.2)	60.1 (38.2)	73.3 (34.5)	0.116
Weight	75.3 (33.3)	75.8 (32.0)	0.920	75.6 (30.6)	74.5 (33.6)	77.0 (31.6)	0.933
Flatulence	43.6 (32.2)	38.3 (34.6)	0.566	38.8 (32.7)	44.7 (33.2)	33.3 (36.5)	0.667
Leakage	47.1 (36.2)	35.0 (36.6)	0.241	61.1 (44.3)	41.9 (34.6)	27.7 (38.9)	0.299
Sore skin around stoma	44.8 (39.1)	40.0 (38.3)	0.650	66.6 (42.1)	42.8 (37.5)	33.3 (36.5)	0.287
Bags changes	20.1 (22.4)	15.8 (23.2)	0.427	22.2 (25.0)	20.9 (23.6)	5.5 (8.6)	0.328
Embarrassment	46.3 (42.4)	44.4 (44.6)	0.680	51.8 (50.3)	51.3 (41.8)	31.4 (40.3)	0.230
Stoma care problems	42.7 (43.1)	36.3 (39.4)	0.481	66.6 (50.0)	40.9 (40.2)	29.6 (37.7)	0.093
Stoma problems	39.8 (20.0)	33.8 (20.3)	0.336	48.1 (31.7)	38.8 (16.9)	23.1 (20.9)	0.183
Flatulences	29.0 (38.5)	32.4 (35.2)	0.452	36.6 (41.7)	33.6 (37.8)	20.5 (31.1)	0.142
Faecal incontinence	23.4 (35.8)	29.4 (39.1)	0.391	40.0 (44.0)	28.7 (38.3)	14.5 (28.4)	0.050
Sore skin around anus	17.3 (29.6)	23.9 (33.9)	0.300	26.6 (36.8)	21.7 (32.8)	12.8 (24.9)	0.266
Stool frequency	27.8 (30.2)	31.8 (34.7)	0.836	35.8 (34.7)	33.0 (33.7)	18.3 (25.0)	0.029
Embarrassment	27.3 (36.5)	35.8 (40.4)	0.179	41.6 (38.8)	36.0 (40.8)	14.5 (26.2)	0.005
Defecation pb	26.9 (25.3)	30.9 (26.4)	0.499	37.5 (33.0)	30.3 (25.5)	17.5 (19.0)	0.032
Sexual function: Male				33.3 (36.9)	42.7 (37.8)	45.8 (36.5)	0.575
Impotence				48.7 (44.3)	35.2 (38.5)	42.0 (35.1)	0.465
Sexual function: Female				57.5 (36.7)	63.5 (37.7)	82.3 (31.4)	0.109
Dyspareunia				33.3 (36.5)	27.6 (36.8)	9.8 (22.8)	0.098

ARTICLE HIGHLIGHTS

Research background

Health-related quality of life is an abstract and multidimensional concept which can be assessed by the European Organization for Research and Treatment of Cancer (EORTC) questionnaires. Core measurement tools examine issues common to different cancer sites and can be used as a stand-alone questionnaire or in combination with disease specific modules.

Research motivation

The EORTC Quality of Life Questionnaire (QLQ) CR29 questionnaire specific to colorectal cancer (CRC) and its psychometric properties have been tested in several languages and contexts. Recently, The QLQ-CR29 has just been only translated for Moroccan Arabic dialect. However this adaptation was performed on a very limited sample size of 120 patients under the usual requests of the EORTC organization.

Research objectives
The aim of this study is to externally validate this version and assess its psychometric properties on larger Moroccan CRC patients.

Research methods
In order to externally validate the QLQ CR-29, Both Moroccan Arabic modules of QLQ CR-29 and QLQ C-30 were administered to Moroccan colorectal cancer (CRC). Psychometric properties were retested by measuring Cronbach's alpha coefficient for reliability and Intraclass correlation coefficient (ICC) to examine test-retest reproducibility. The multitrait-scaling analysis was performed to demonstrate the validity of the instrument and known-groups comparison was used to test the score's ability to discriminate between different groups of patients. All statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago,IL, USA). Statistically significant results were defined with a $P < 0.05$.

Research results
In total, 221 patients were included in the study and 34 patients completed the questionnaire twice. The urinary Frequency scale and Stool Frequency scale had good internal consistency with alpha Cronbach coefficients of 0.79 and 0.83 respectively, while the same coefficients were moderately lower for the Blood and Mucus in Stool scale (0.61) and the Body Image scale (0.67). The ICCs ranged from 0.88 to 1 indicating good to excellent reproducibility. In multitrait scaling analyses, the criterion for item convergent and divergent validity was satisfactory. The known-group comparison showed statistically significant differences between patients according to age, gender, stoma status, tumor location, and radiotherapy.

Research conclusions
The Moroccan Arabic version of the EORTC QLQ-CR29 is a valid and reliable tool that can be used safely for research and clinical purposes in Moroccan CRC patients.

Research perspectives
This tool can safely be used in research and clinical purpose and can be also used in the validation of other patient-reported outcome measure tools.

FOOTNOTES

Author contributions: Souadka A and Bachri H have contributed to the conception and design of the study, acquisition of the data, the analysis and the interpretation of data; Souadka A, Bachri H and Essangri H wrote the first draft; El Bahaoui N, Majbar AM and Benkabbou A critically reviewed the draft for important intellectual content; Mohsine R was involved in revising critically the corrected manuscript and all authors read and gave the final approval of the version to be published.

Institutional review board statement: The Approval of the study protocol was obtained from the institutional ethics review board (number: 79/17) and all patients enrolled in the study provided a written, informed consent allowing the use of their data for clinical studies at the time of their initial visit.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: Derived data supporting the findings of this study are available from the corresponding author a.souadka@um5r.ac.ma upon reasonable request.

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ORIGINAL ARTICLE

Observational Study

Biliary fistula and late recurrence of liver hydatid cyst: Role of cysto-biliary communication: A prospective multicenter study

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Abstract

BACKGROUND

Hydatid cyst disease (HCD) is common in certain locations. Surgery is associated with postoperative biliary fistula (POBF) and recurrence. The primary aim of this study was to identify whether occult cysto-biliary communication (CBC) can predict recurrent HCD. The secondary aim was to assess the role of cystic fluid bilirubin and alkaline phosphatase (ALP) levels in predicting POBF and recurrent HCD.

AIM

To identify whether occult CBC can predict recurrent HCD. The secondary aim was to assess the role of cystic fluid bilirubin and ALP levels in predicting POBF and recurrent HCD.

METHODS

From September 2010 to September 2016, a prospective multicenter study was undertaken involving 244 patients with solitary primary superficial stage cystic echinococcosis 2 and cystic echinococcosis 3b HCD who underwent laparoscopic partial cystectomy with omentoplasty. Univariable logistic regression analysis assessed independent factors determining biliary complications and recurrence.

RESULTS

There was a highly statistically significant association ($P \leq 0.001$) between cystic fluid biochemical indices and the development of biliary complications (of 16 patients with POBF, 15 patients had high cyst fluid bilirubin and ALP levels), where patients with high bilirubin-ALP levels were 3405 times more likely to have biliary complications. There was a highly statistically significant association ($P \leq 0.001$) between biliary complications, biochemical indices, and the occurrence of recurrent HCD (of 30 patients with recurrent HCD, 15 patients had high cyst fluid bilirubin and ALP; all 16 patients who had POBF later developed recurrent HCD), where patients who developed biliary complications and high bilirubin-ALP were 244.6 and 214 times more likely to have recurrent hydatid cysts, respectively.

CONCLUSION

Occult CBC can predict recurrent HCD. Elevated cyst fluid bilirubin and ALP levels predicted POBF and recurrent HCD.

Key Words: Cysto-biliary communication; *Echinococcus granulosus*; Hydatid disease recurrence; Hydatid fluid analysis; Laparoscopy

Core Tip: There has been no research on occult cysto-biliary communication (CBC) prediction for recurrent hydatid cyst disease (HCD) or the role of elevated cyst fluid bilirubin and alkaline phosphatase (ALP) levels in predicting postoperative biliary fistula and recurrent HCD. The main finding of this study was that there was a statistically significant association ($P \leq 0.001$) between biochemical indices and the development of biliary complications, where patients with high bilirubin-ALP levels were 3405 times more likely to have biliary complications. There was a highly statistically significant association between biliary complications, biochemical indices, and the occurrence of recurrent HCD, where patients who developed biliary complications and high bilirubin-ALP were 244.6 and 214 times more likely to have recurrent hydatid cysts, respectively.

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INTRODUCTION

Hydatid cyst disease (HCD) is caused by *Echinococcus granulosus*, which infects humans in many areas worldwide. Different organs may be affected by HCD[1-2]; however, the liver is mainly affected by HCD (50%-70%)[3]. The World Health Organization's Informal Working Group on Echinococcosis (WHO-IWGE) advocated a standardized consensus in diagnosis, treatment, and follow-up[4].

Medical treatment alone is ineffective, whereas laparoscopic or open surgical management of HCD is an integral treatment component[5-6]. With advances in minimal access surgery, laparoscopic HCD surgery is increasingly being performed, varying from the more conservative choice of partial cystectomy and omentoplasty to the more radical choice of pericystectomy or hepatic resection determined by cyst location, cyst size, risk of complications, and surgical expertise [7]. As HCD is benign, liver resections are avoided as much as possible to reduce perioperative morbidity, such as liver failure[8]. Although a case report used the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy procedure, it has not yet been demonstrated[9].

Cysto-biliary communication (CBC), which presents as a postoperative biliary fistula (POBF), is a common postoperative complication of hepatic HCD, with an incidence of 37%. CBC may be occult or manifest with various clinical symptoms. In occult CBC, cyst fluid, scolices, small daughter cysts, and laminated and germinal layer fragments migrate into the biliary tract and remain asymptomatic or undetectable on imaging. If an occult CBC is missed during surgery, POBF manifests as an external biliary fistula, biliary peritonitis, or intra-abdominal abscess[10-11]. Another concern with HCD surgery is recurrent HCD, which occurs in 11% of cases[12]. The primary aim of this study was to determine whether occult CBC, expressed as POBF, is associated with recurrent HCD. The secondary aim was to determine whether elevated cyst fluid bilirubin and alkaline phosphatase (ALP) levels predict occult CBC and, thus, POBF and recurrent HCD.

MATERIALS AND METHODS

Study design and participants

From September 2010 to September 2016, a prospective observational multicenter study was carried out at our university hospitals involving 244 patients with stages cystic echinococcosis 2 (CE2) and cystic echinococcosis 3b (CE3b) according to the WHO-IWGE classification. Patients with large, solitary, symptomatic, or asymptomatic superficial cysts abutting critical vascular and biliary structures were included in this study. Exclusion criteria were: (1) Stage CE1, CE3a, and CE4 HCD patients (WHO- IWGE recommendation); (2) preoperative factors: Total bilirubin > 2.0 mg/dL and direct bilirubin > 1.5 mg/dL; (3) prior liver interventions: Previous percutaneous treatment, recurrence of HCD, previous liver surgery; (4) radiological factors: Common bile duct (CBD) dilatation > 10 mm, extrahepatic cysts affecting an entire hemiliver, complicated (ruptured) or deep location that cannot be accessed by laparoscopy and hydatid cysts in both lobes of the liver; (5) patient factors: Referenceused intervention, surgical contraindication, pregnancy, lost to follow-up, refused to take albendazole, or patients who had albendazole-related complications (deranged liver function); and (6) intraoperative factors: Manifest CBC. This study was approved by the Institutional Review Board committees and registered as a clinical trial (ClinicalTrials.gov ID: NCT05116735) and was conducted following the Helsinki Declaration and STROBE[13].

Definitions of outcomes and measurements

POBF was defined as a bilirubin concentration in the drain fluid at least three times higher than the serum bilirubin concentration on or after postoperative day three[14]. Hydatid recurrence was defined as the appearance of new active cysts after surgery[15]. Postoperative residual fluid cavities were not classified as recurrent HCD[12]. Postoperative morbidity was assessed using the Clavien-Dindo classification[16]. Hydatid cyst fluid bilirubin and ALP levels were measured using an automatic biochemical analyzer (AU-400, Olympus)[17]. All hospitals used the same instrument to measure bilirubin and ALP levels in the cyst fluid. All the machines were calibrated at each institution to ensure consistent reporting. The time from surgery to disease relapse at any site was described as recurrence-free survival.

Perioperative procedure and follow-up

A multidisciplinary team, including surgical, radiological, and anesthetic specialists, preoperatively evaluated all patients. Abdominal ultrasound, contrast-enhanced computed tomography (CT), and magnetic resonance cholangiopancreatography were performed at the discretion of the leading surgeon[6]. The protocol therapy in our hospitals for

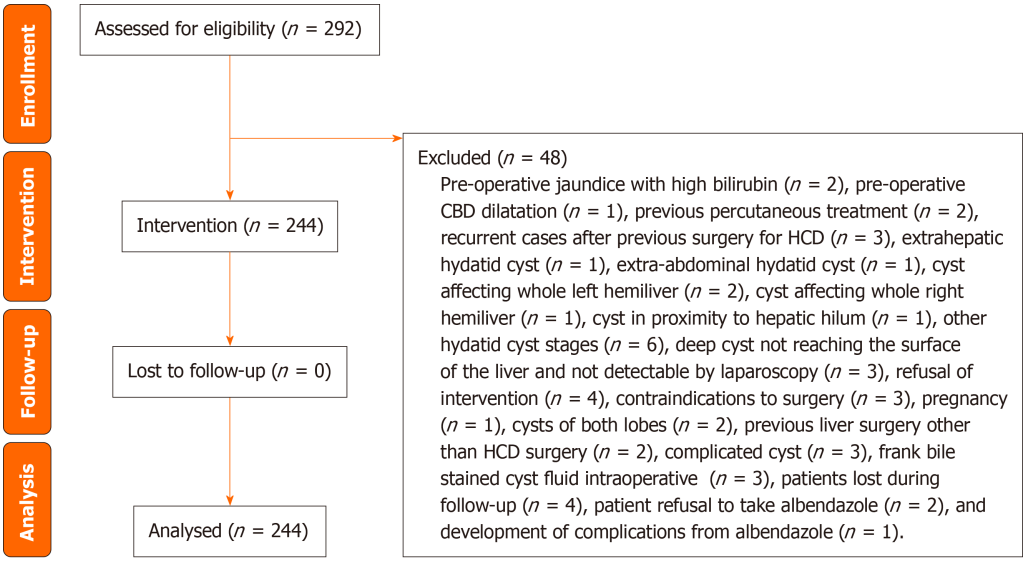

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Figure 1 Flow diagram of the inclusion and exclusion criteria. CBD: Common bile duct; HCD: Hydatid cyst disease.

albendazole was 10 mg/kg ten days before surgery and continued for six months following surgery with a two-week interval between each month. Complete blood counts and liver function monitoring were routinely performed. The surgical technique has been previously reported in detail[18]. In short, pneumoperitoneum with an intra-abdominal pressure of 14 mmHg was established. Fine needle aspiration of the cystic fluid was performed to rule out manifest CBC. The aspirated cyst fluid was analyzed for fluid bilirubin and ALP levels before injection of hypertonic saline, and the bilirubin and ALP levels were determined after surgery. The cystic wall was partially removed using a harmonic scalpel. To detect occult CBC, after the cystic cavity was fully evacuated and complete hemostasis was achieved, the intra-abdominal pressure was lowered to 10 mmHg. Visible orifices of the CBC were searched by thorough laparoscopic exploration of the cyst cavity; 20% hypertonic saline-soaked gauze was placed in the cystic cavity to observe the presence of bile while compressing either the gallbladder or CBD to stimulate bile backflow through the CBC (if present, the CBC was sutured).

Furthermore, we injected air, saline, or methylene blue dye in succession in all patients *via* cystic duct cannulation with CBD occlusion, hoping to increase CBC detection rates (three cases changed from occult CBC to manifest CBC intraoperatively and were excluded from the study). Omentoplasty was performed by inserting a right gastroepiploic-based omental flap into the cavity. A drain was placed in the subhepatic area. After three days, the drain was removed if there was no evidence of bile leakage. The patients were discharged on the fifth postoperative day. Follow-up visits were scheduled after one month, three months, six months, one year, and then every six months for the next four years. The drainage tube was left longer until fistula resolution was achieved in patients with bile leaks. After surgery, an ultrasound scan was used to check the cyst cavity at one, three, six months, one year, and then every six months until completion of the follow-up period (5 years). If the ultrasound results were inconclusive, a CT scan was performed. No mortality was observed in this study.

Statistical analysis

Statistical Package for Social Science software was used to analyze the collected data (version 20.0. IBM Corp., Armonk, NY, USA). Continuous variables with a normal distribution were reported as mean and SD, while data with a non-normal distribution were presented as medians and ranges. Absolute and relative frequencies were used to summarize categorical variables. The Chi-square test (χ^2) or Fisher's exact test was used to examine categorical variables. Independent factors determining biliary complications and recurrence were analyzed using univariate logistic regression analysis. The odds ratio (OR) was calculated to compare the relative odds of biliary complications and recurrence of HCD. The 95%CI was used to estimate OR precision. The hydatid cyst-recurrence-free time was determined using the Kaplan–Meier method. Statistically significant and highly statistically significant variables were defined as P values < 0.05 and < 0.001, respectively.

RESULTS

A flowchart of the eligibility criteria is presented in Figure 1. A total of 292 patients with hepatic HCD were referred to our clinics based on abdominal ultrasound results. Forty-eight patients were excluded: Pre-operative jaundice with high bilirubin (n = 2), pre-operative CBD dilatation (n = 1), previous percutaneous treatment (n = 2), recurrent cases after previous surgery for HCD (n = 3), extrahepatic hydatid cyst (n = 1), extra-abdominal hydatid cyst (n = 1), cyst affecting whole left hemiliver (n = 2), cyst affecting whole right hemiliver (n = 1), cyst in proximity to hepatic hilum (n = 1), other

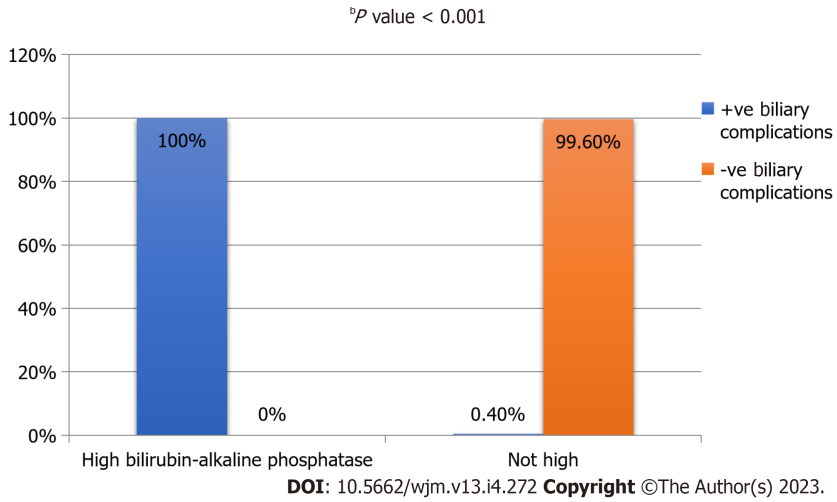

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Figure 2 Relation between the biochemical indices and development of biliary complications among the studied patients (*n* = 244). ^{b}P < 0.01. + ve: Presence of biliary complications; - ve: Absence of biliary complications.

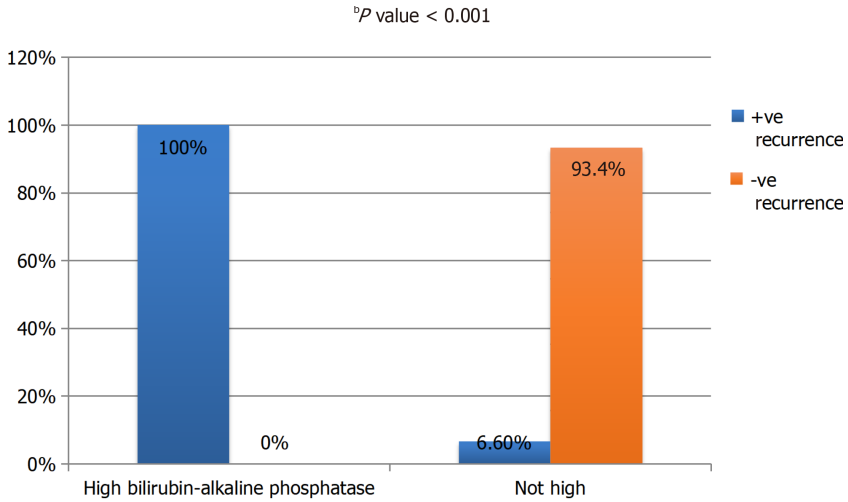

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Figure 3 Relation between the biochemical indices and recurrence of hydatid cyst among the studied patients (*n* = 244). ^{b}P < 0.01. + ve: Occurrence of recurrence; - ve: No recurrence.

hydatid cyst stages (*n* = 6), deep cyst not reaching the surface of the liver and could not be detected by laparoscopy (*n* = 3), refused intervention (*n* = 4), contraindications to surgery (*n* = 3), pregnancy (*n* = 1), cysts of both lobes (*n* = 2), previous liver surgery other than HCD surgery (*n* = 2), complicated cyst (*n* = 3), intraoperative frank bile stained cyst fluid (*n* = 3), patients lost during follow-up (*n* = 4), patient refusal to take albendazole (*n* = 2), and development of complications due to albendazole (*n* = 1). Following the exclusion of 48 patients, a total of 244 patients were enrolled in this study.

The patients' demographic and preoperative characteristics are summarized in Table 1. This study included 244 patients with a mean age of 42.67 ± 9.97 years. The mean cyst diameter was 9.49 ± 3.54 cm, and the most common symptom was abdominal pain (*n* = 125, 51.2%). Most patients had a cyst classification of CE3b (*n* = 183, 75%) with a predominant right hemiliver location (*n* = 184, 75.4%).

Table 2, Figures 2 and 3 show the intraoperative and postoperative findings, respectively. The mean operative time was 107.32 ± 6.92 min, with cystic fluid spilling (4.9%) and high bilirubin-high ALP in cyst fluid (6.1%). Biliary complications occurred in 16 patients (6.6%), and recurrent HCD occurred in 30 patients (12.3%).

Table 3 shows that the mean time to biliary fistula detection was 3.13 ± 1.78 d, and the resolution of bile leak was 14.38 ± 6.12 d. Patients with POBF (*n* = 16/244, 6.6%) had mainly external biliary fistula (*n* = 9/16, 56.2%). Most cases were grade B (7/16, 43.7%). The mean time to recurrent HCD was 2.48 ± 0.98 years with a cyst size of 4.93 ± 2.72 cm. Recurrent HCD was most common in the right hemiliver (18/30, 60%) and with CE2 as the cyst stage (25/30, 83.3%). There was no mortality in our study. A highly statistically significant association ($P \leq 0.001$) was observed between biochemical indices and the development of biliary complications, where patients with high bilirubin-ALP were 3405 times more likely to have biliary complications (Table 4). There was a highly statistically significant association ($P \leq 0.001$) between biliary complications, biochemical indices, and the occurrence of recurrence HCD where patients who developed biliary complications and high bilirubin-ALP were 244.6 and 214 times more likely to have recurrent hydatid cyst, respectively

Table 1 Demographic and preoperative characteristics of the patients (*n* = 244), *n* (%)

Characteristics	*n* = 244
Age (year) mean ± SD	42.67 ± 9.97
≤ Median (43)	136 (55.7)
> Median (43)	108 (44.3)
Sex	
Male	163 (66.8)
Female	81 (33.2)
ASA	
I	176 (72.1)
II	47 (19.3)
III	21 (8.6)
Positive family history	15 (6.1)
Clinical presentation	
Asymptomatic	19 (7.8)
Pain	125 (51.2)
Mass	48 (19.7)
Nausea & vomiting	32 (13.1)
Dyspepsia	20 (8.2)
Cyst size (cm) mean ± SD	9.49 ± 3.54
≤ Median (9)	130 (53.3)
> Median (9)	114 (46.7)
Cyst site	
Right lobe	184 (75.4)
Left lobe	60 (24.6)
Cyst stage	
CE2	61 (25)
CE3b	183 (75)

ASA: American Society of Anesthesiologists; CE: Cystic echinococcosis.

(Table 5, Figure 4).

DISCUSSION

This study evaluated the association between occult CBC, POBF, and recurrent HCD. The study results further highlight the importance of hydatid cyst fluid analysis in detecting occult CBC. To the best of our knowledge, no research published in the literature has addressed the relationship between occult CBC and the development of recurrent HCD or the relationship between elevated cyst fluid bilirubin and ALP and the development of POBF and recurrent HCD. This study showed that occult CBC occurred in 6.6% of patients and recurrent HCD occurred in 12.3% of patients. Of the 16 patients with POBF, 15 had high cyst fluid bilirubin and ALP levels, and patients with high bilirubin-ALP were 3405 times more likely to have biliary complications. Of the 30 patients with recurrent HCD, 15 patients had high cyst fluid bilirubin and ALP levels; all 16 patients with POBF later developed recurrent HCD, and patients who developed biliary complications and high bilirubin-ALP were 244.6 and 214 times more likely to have recurrent hydatid cysts, respectively. The detection of occult CBC is essential. In our study, occult CBC and the subsequent development of postoperative biliary leak occurred in 16 patients (6.6%), which was lower than that in the two studies (27% and 16%, respectively)[19-20]. The low incidence of POBF in our study may be due to variations in sample size, different surgical approaches, and inclusion criteria, especially deep/centrally located cysts, such as those in medial segments such as IVa, V, and VIII, extended deep into the liver parenchyma and was closely related to major biliovascular structures with a higher incidence

Table 2 Intraoperative and postoperative outcomes (*n* = 244), *n* (%)

Intraoperative outcome	*n* = 244
Operative time (min) (mean ± SD)	107.32 ± 6.92
≤ Median (106)	126 (51.6)
> Median (106)	118 (48.4)
Blood transfusion	
1 unit	4 (1.6)
2 units	2 (0.8)
Cystic fluid spillage	12 (4.9)
Conversion	7 (2.9)
Causes of conversion	
Extensive adhesion	5 (2.1)
Organ injury	1 (0.4)
Difficult cyst detection	1 (0.4)
Anaphylaxis	2 (0.8)
Cyst fluid biochemical indices	
High both bilirubin-high alkaline phosphatase	15 (6.1)
Postoperative outcomes	*n* = 244
Postoperative hospital stay (days) mean ± SD	3.44 ± 2.51, 3 (2-20)
ICU admission	9 (3.7)
Early postoperative complications	28 (11.5)
Type of early postoperative complications	
Wound infection	7 (2.9)
Cyst cavity bile collection	6 (2.5)
Ileus	2 (0.8)
Subphrenic abscess	4 (1.6)
Subphrenic hematoma	3 (1.2)
Cholangitis	4 (1.6)
Pneumonia	1 (0.4)
Atelectasis	1 (0.4)
None	215 (88.1)
Clavien-Dindo classification	
0	213 (87.3)
I	8 (3.3)
II	11 (4.5)
III	12 (4.9)
Biliary complications	16 (6.6)
Late postoperative complications	
Port/incisional site hernia	7 (2.9)
Recurrence	30 (12.3)

ICU: Intensive care unit.

Table 3 Characteristics of biliary complications and recurrence (*N* = 16), *n* (%)

Biliary complications	*n* = 16
Type	
External biliary fistula	9 (56.2)
Cyst cavity biliary abscess	4 (25)
Biliary peritonitis	3 (18.8)
Grade	
Grade A	6 (37.5)
Grade B	7 (43.7)
Grade C	3 (18.8)
Time of development (days) mean ± SD	3.13 ± 1.78
Treatment	
Conservative	6 (37.5)
Ultrasound guided percutaneous drainage	7 (43.7)
Reoperation	3 (18.8)
Time to leakage cessation (days) mean ± SD	14.38 ± 6.12
Recurrence	*n* = 30
Site	
Right lobe	18 (60)
Left lobe	6 (20)
Peritoneum	4 (13.3)
Spleen	2 (6.7)
Clinical presentation	
Asymptomatic	7 (23.3)
Pain	13 (43.3)
Mass	4 (13.3)
Nausea & vomiting	2 (6.7)
Infection	2 (6.7)
Rupture	1 (3.3)
Jaundice	1 (3.3)
Time to diagnosis (yr) mean ± SD	2.48 ± 0.98
Size (cm) mean ± SD	4.93 ± 2.72
Stage	
CE2	25 (83.3)
CE3b	5 (16.7)
Treatment	
Pericystectomy	17 (56.7)
Left hepatectomy	6 (20)
Abdominal exploration and excision of recurrent abdominal HCD	4 (13.3)
Splenectomy (for recurrent splenic HCD)	2 (6.7)
CBD stent + pericystectomy	1 (3.3)

CE: Cystic echinococcosis; CBD: Common bile duct; HCD: Hydatid cyst disease.

Table 4 Relation between the independent factors and development of biliary complications among the studied patients by univariate analysis (*n* = 244)

Factors	Biliary complications (*n* = 16)		No biliary complications (*n* = 228)		*P* value	Univariate OR (95%CI)
	n	%	*n*	%		
Sex						
Male (*n* = 163)	9	5.5	154	94.5	0.354[1]	Reference
female (*n* = 81)	7	8.6	74	91.4		1.62 (0.58-4.52)
ASA						
I (*n* = 176)	9	5.1	167	94.9	0.160[1]	1.08 (0.12-8.96)
II (*n* = 47)	6	12.8	41	87.2		2.93 (0.33-25.98)
III (*n* = 21)	1	4.8	20	95.2		Reference
Family history						
+ ve (*n* = 15)	8	53.3	7	46.7	< 0.001[2,b]	31.6 (9.18-108.6)
- ve (*n* = 229)	8	3.5	221	96.5		Reference
Cyst size (cm)						
≤ 9 cm (*n* = 130)	3	2.3	127	97.9	0.004[1,a]	Reference
> 9 cm (*n* = 114)	13	11.4	101	88.6		5.45 (1.51-19.64)
Cyst site						
Right lobe (*n* = 184)	13	7.1	171	92.9	0.575[2]	1.44 (0.39-5.25)
Left lobe (*n* = 60)	3	5	57	95		Reference
Cyst stage						
CE2 (*n* = 61)	15	24.6	46	75.4	< 0.001[2,b]	59.3 (7.64-460.9)
CE3b (*n* = 183)	1	0.5	182	99.5		Reference
Operative time (min)						
≤ 106 min (*n* = 126)	9	7.1	117	92.9	0.703[1]	1.22 (0.44-3.39)
> 106 min (*n* = 118)	7	5.9	111	94.1		Reference
Blood transfusion						
Yes (*n* = 6)	4	66.7	2	33.3	< 0.001[2,b]	37.7 (2.26-226.5)
No (*n* = 238)	12	5	226	95		Reference
Cystic fluid spillage						
Yes (*n* = 12)	2	16.7	10	83.3	0.147[2]	3.11 (0.62-15.60)
No (*n* = 232)	14	6	218	94		Reference
Conversion						
Yes (*n* = 7)	5	71.4	2	28.6	< 0.001[2,b]	51.4 (8.94-294.9)
No (*n* = 237)	11	4.6	226	95.4		Reference
Anaphylaxis						
Yes (*n* = 2)	0	0	2	100	0.707[1]	Reference
No (*n* = 244)	16	6.6	226	93.4		0.14 (0.01-1.65)
Cyst fluid biochemical indices						
High bilirubin-alkaline phosphatase (*n* = 15)	15	100	0	0.0	< 0.001[2,b]	3405 (202-57164)
Not high (*n* = 229)	1	0.4	228	99.6		Reference
Hospital stay (days)						

≤ 3 d (*n* = 184)	0	0.0	184	100	< 0.001[2,b]	Reference
> 3 d (*n* = 60)	16	26.7	44	73.3		67 (8.64-518.15)
ICU admission						
Yes (*n* = 9)	5	55.6	4	44.4	< 0.001[2,b]	25.5 (5.99-108.24)
No (*n* = 235)	11	4.7	224	95.3		Reference
Early postoperative complications						
Yes (*n* = 28)	13	46.4	15	53.6	< 0.001[2,b]	61.5 (15.8-239.8)
No (*n* = 216)	3	1.4	213	98.6		Reference

[1]Chi square test (χ^2).
[2]Fisher's exact test.
[a]*P* ≤ 0.05: Statistically significant.
[b]*P* ≤ 0.001: Highly statistically significant.
OR: Odds Ratio; ICU: Intensive care unit, ASA: American Society of Anesthesiologists; CE: Cystic echinococcosis; + ve: Positive family history; - ve: Negative family history.

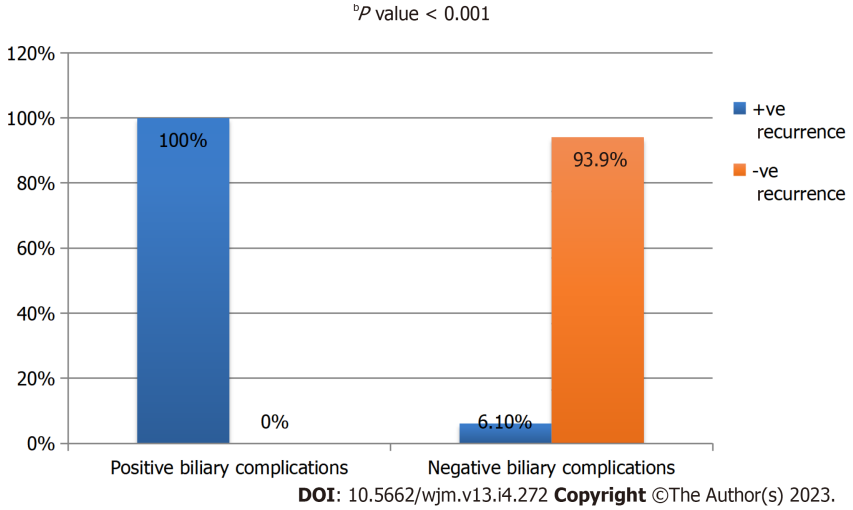

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Figure 4 Relation between the biliary complications and recurrence of hydatid cyst among the studied patients (*n* = 244). [b]*P* < 0.01. + ve: Occurrence of recurrence; - ve: Absence of recurrence.

of CBC in these studies. Furthermore, we meticulously searched for tiny CBC using various techniques. Another challenge during the laparoscopic surgical approach for liver HCD is that pneumoperitoneum increases intra-abdominal pressure and may prevent bile leakage into the cyst. We faced this challenge through adequate laparoscopic exploration of the cyst cavity after cyst deroofing, intraoperative dye injection, and white gauze left inside the residual cavity for a few minutes and lowering the intra-abdominal pressure to 10 mmHg, which could facilitate CBC detection. Ultimately, this helped decrease the incidence of POBF. Of the 16 patients who developed POBF, 15 (15/16) had high cyst fluid bilirubin and ALP levels. CBC is the cause of high levels of these biochemicals in cyst fluid. The high level of cyst fluid in the postoperative period led us to suspect the development of POBF in these patients. Another point of contention is the relationship between cyst size and the development of CBC. The relationship between cyst size and CBC varies between studies, with numerous studies reporting a cyst size cut-off of 10 cm for CBC[21-24]. We found a significant correlation between cyst size and POBF, with cysts larger than the median 9 cm being 5.45 times more likely to develop POBF. A larger cyst is more likely to deform the biliary pedicle anatomy owing to the greater exposed surface area, thus predisposing the patient to CBC. Therefore, size has a direct relationship with the CBC. Furthermore, it has been reported that intracystic pressure increases with the diameter of the hepatic cyst, increasing the likelihood of CBC[25]. In our experience, POBF occurred on the third postoperative day, mainly as an external biliary fistula (9/16, 56.2%). Most patients had grade B disease (7/16, 43.7%). Most POBFs were treated conservatively or with ultrasound-guided percutaneous drainage, and all patients demonstrated clinical resolution within two weeks. In our study, endoscopic biliary stenting was unnecessary except in patients with persistent bile leaks.

Recurrence of HCD is the second most common complication for both surgeons and patients. Failure to remove all viable cysts and protoscolices, particularly long-standing cysts with host tissue adventitial layer (pericyst) branching into the surrounding tissue, may be responsible for recurrence. Although the laparoscopic approach has many advantages during HCD surgery, drawbacks include difficulty in accessing a cyst, difficult aspiration with a fine needle that may be

Table 5 Relation between the independent factors and recurrence of hydatid cyst by univariate analysis (*n* = 244)

Factors	Recurrence (*n* = 30)		No recurrence (*n* = 214)		*P* value	Univariate OR (95%CI)
	n	%	*n*	%		
Sex						
Male (*n* = 163)	18	0.11	145	0.89	0.398[1]	Reference
Female (*n* = 81)	12	0.148	69	0.852		1.40 (0.62-3.07)
ASA						
I (*n* = 176)	21	0.119	155	0.881	0.792[1]	1.29 (0.28-5.924)
II (*n* = 47)	7	0.149	40	0.851		1.66 (0.31-8.78)
III (*n* = 21)	2	0.095	19	0.905		Reference
Family history						
+ve (*n* = 15)	15	1	0	0	< 0.001[2,b]	214 (26.45-1731.7)
-ve (*n* = 229)	15	0.066	214	0.934		Reference
Cyst size (cm)						
≤ 9 cm (*n* = 130)	7	0.054	123	0.946	< 0.001[1,b]	Reference
> 9 cm (*n* = 114)	23	0.202	91	0.798		4.44 (1.83-10.80)
Cyst site						
Right lobe (*n* = 184)	23	0.125	161	0.875	0.864[1]	1.08 (0.44-2.66)
Left lobe (*n* = 60)	7	0.117	53	0.883		Reference
Cyst stage						
CE2 (*n* = 61)	27	0.443	34	0.557	< 0.001[1,b]	47.7 (13.7-165.95)
CE3b (*n* = 183)	3	0.016	180	0.984		Reference
Operative time (min)						
≤ 106 min (*n* = 126)	16	0.127	110	0.873	0.843[1]	1.08 (0.50-2.324)
> 106 min (*n* = 118)	14	0.119	104	0.881		Reference
Blood transfusion						
Yes (*n* = 6)	5	0.833	1	0.167	< 0.001[2,b]	42.6 (4.78-397.4)
No (*n* = 238)	25	0.105	213	0.895		Reference
Cystic fluid spillage						
Yes (*n* = 12)	12	1	0	0	< 0.001[2,b]	142 (17.5-1160.4)
No (*n* = 232)	18	0.078	214	0.922		Reference
Conversion						
Yes (*n* = 7)	6	0.857	1	0.143	< 0.001[2,b]	53.3 (6.15-461.2)
No (*n* = 237)	24	0.101	213	0.899		Reference
Anaphylaxis						
Yes (*n* = 2)	2	1	0	0	< 0.001[2,b]	15.3 (1.34-174.1)
No (*n* = 244)	28	0.116	214	0.884		Reference
Cyst fluid biochemical indices						
High bilirubin-alkaline phosphatase (*n* = 15)	15	1	0	0	< 0.001[2,b]	214 (26.45-1731.7)
Not high (*n* = 229)	15	0.066	214	0.934		Reference
Hospital stay (days)						
≤ 3 d (*n* = 184)	10	0.054	174	0.946	< 0.001[1,b]	Reference
> 3 d (*n* = 60)	20	0.333	40	0.667		8.7 (3.78-20.02)

ICU admission						
Yes (n = 9)	8	0.889	1	0.111	< 0.001[2,b]	77.5 (9.25-648.4)
No (n = 235)	22	0.094	213	0.906		Reference
Early postoperative complications						
Yes (n = 28)	22	0.786	6	0.214	< 0.001[2,b]	95.33 (30.3-299.9)
No (n = 216)	8	0.037	208	0.963		Reference
Biliary complications						
Yes (n = 16)	16	1	0	0	< 0.001[2,b]	244.6 (30.21-1981)
No (n = 228)	14	0.061	214	0.939		Reference
Port/incisional site hernia						
Yes (n = 7)	7	1	0	0	< 0.001[2,b]	65.13 (7.67-553.1)
No (n = 237)	23	0.097	214	0.903		Reference

[1]Chi square test (χ^2).
[2]Fisher's exact test.
[a]$P \leq 0.05$: Statistically significant.
[b]$P \leq 0.001$: Highly statistically significant.
OR: Odds Ratio; ICU: Intensive care unit; ASA: American Society of Anesthesiologists; CE: Cystic echinococcosis; + ve: Positive family history; - ve: Negative family history.

obstructed by fragments of the laminated and germinal layers, and puncture of the cyst under pressure with an associated risk of intraoperative spillage and thus recurrence that may reach up to 22%[26-27]. According to our results, 12.3% of the patients developed recurrent HCD, which was lower than in two previous reports. This was due to differences in technique, cyst size, or follow-up duration. We routinely release the pneumoperitoneum to reduce intra-abdominal pressure during puncture and aspiration of the cyst, aiming to decrease intra-abdominal spillage. However, unrecognized spillage of cyst contents due to multiple cyst punctures by fine needles could contribute to spillage and dissemination, which may contribute to recurrence. In our opinion, the larger sample size, intense and longer follow-up protocol in our study is a true reflection of the real recurrence risk. The proposed solutions to these recurrence challenges have been developed by Bickel *et al*[28] and Palanivelu *et al*[29]. These two previous studies did not report recurrence, as both provided contamination-free management of HCD with a large-diameter suction needle and suction apparatus that allowed cyst aspiration without multiple punctures.

According to our results, 12.3% of patients developed recurrent HCD, higher than in two previous reports. This was due to differences in technique, cyst size, or follow-up duration. The follow-up period for Bickel *et al*[28] was 4.1 years, and for Palanivelu *et al*[29], was 5.8 years. In our study, the mean duration to diagnosis of recurrent HCD was 2.48 ± 0.98 years, and the mean cyst size at recurrence was 4.93 ± 2.72 cm. The recurrent cyst size was less than the original preoperative cyst size, most likely due to regular follow-up, and thus cysts were detected earlier before becoming symptomatic. Ultrasound scans were primarily used to detect recurrent HCD during the follow-up period. CT was performed in patients with inconclusive ultrasound results. The diagnostic accuracies of ultrasonography and CT scans were 90% and 100%, respectively, and we did not rely on routine serological testing owing to its low specificity[30-31]. Occult CBC with POBF indicates cyst invasion and, consequently, recurrence. Our data showed that POBF was strongly associated with recurrence (all patients with POBF later developed recurrent HCD), possibly due to the laminated layer and germinal layer invasion into the surrounding liver tissue or biliary tree. Hydatid cyst generally is an "expansive" disease, not "infiltrative." However, with growth in size, distorted anatomy, and elevated intracystic pressure, the adjacent liver parenchyma may develop pressure necrosis. CBC can lead to POBF, which, if persistent, can cause the formation of cystic recurrence, particularly starting from the fragment of cyst lying on the biliary and vascular structure that was not removed during the operation. We equate the management of HCD with oncologic principles: (1) Multidisciplinary management; (2) treatment with intent to cure; (3) active monitoring for recurrence; and (4) long duration of follow-up beyond five years.

Regarding recurrent HCD treatment, there is consensus that non-surgical treatment is preferable for small asymptomatic cysts in elderly patients with comorbidities. The surgical approach is preferred for patients with large, symptomatic, and complicated cysts[32]. However, in our study, radical surgery was recommended unless contraindicated. In our experience, a patient with a predicted life expectancy of 5-10 years should be offered surgery. Informed decision-making is essential because once a decision is made for nonoperative watchful waiting, the clock does not stop. There is a possibility that the cyst may expand, leading to complications, and surgery may become more complicated with an increased risk of morbidity. Thus, early and timely surgery in patients with recurrent small HCD may be advantageous. The most common re-operative procedures in our experience were open pericystectomy (56.7%) and open left hepatectomy (20%). Laparoscopic splenectomy was performed for recurrent HCD of the spleen. Laparoscopic excision was performed in patients with recurrent intraperitoneal HCD.

The limitation of this study is that we omitted patients with multiple or recurrent HCD and those managed with open surgery. In addition, we did not perform a multivariate analysis due to the small number of patients with CBC and recurrent HCD. The low incidence of complications namely POBF and recurrence constitutes a limitation for conducting a reliable regression analysis to predict these outcomes. It may compromise the statistical power and validity of the model, impeding the identification of significant predictors and the generalization of the results to larger populations. Despite these limitations, the information presented in this study adds to the current body of scientific evidence, and the study has the merits of large sample size and multicenter collaboration.

CONCLUSION

Occult CBC can predict recurrent HCD. Elevated cyst fluid bilirubin and ALP levels predicted POBF and recurrent HCD.

ARTICLE HIGHLIGHTS

Research background

Different methods have been used to treat hydatid cyst of the liver but there are no conclusive results. The two most common complications are postoperative biliary fistula and recurrent hydatid cyst disease (HCD).

Research motivation

We were motivated to conduct this study to evaluate the incidence of occult cysto-biliary communication (CBC) and HCD recurrence after laparoscopic partial resection and omentoplasty.

Research objectives

The objectives of the study were to determine the incidence of occult CBC and HCD recurrence rate with the aim of reducing these two complications. The second objective was to detect an association between high cystic fluid biochemical indices and the incidence of developing postoperative biliary fistula and HCD recurrence.

Research methods

A prospective observational study was conducted involving 244 patients with stage cystic echinococcosis 2 and cystic echinococcosis 3b according to the World Health Organization's Informal Working Group on Echinococcosis classification who underwent laparoscopic partial cystectomy with omentoplasty.

Research results

There was a highly statistically significant association between cystic fluid biochemical indices and the development of biliary complications. There was a highly statistically significant association between biliary complications, biochemical indices, and the occurrence of recurrent HCD.

Research conclusions

This study is the first to propose that occult CBC can predict recurrent HCD. Elevated cyst fluid bilirubin and alkaline phosphatase levels predicted POBF and recurrent HCD. These findings will encourage surgeons to detect occult CBCs to avoid morbidity and mortality due to POBF and recurrent HCD.

Research perspectives

Future studies should focus on the detection of CBCs to decrease the incidence and morbidity of POBF and HCD recurrence.

FOOTNOTES

Author contributions: All authors contributed to the study conception and design, material preparation, data collection, and analysis; All authors commented on the previous versions of the manuscript; All authors have read and approved the final manuscript.

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Clinical trial registration statement: This study is registered at https://clinicaltrials.gov/. The registration identification number is ID: NCT05116735.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Data sharing statement: Data are available from the corresponding author on reasonable request at tameralnaimy@hotmail.com.

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ORIGINAL ARTICLE

Prospective Study

Role of endoscopic ultrasound and endoscopic ultrasound-guided tissue acquisition in diagnosing hepatic focal lesions

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Abstract

BACKGROUND

Endoscopic ultrasonography (EUS) has become an established method in diagnostic and therapeutic procedures in gastroenterology; however, it has recently gained a growing role in hepatology.

AIM

To evaluate the role of EUS features, strain elastography (SE), and EUS-tissue acquisition in diagnosing hepatic focal lesions (HFLs) that could affect further management.

METHODS

This cross-sectional study included 215 patients with pancreatic, biliary, or

gastrointestinal malignancies referred for EUS examination. HFLs were identified in 43 patients (20%), and EUS-guided tissue acquisition was performed from these lesions.

RESULTS

EUS features were highly sensitive (100%) but much less specific (57%) in diagnosing HFLs; the overall accuracy was 94%. Real-time elastography was also very sensitive (97%) but less specific (67%) in diagnosing HFLs; however, the overall accuracy was 92%. EUS tissue acquisition was extremely sensitive (100%) and specific (100%), with a 100% overall diagnostic accuracy.

CONCLUSION

The diagnostic utility of EUS-guided tissue acquisition was extremely accurate in diagnosing HFLs. EUS characteristics and real-time SE accurately predicted the histological diagnosis of both benign and malignant HFLs.

Key Words: Endoscopic ultrasonography; Hepatic focal lesions; Fine needle aspiration; Fine needle biopsy; Elastography

Core Tip: This cross-sectional study included 43 patients with hepatic focal lesions among 215 pancreatic, biliary, or gastrointestinal malignant lesions referred for Endoscopic ultrasonography (EUS) examination. EUS tissue acquisition was highly sensitive (100%) and specific (100%), with an overall diagnostic accuracy of 100%.

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INTRODUCTION

Endoscopic ultrasonography (EUS) is one of the main tools used to evaluate the upper and distal parts of the lower gastrointestinal tract and to define pancreatic and hepatobiliary features. The utility of EUS in diagnosing and managing hepatic focal lesions (HFLs) has gained special concern nowadays due to the proximity of the scope to the liver, and its excellent spatial resolution enables real-time images and guided intervention[1-4].

Liver diseases are among the most common worldwide and manifest as diffuse liver diseases and focal hepatic lesions, ranging from benign to malignant. To make a definitive diagnosis of liver diseases, biochemical and imaging investigations and, in some instances, liver biopsies are typically used[2]. The application of EUS in diagnosing liver diseases is a promising technique and should be considered a first-line therapeutic option in selected cases[4].

EUS-guided diagnosis of focal liver lesions by endosonographic features and cytological and histopathological examination of biopsies obtained *via* fine needle aspiration/biopsy (EUS-FNA/FNB) has been shown to significantly improve the diagnosis of solid liver lesions compared to traditional imaging tools[1].

US and computed tomography (CT)-guided FNA/FNB of focal liver lesions are safe and provide high diagnostic accuracy; however, it is sometimes challenging to access subdiaphragmatic and posteriorly located lesions.

Compared to percutaneous and transjugular routes, EUS-FNA/FNB may have better accessibility and diagnostic yield and may be superior for a targeted approach to focal lesions. It provides higher-quality images and allows for more patient comfort[3]. However, there is limited data regarding the accuracy of EUS-guided biopsy of HFLs[5].

Elastography is a US-based imaging modality that provides information about tissue stiffness and can be considered a virtual biopsy. Several elastographic approaches have been developed, such as transient elastography, strain elastography (SE), histograms, and shear wave imaging, which include point shear wave elastography and 2D shear wave elastography[6].

This study evaluated the diagnostic utility of EUS sonographic features, SE, and EUS-FNA/FNB in differentiating benign from malignant liver lesions, including primary and metastatic lesions that may affect further management.

MATERIALS AND METHODS

This cross-sectional study included 215 Egyptian patients who were referred to the internal medicine department, Kasr Al-Aini hospitals, Cairo University for EUS and EUS-FNA/FNB for an assessment of pancreatic or gastrointestinal tumors without or with HFLs detected by contrast abdominal CT or magnetic resonance imaging (MRI). After the EUS examination, 43 out of 215 (20%) patients had HFLs for which EUS-FNA/FNB was performed. All the required data is

collected from the hospital's medical record after ethical approval is obtained from our hospital's ethical committee.

Exclusion criteria include patients unfit for deep sedation and patients with bleeding disorders contraindicating EUS-FNA/FNB.

All patients were subjected to a thorough history taking, clinical examination, abdominal US, CT, or MRI abdomen, and routine laboratory investigations such as complete blood count, hepatic and renal function tests, and coagulation profile, in addition to virological tests for human immunodeficiency virus, hepatitis C virus, and hepatitis B virus and tumor markers including CA-19-9 and alpha-fetoproteins.

EUS and EUS-FNA/FNB were performed by a single endoscopist. It was conducted under deep sedation using a Pentax linear array echoendoscope type EG-3870UTK attached to a Hitachi ultrasound AVIUS machine. A detailed description of the primary tumor and the HFLs regarding their site, size, shape, and number was applied. Based on EUS features, we considered the mass as malignant if any one of the following criteria is present: (1) The presence of peripheral hypoechoic halo; and (2) The presence of mass effect as compression or interruption of the course of a blood vessel or a biliary radicle, or the presence of contour bulge.

Real-time SE scoring was done to all HFLs. We considered grades 1 and 2 as benign and grades 3 and 4 as malignant lesions. EUS-FNA was conducted with 22G Echotip needles from Cook Company; however, the FNB was conducted with 22G Acquire needles from Boston Scientific Company. All biopsies were done by high pressure technique and fanning, at least two passes, no Rapid On-Site evaluation (ROSE) was available in any of the cases. We have targeted the nearest mass to the Echoendoscope, with no intervening vessels along the needle tract and with the presence of a rim of normal liver tissue between the liver capsule and targeted mass to minimize bleeding. The material was spread over a glass slide and fixed by 95% alcohol, whereas formalin blocks were prepared and sent to a single experienced cytologist.

The gold standard of malignant lesions is the FNB as it has extremely high specificity, about 95%-100% in most articles in the literature. All benign-looking lesions were followed up with the disappearance of all cholangitis abscesses under antibiotic therapy, while the two benign liver nodules were constant in size over 6 mo.

The collected data from the 43 patients with HFLs was organized and statistically analyzed using appropriate methods.

RESULTS

The average age of the patients examined was 56, the majority were male (74.42%), and the most common co-morbidities were diabetes mellitus (10 patients; 23.25%), systemic hypertension (8 patients; 18.6%), and ischemic heart disease (6 patients; 13.95%). Most of the HFLs were present in the left lobe of the liver (67.44%).

The cytopathological confirmed malignant lesions were found in 35 (81.4%) of patients, while benign lesions were found in 8 (18.6%) of patients (Table 1). The eight benign lesions were six cholangitis abscesses and two benign liver lesions, likely areas of focal fat depletion. All benign lesions were followed up with the disappearance of all cholangitic abscesses under antibiotic therapy, while the two benign liver nodules were constant in size over 6 mo. The other 35 malignant lesions were five primary hepatocellular carcinomas, one neuroendocrine tumor, and 29 metastatic liver lesions (Figure 1) from malignant pancreatic masses, as proved by cytopathological and histopathological examination after EUS-FNA/FNB (Figure 2A). The mean size was 23.47 mm × 39.19 mm, with an average number of needles passing 1.49 (0.51).

EUS-FNA/FNB was accurate in diagnosing HFLs with 100% sensitivity, specificity, and diagnostic accuracy.

EUS features provisionally diagnosed 38 patients (88.37%) with malignant lesions and five patients (11.63%) with benign ones (Table 2). Thus, 5 out of 8 benign lesions could be correctly diagnosed based on EUS features. On the other hand, 38 cases were reported with malignant lesions, while the actual number evident by histopathology was only 35; thus, three benign cases were incorrectly diagnosed as malignant lesions (Table 3).

Based on Real-Time elastography scoring, 5 patients were suggested to have benign lesions while 38 lesions were suggested to have malignant lesions. Real-time elastography (Figures 2B and 3) was very sensitive (97%) but less specific (67%) in the diagnosis of HFLs; however, the overall accuracy was 92% (Tables 4 and 5).

EUS-FNA needles were used in 20 patients while EUS-FNB were used in 23 patients. No complications were reported in the study. EUS-FNA was done in 20 patients while EUS-FNB was done in 23 patients.

DISCUSSION

Percutaneous CT or US-guided biopsy is the classical diagnostic method for liver masses. However, it has shown some difficulties in diagnosing small liver lesions less than 2 cm, with common complications and many contraindications limiting its use[7,8].

EUS has been broadly used for identifying and managing GIT and pancreaticobiliary diseases[3]. It has become an excellent tool to confirm the pathological diagnosis in combination with EUS-FNA/FNB.

Compared to percutaneous liver biopsy (PC-LB), EUS-guided liver biopsy (ELB) is a new approach to liver parenchyma sampling that has shown promise for safety, patient comfort, and good tissue yield[9]. ELB also allows sampling from multiple sites in the liver, both in the right and left lobes[9,10].

Few studies have verified the efficacy and safety of ELB; however, the review of Sbeit reported a variable diagnostic yield for EUS-guided liver biopsy in focal liver lesions (91%-100%)[4].

Table 1 Cytopathological diagnosis of hepatic focal lesions

Variable	Total, *n* = 43	
	n	%
Cytopathological diagnosis		
Benign	8	18.60
Malignant	35	81.40
Inflammatory	8	18.60
Cholangitic abscess	6	13.94
Cirrhotic nodule	2	4.65
Primary	6	13.95
Hepatocellular carcinoma	5	11.63
Neuroendocrine tumor	1	2.32
Secondary	29	67.44

Table 2 Endoscopic ultrasonography finding of patients with hepatic focal lesions

Variable	Total, *n* = 43
No. of passes	1.49 (0.51)
Shortest diameter size in mm	19 ± 12.8/(3-67)
Longest diameter size in mm	26 ± 19.1/(4-109)
Diagnosis	
Benign	5 (11.63)
Malignant	38 (88.37)

Data are presented as *n* (%) or mean ± SD/(range).

Table 3 Comparison between endoscopic ultrasonography diagnosis and histopathology results

Variable	EUS, *n* = 43		Histopathology, *n* = 43	
	n	%	*n*	%
Benign	5	11.63	8	18.60
Malignant	38	88.37	35	81.40

EUS: Endoscopic ultrasonography.

Table 4 Diagnostic utility of elastography in predicting benign and malignant hepatic focal lesions

Elastography, *n* = 43	*n* (%)
Benign	
Grade 1	0
Grade 2	5 (11.6)
Malignant	38 (88.4)
Grade 3	10 (23.3)
Grade 4	28 (65.1)

Table 5 Comparison between different endoscopic ultrasonography tools regarding their utility in diagnosis of hepatic focal lesions

Tool	Sensitivity	Specificity	PPV	NPV	Overall accuracy
Elastography	97	67	94	80	92
EUS	100	57	94	100	94
FNA/FNB	100	100	100	100	100

EUS: Endoscopic ultrasonography; FNA/FNB: Fine needle aspiration/biopsy.

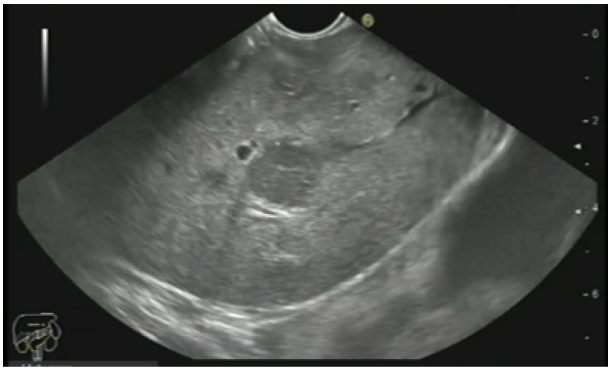

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Figure 1 Multiple hepatic focal lesions due to liver metastasis.

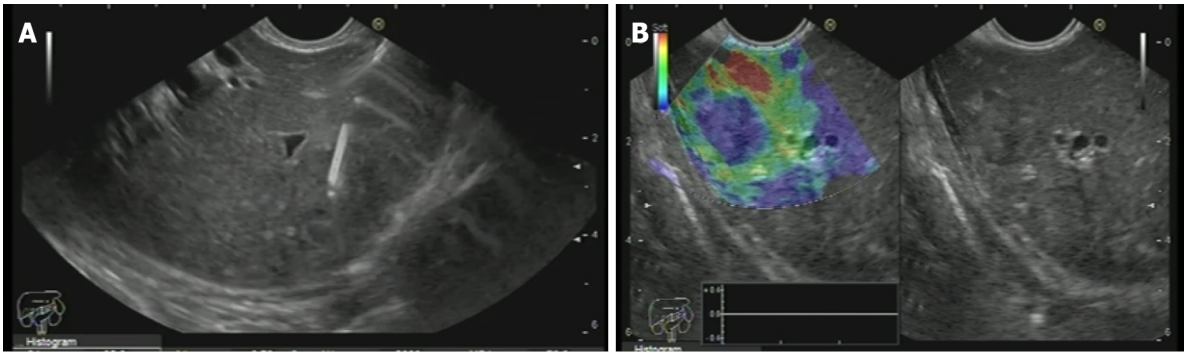

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Figure 2 A metastatic focal hepatic mass. A: Endoscopic ultrasound guided fine needle biopsy from hepatic focal lesion; B: A metastatic focal hepatic mass with grade 4 Elasticity score.

This study aimed to evaluate EUS and EUS-FNA/FNB's diagnostic efficacy in diagnosing liver lesions, whether benign or malignant, including primary and metastatic lesions.

In this study, EUS detected and sampled all HFLs, whereas 88.37% of patients had malignant lesions (liver metastasis) and 11.63% had benign ones. The mean elastographic strain ratio of the HFLs was 3.6 (0.7), and the mean size was 23.47 mm × 39.19 mm, with an average number of needles passing 1.49 (0.51). Finally, considering the cytopathological diagnosis of the biopsy, it proved malignant lesions in 81.4 percent of patients, while benign lesions were found in 18.6%. The eight benign lesions were six cholangitis abscesses and two benign-looking liver lesions. All benign-looking lesions were followed up with the disappearance of all cholangitis abscesses under antibiotic therapy, while the two benign liver nodules were constant in size over 6 mo. The other 35 malignant lesions were five primary hepatocellular carcinomas, one neuroendocrine tumor, and 29 liver metastatic lesions. This finding was consistent with Oh *et al*[11], who investigated the role of EUS-FNA in targeting right-sided liver masses and found that 39 (80.9%) of 47 patients were proven to have malignant lesions. The mean tumor size was 26 mm. The median number of needle passes was 3. On microscopic examination, tissue specimens obtained by EUS-FNA were determined to be adequate in 42 of 46 patients (91.3%). The pathological diagnosis was malignancy in 23 of 46 patients (50%), suspicious for malignancy in 6 patients (13%), atypical in 4 patients (8.7%), and negative for malignancy in 9 patients (19.6%).

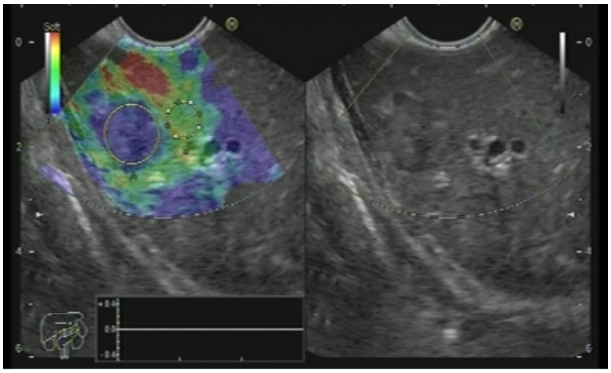

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Figure 3 A metastatic focal hepatic mass with high Strain ratio.

Another study by Chon *et al*[12] discussed the role of ELB in diagnosing solid liver lesions. The study included 58 patients (35 males and 23 females) with a mean age (68.0 ± 10.6 years). The mean size of the mass was 21.4 ± 9.16 mm × 11.5 ± 8.15 mm. The biopsy target site was the left lobe in 39 patients, the right lobe in 16 patients, and the caudate lobe in 3 patients. The number of trans-gastric and trans-duodenal route procedures was 39 (67.2%) and 19 (32.8%), respectively. The mean needle pass number was 2.6 ± 0.8, ranging from 1-5 per lesion. The final diagnosis was performed in 52 cases out of 58; all were malignant, either HCC or metastatic.

Adler *et al*[13] performed a multicenter retrospective review of 200 patients, specifically looking at safety and performance when sampling solid lesions. They reported excellent diagnostic yield at 98.5%; however, 6.5% of the patients needed a repeat procedure at some point. No adverse events were identified in the population.

In our study, EUS features were highly sensitive (100%) and less specific (57%) in diagnosing HFL, with an overall accuracy of 94%. Real-time elastography was also highly sensitive (97%) and less specific (67%) for diagnosing HFL; overall accuracy was 92%. EUS tissue acquisition was extremely sensitive (100%) and specific (100%), with an overall diagnostic accuracy of 100%.

Similarly, in 2019, Chon *et al*[12] stated that the diagnostic accuracy for EUS-FNB was 89.7%, but both specimen adequacy for histology, and available immunohistochemistry stain were 91.4%. The sensitivity and specificity of EUS-FNB were 89.7% and 100%, respectively[12].

Two recent meta-analyses reported that ELB and PC-LB are comparable in terms of safety and diagnostic performance [14,15]; however, ELB was more cost-effective than PC-LB regarding lower costs per patient and higher quality-adjusted life years[15].

EUS has the advantage of sampling and evaluating both lobes of the liver and small liver lesions that may have been missed by other non-invasive imaging modalities[16]. This accurately depicts liver histology and potentially addresses concerns about sampling error[17].

A further advantage of ELB over PC-LB was that it permitted more straightforward access to the right and left regions of the liver, thereby reducing the variability in diagnosis. Furthermore, ELB provided a much shorter recovery period (around 4 h) than PC-LB (usually a minimum of 10 h)[18].

In the Oh study, there were no statistical differences in the diagnostic accuracy of ELB between right and left lobe sites (25/28, 89.3% *vs* 13/14, 92.9%, $P = 0.86$), and none of the patients experienced procedure-related adverse events[18]. Similarly, no significant adverse events had been encountered in our study. Liver biopsy is very safe as liver is very near to the Echoendoscope. Also, if intrahepatic hematoma occurred, the blood will trickle to one of the portal or hepatic vessels, so the patient will bleed into its own circulation.

More recently, the meta-analysis by Zeng *et al*[15] suggests that the use of Acquire Franseen-tip needles may increase the ability to obtain more diagnostic samples than Sharkcore Fork-tip needles and that the use of FNB needles may be associated with a higher risk of adverse events than FNA needles[15].

Cholongitas *et al*[19] conducted a systematic review and meta-analysis of over 10000 percutaneous liver biopsies and found that an average of 7.5 core biopsy passes (CPT) and a target specimen length (TSL) of 17.7 mm were necessary for adequate pathological evaluation. However, when the biopsy was obtained through the transjugular route, adequacy was defined as 6.5 CPT and a TSL of 12 mm. While there is no established optimal definition of specimen adequacy for endoscopic ultrasound-guided liver biopsy (EUSLB), the American Association for the Study of Liver Diseases (AASLD) recommends a minimum of 11 CPTs as the definition of adequacy, regardless of the sampling route[19-22]. Additionally, the AASLD guideline suggests a TSL greater than 15 mm to define adequacy, with an ideal size of 30 mm. In this study, all routes of tissue sampling achieved at least 11 CPTs and a TSL greater than 15 mm. However, only EUSLB achieved the ideal TSL of 30 mm or more, which is considered optimal[23].

The study conducted by Ching-Companioni *et al*[24] demonstrated that endoscopic ultrasound-guided liver biopsy (EUS-LB) using a novel 19G FNB needle produced longer and less fragmented biopsy specimens compared to the standard 19G FNA needle. Furthermore, there was a reduced occurrence of specimen fragmentation during post-processing, and the yield of CPT was higher. These findings suggest that utilizing a 19G FNB needle represents an advancement over the conventional 19G FNA needle for EUS-LB[24].

In a prospective crossover randomized controlled trial, which is an appropriate model for assessing two types of tools, the researchers reached the conclusion that EUS-FNB is highly effective for solid liver masses. The newly developed antegrade-bevel needle demonstrated comparable efficacy and incidence of adverse events to the original reverse-bevel needle. However, the antegrade-bevel needles were able to obtain a larger amount of biopsy tissue compared to the reverse-bevel needles[25].

In a systematic review and meta-analysis examining the feasibility, safety, and usefulness of EUS-LB in patients undergoing parenchymal liver biopsy, the researchers found that the combined analysis of multiple studies demonstrated a significant diagnostic success rate of over 90%. This rate is similar to the diagnostic yield achieved by traditional PC-LB [26].

In another meta-analysis study, a comprehensive analysis was conducted on published studies examining the effectiveness and safety of EUS-LB for liver parenchymal diseases and focal liver lesions. The study assessed various outcomes including diagnostic yield, specimen adequacy, qualified specimens with the assistance of ROSE, and adverse events. The pooled analysis revealed that EUS-LB proved to be a highly effective and safe technique, with a successful pathological diagnosis rate of 95%, an adequate specimen rate of 84%, and an adverse events rate of 3%. Subgroup analyses were also performed, which indicated that Acquire Franseen-tip needles exhibited a higher diagnostic yield compared to SharkCore Fork-tip needles (99% *vs* 88%, $P = 0.047$). Moreover, FNB needles showed a higher risk of adverse events in comparison to FNA needles (6% *vs* 1%, $P = 0.028$). Interestingly, no significant differences were observed between 19 G and 22 G needles. Additionally, no significant disparities were identified between FNB and FNA needles in relation to our primary outcomes[15].

In order to improve the quality and accuracy of EUS, elastography has been developed, which allows the assessment of liver tissue firmness and the characterization of HFL. Real-time elastography showed high sensitivity (92.5%) and specificity (88.8%) with reasonable accuracy (88.6%) in a study by Sandulescu *et al*[27].

Innovations in needle technology and new approaches using ELB are in development, with the possibility of concomitant procedures such as EUS portal pressure gradient measurement, another emerging area in the field of endohepatology, in the coming years[8].

CONCLUSION

The diagnostic utility of EUS-LB with FNA/FNB was perfect and the best diagnostic tool for the definitive diagnosis of the HFLs. Furthermore, EUS features during the procedures provided an excellent and accurate prediction of the histological diagnosis, determining whether the lesion was benign or malignant.

ARTICLE HIGHLIGHTS

Research background

Endoscopic ultrasonography (EUS) has become an established method in diagnostic and therapeutic procedures in gastroenterology; however, it has recently gained a growing role in hepatology.

Research motivation

EUS tissue acquisition was highly sensitive (100%) and specific (100%), with an overall diagnostic accuracy of 100%.

Research objectives

This study aimed to evaluate the role of EUS features, strain elastography (SE), and EUS-tissue acquisition in diagnosing hepatic focal lesions (HFLs) that could affect further management.

Research methods

This cross-sectional study included 215 patients with pancreatic, biliary, or gastrointestinal malignancies referred for EUS examination. HFLs were identified in 43 patients (20%), and EUS-guided tissue acquisition was performed from these lesions.

Research results

EUS features were highly sensitive (100%) but much less specific (57%) in diagnosing HFLs; the overall accuracy was 94%. Real-time elastography was also very sensitive (97%) but less specific (67%) in diagnosing HFLs; however, the overall accuracy was 92%. EUS tissue acquisition was extremely sensitive (100%) and specific (100%), with 100% overall diagnostic accuracy.

Research conclusions

The diagnostic utility of EUS-guided tissue acquisition was extremely accurate in diagnosing HFLs. EUS characteristics and real-time SE accurately predicted the histological diagnosis of both benign and malignant HFLs.

Research perspectives

This cross-sectional study included 43 patients with HFLs among 215 pancreatic, biliary, or gastrointestinal malignant lesions referred for EUS examination. EUS tissue acquisition was highly sensitive (100%) and specific (100%), with an overall diagnostic accuracy of 100%.

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FOOTNOTES

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SYSTEMATIC REVIEWS

Post-COVID-19 cholangiopathy: Systematic review

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on global health, primarily characterized by severe respiratory illness. However, emerging evidence suggests that COVID-19 can also lead to secondary sclerosing cholangitis (SC), referred to as post-COVID-19 cholangiopathy.

AIM

To synthesize currently reported cases to assess the current state of knowledge on post-COVID-19 cholangiopathy.

METHODS

Medical Subject Headings and Health Sciences Descriptors were used to retrieve relevant studies, which were combined using Boolean operators. Searches were conducted on electronic databases including Scopus, Web of Science, and MEDLINE (PubMed). Studies published in English, Spanish, or Portuguese were included, with no restrictions on the publication date. Additionally, the reference lists of retrieved studies were manually searched. Simple descriptive analyses were used to summarize the results. Then the data were extracted and assessed based on Reference Citation Analysis (https://www.referencecitationanalysis.com/).

RESULTS

The initial search yielded a total of 192 articles. After screening, 85 articles were excluded due to duplication, leaving 107 articles for further review. Of these, 63 full-length articles met the inclusion criteria and were included in the analyses. Most of the patients were male and exhibited elevated liver function tests (93.8%). Magnetic resonance imaging revealed duct thickening with contrast enhancement (47.7%), as well as beading of the intrahepatic ducts (45.7%) with peribiliary contrast enhancement on diffusion (28.7%). Liver biopsy results confirmed SC in most cases (74.4%). Sixteen patients underwent liver transplantation, with three

experiencing successful outcomes.

CONCLUSION

Post-COVID-19 cholangiopathy is a serious condition that is expected to become increasingly concerning in the coming years, particularly considering long COVID syndromes. Although liver transplantation has been proposed as a potential treatment option, more research is necessary to establish its efficacy and explore other potential treatments.

Key Words: Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus 2; Cholangiopathy; Liver function tests; Liver transplantation

Core Tip: Post-coronavirus disease 2019 (COVID-19) cholangiopathy is a rare but serious complication that can occur after contracting COVID-19. It is characterized by inflammation and damage to the bile ducts. To better understand this condition and its treatment, we conducted a systematic review of post-COVID-19 cholangiopathy cases. Sixty-three articles met the inclusion criteria, representing 540 patients. Males over 50-years-old were more prone to this condition, which is often accompanied by elevated liver function, bile duct thickening, and kidney failure after prolonged use of mechanical ventilation. Further research is needed to confirm the effectiveness of liver transplantation in treating post-COVID-19 cholangiopathy.

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INTRODUCTION

On March 2020, the World Health Organization declared a global health pandemic after the first case was recognized on December 2019 in Wuhan City, China, of what was called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. This led to catastrophic events in the world resulting in more than 6 million deaths globally. The pandemic has led to a great financial and humanitarian loss due to prolonged lockdowns, which have had a tragic effect on the global economy[2].

Also, coronavirus disease 2019 (COVID-19) keeps enduring second and third waves of outbreaks in many countries, probably caused by mutant new variants of the virus[2]. Despite the accelerated speed of vaccine development for the prevention of COVID-19 to control the disease and robust mass vaccination worldwide including booster doses, these new SARS-CoV-2 variants threaten the progress made so far with the purpose of controlling the spread of the disease[2, 3].

Respiratory symptoms are the most common manifestation of the disease, which range from mild to severe and may include fever, dry cough, shortness of breath, anosmia, ageusia, and fatigue[4]. It may lead to viral pneumonia with severe complications such as acute respiratory failure, acute respiratory distress syndrome requiring intubation, mechanical ventilation (MV), and intensive care management[5,6].

In addition to respiratory symptoms, COVID-19 might also cause a range of extrapulmonary manifestations including cardiovascular, neurological, and renal complications[7]. Gastrointestinal symptoms, including diarrhea, nausea, and vomiting, are also commonly reported[8]. Post-COVID-19, derangement of liver enzymes is a potential complication observed in admitted COVID-19 patients, with a prevalence ranging from 14% to 83%[9]. Other liver-related conditions such as autoimmune hepatitis, vascular thrombosis, and hemophagocytic lymphohistiocytosis have also been associated with the post-COVID-19 period[9,10].

However, one emerging complication of COVID-19 is post-COVID-19 cholangiopathy (PCC), a novel clinical entity characterized by inflammation and damage to the bile ducts in individuals who have recovered from COVID-19 infection [11]. The clinical presentation of PCC can vary, but common symptoms may include abdominal pain, fever, and jaundice [12]. PCC has been observed in patients without a history of prior liver disease. This condition can manifest in various clinical settings, such as in individuals with severe COVID-19 infection requiring MV, as well as in those experiencing milder forms of the disease[5,13]. The prevalence of PCC is not well understood, and it is not clear if it is more common in certain patient populations. Some researchers have suggested a potential association between certain drugs, including immunomodulator agents, ketamine, and antiviral medications, and the development of PCC. However, the available evidence regarding these drugs causing cholangiopathy remains insufficient[9].

This systematic review comprehensively analyzes and synthesizes the existing evidence pertaining to PCC. The primary objective is to explore the clinical presentation and management approaches documented in the available cases reported in the literature. By conducting this review, we provide a comprehensive overview of the current understanding

and knowledge gaps surrounding PCC, which can contribute to the development of effective strategies for diagnosis and treatment in clinical practice.

MATERIALS AND METHODS

Study design

This study was conducted in accordance with the guidelines for preferred reporting items for systematic reviews and meta-analyses (PRISMA) protocol guidelines[14].

Data sources

The studies included in this review were identified using the search strategy: in ("COVID-19" OR "SARS-COV-2") AND ("cholangiopathy" OR "cholangitis" OR "liver transplantation"). This search command was run on the electronic databases Scopus, Web of Science, and Medline (PubMed). Languages were restricted to English, Spanish, and Portuguese. There was no date of publication restrictions. The reference lists of the retrieved studies were also manually searched. The databases were searched in March 2023. Reference Citation Analysis (https://www.referencecitationanalysis.com/) was used to supplement the search.

Inclusion and exclusion criteria

Inclusion criteria were clinical case reports or case series of post-COVID cholangiopathy. Studies needed to include detailed information about the clinical presentation, diagnosis, management, and outcomes. Articles unrelated to the topic were excluded as were those that did not provide sufficient detail about the cases. If there was more than one study published using the same case, the variables were complemented with both articles. Studies published only as abstracts were included, as long as the available data made data collection possible.

Study selection and data extraction

A comprehensive search of various databases was conducted using the search terms listed in the COVID-19, cholangitis, and liver transplantation ("COVID-19" OR "SARS-COV-2") AND ("cholangiopathy" OR "cholangitis" OR "liver transplantation"). The initial screening process involved reviewing titles and abstracts to identify potentially relevant studies. These studies were then analyzed in full, and some were excluded due to a lack of clinical information. Two reviewers independently extracted data from eligible studies using a standardized form and assessed the characteristics of the subjects and outcomes measured. Any discrepancies in study selection or data extraction were resolved by a third party.

Data collection

Variables included were age, sex, clinical presentation, liver function tests, renal function test, imaging findings, histopathology, whether or not the patient had undergone orthotopic liver transplantation (OLT), and outcome.

Data processing and analysis

Data were analyzed and summarized using descriptive techniques such as frequency, means, and median. The analyses were performed using Microsoft Excel 2010.

RESULTS

The search strategy retrieved 192 articles; 85 articles were excluded because they were duplicates and 107 articles were screened in the review. A total of 88 full-length articles were included and retrieved, of which 63 were included in the review. The PRISMA flowchart illustrating the search strategy is shown in Figure 1. Studies reviewed were either a case report or a case series.

This systematic review included a total of 540 patients, of whom 69 (12.7%) were male, 26 (4.8%) were female, and 445 (82.5%) did not note their sex. The majority of patients (66, 12.2%) were over 50-years-old. Almost all patients (93.8%) had elevated liver enzymes in the acute phase, with an increase of these levels in the chronic phase. Total bilirubin was elevated in 343 patients (63.5%), while only 80 (14.8%) had levels lower than 1.2 mg/dL. Data on bilirubin levels were not reported for 19 cases. Levels of alkaline phosphatase were high among 488 patients (90.3%) and gamma-glutamyl transferase were consistently elevated, often surpassing 1000 U/L.

In this study, based on imaging findings, 225 of 540 (41.6%) patients had biliary ductal dilatation with fibrosis on ultrasound, while 50 (9.2%) patients did not show any alteration. Furthermore, according to magnetic resonance imaging (MRI) results, 258 (47.7%) patients had bile duct thickening with contrast enhancement, 247 (45.7%) had beading of the intrahepatic ducts, and 155 (28.7%) had peribiliary enhancement on diffusion.

Moreover, 223 (41.3%) patients with PCC had respiratory failure type 2, which was characterized by acute respiratory distress syndrome (ARDS). Some of these patients underwent bilateral lung transplantation, but unfortunately 1 patient died. Additionally, 355 patients (65.7%) had acute renal injury that required either dialysis or renal transplantation after OLT. Data on renal function were not reported for 16 patients. According to liver biopsy results, 402 patients (74.4%) had

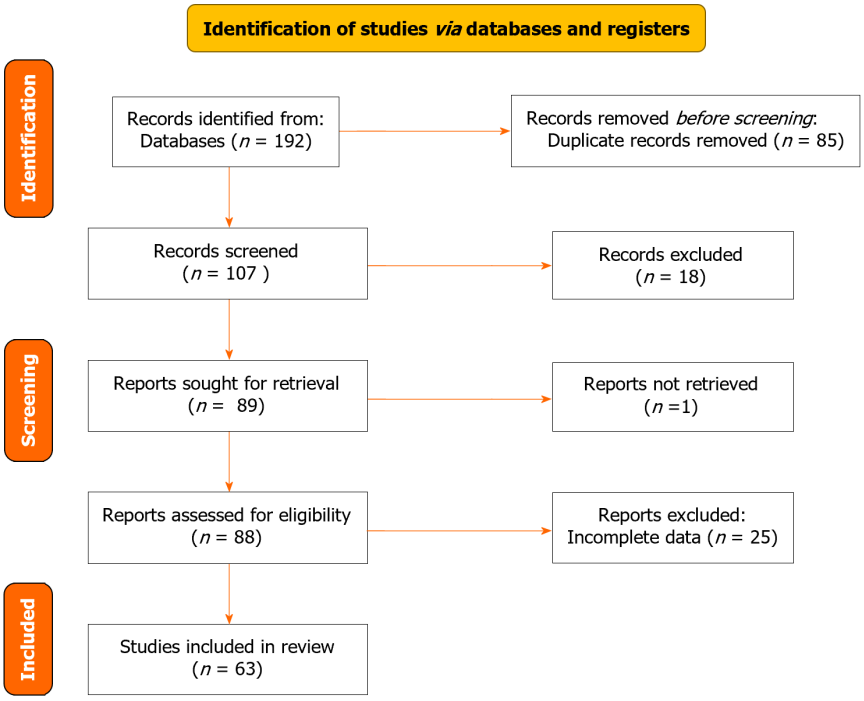

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Figure 1 The preferred reporting items for systematic reviews and meta-analyses flowchart for the systematic review.

sclerosing cholangitis (SC). Moreover, 16 patients (2.96%) with post-COVID-19 cholangitis underwent OLT. Of these, 15 patients experienced successful outcomes, with an improvement in liver enzyme levels post-transplantation.

DISCUSSION

After the first of case of SARS-CoV-2 disease in 2019[1], a novel clinical entity emerged. This condition has been reported in a small number of patients who have recovered from the virus and is characterized by elevated liver enzymes, biliary ductal dilatation on imaging, and histopathological findings of secondary SC (SSC)[11]. This systematic review examined the clinical presentations and outcomes of 540 patients with PCC, a rare complication of COVID-19 that affects the biliary system.

It is important to consider the differential diagnosis, as other diseases may present with a similar presentation[15]. Ketamine-induced cholangiopathy can lead to fusiform dilatation of the common bile ducts, without evidence of extrinsic or intrinsic obstruction[16]. The severity depends on the duration of using ketamine, and it is reversible in abstinent patients. Another difference is ischemic cholangitis, which occurs as a consequence of deficient blood flow to the bile duct wall[17]. This can affect the bile ducts leading to segmental strictures and cholangiectasis, resulting in mechanical restriction of bile acid flow.

SC is a medical condition characterized by the destruction of bile ducts due to inflammation and fibrosis and severe progressive stenosis of the bile tracts including three types: primary SC (PSC); immunoglobulin G-related SC (IgG-SC); and secondary cholangitis such as bacterial cholangitis, viral cholangitis (cytomegalovirus), postoperative biliary stenosis, and choledocholithiasis. Usually the patients present with similar cholestatic features such as itching and jaundice, and blood tests reveal high cholestatic enzymes[18,19]. Although the clinical presentation of PSC and IgG4-SC are nearly the same, they differ in treatment response, outcomes and comorbidities, and how to differentiate it from cholangiocarcinoma[18,19]. The difference between them is that IgG4-SC patients respond actively to prednisolone and steroid therapy, whereas PSC has no standard treatment approved; only ursodeoxycholic acid can be used in some patients, but it does not improve the overall prognosis[18-21].

Distinguishing and differentiating between PSC-high IgG and IgG-SC is challenging. A promising study that calculated serum IgG4:IgG1 ratios showed excellent specificity in distinguishing IgG4-SC from PSC-high IgG4[18,19]. The most common diagnostic test for PSC is cholangiography, which shows a pruned tree appearance, beaded ducts, and band-like stricture; thus, endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography is highly recommended. PSC is also highly associated with inflammatory bowel disease (ulcerative colitis more than Crohn's disease); thus, a colonoscopy is recommended for the diagnosis, which increases the risk of cholangiocarcinoma and gallbladder carcinoma[18,19]. Therefore, more studies are required on the diagnostic procedures of PSC, IgG4-SC, and cholangiocarcinoma and their treatment and management[18,19].

The present results on PCC showed that most patients are male (12.7%) older than 50-years-old, consistent with the previous literature[9]. Every patient had elevated liver enzymes in the acute phase, and their levels increased in chronic

Table 1 Baseline features in 540 patients with post-COVID-19 cholangiopathy, *n* (%)

Variable	Patients, *n* = 540 (100)
Sex	
Male	69 (12.7)
Female	26 (4.8)
Age > 50 year	66 (12.2)
Liver enzymes	
High (> 45)	507 (93.8)
Total bilirubin	
High (> 1.2 mg/dL)	343 (63.5)
Alkaline phosphatase	
High (> 147 IU/L)	488 (90.3)
Ultrasound findings	
Biliary ductal dilatation with fibrosis	225 (41.6)
MRI Findings	
Bile duct thickening and enhancement	258 (47.7)
Beading of intrahepatic ducts	247 (45.7)
Peribiliary diffusion	155 (28.7)
Histopathology with secondary sclerosing cholangitis	402 (74.4)
Orthotopic liver transplantation	16 (2.96)

COVID-19: Coronavirus disease 2019; MRI: Magnetic resonance imaging.

phase if left untreated.

Also, ultrasound findings showed that 225 patients (41.6%) presented with biliary ductal dilatation. The MRI findings in this systematic review showed that only a small number of patients (28.7%) had peribiliary enhancement on diffusion, while a larger number of patients (47.7%) had bile duct thickening and enhancement, and 247 patients (45.7%) had beading of the intrahepatic ducts. By contrast, a previous retrospective study by Faruqui *et al*[13] showed that a higher proportion of patients (11/12, 92%) had beading of the intrahepatic ducts, 7/12 (58%) had bile duct wall thickening with enhancement, and 10/12 (83%) had peribiliary diffusion high signal[11]. Details can be found in Table 1 and Table 2.

PCC appears to have different histologic characteristics compared to SSC in critically ill patients caused by other factors. Biopsy samples from patients with PCC show extensive degeneration and injury of cholangiocytes, as well as unique microvascular features such as swelling of hepatic artery endothelial cells, phlebitis in the portal vein, and sinusoidal obstruction syndrome[5]. Several studies have suggested that COVID-19 cholangiopathy is the result of progressive paucity of bile ducts; however, the exact pathophysiology is not well known[11]. Our histopathology biopsy results showed SSC in 402 patients (74.4%).

On the other hand, PCC presentation is difficult to treat, and sometimes requires OLT[5,6,21]. Almost all patients presented with respiratory failure type 2 as they had ARDS, and 1 patient had bilateral lung transplant and unfortunately died. Every patient presented with acute kidney injury, which required either dialysis or renal transplantation post OLT. As described in the literature, PCC is often accompanied by respiratory failure and acute renal injury[22-25]. Also, some cases of biliary casts have been described, removed *via* ERCP. The diagnosis and management of post-COVID 19 cholangiopathy requires an ERCP, especially in the presence of a dilated choledocus in imaging studies[9,26].

Also, 16 patients (2.96%) underwent OLT, which can be a viable treatment option for this condition[5,27]. One of these cases was reported by Durazo *et al*[5], which comprised SSC in a 47-year-old patient who was recovering from severe acute respiratory distress syndrome caused by COVID-19 infection. He was admitted to the intensive care unit for prolonged MV (29 d) and was listed for liver transplantation with a model for end-stage hepatic disease score of 37. On day 108 from his presentation, the patient underwent successful OLT with a whole liver allograft from a deceased donor.

CONCLUSION

In conclusion, this paper presents an extensive review of post-COVID-19 cholangiopathy published in medical journals. Our analysis indicates that post-COVID-19 cholangiopathy is a serious systemic illness that can affect the liver in addition to the lungs. Most cases were found in males over 50-years-old, and patients with cholangiopathy exhibited elevated liver

Table 2 Summary of systemically reviewed clinical cases

Ref.	Age, yr	Sex	Clinical presentation	Elevated liver enzyme	U/S findings	MRI findings	Respiratory failure	Renal failure	Histopathology	OLT	Outcome
Roth *et al* [28], 2021	38	Male	Post-COVID-19 cholangiopathy	Yes	Intrahepatic bile ducts beading, with sub-segmental strictures and dilatation	Beading of intrahepatic ducts	Yes, required MV; On supplemental oxygen, then off on day 63 and decannulated	Yes, recovered	Portal tract findings; Mild duct paucity, moderate bile duct swelling & reaction; Mild portal tract inflammation; Endothelial hepatic artery swelling; Portal veins with focal endo phlebitis	Not done	Recovered
	25	Male	Post-COVID-19 cholangiopathy	Yes	Hepatomegaly, extrahepatic bile duct dilatation, intrahepatic bile duct dilatation	Beading of intrahepatic ducts	Yes, required MV; On supplemental oxygen, then off on day 112 and decannulated	Yes, recovered	Portal tract findings; Moderate duct paucity, moderate bile duct swelling & reaction. Moderate portal tract inflammation; Endothelial hepatic artery swelling; Portal veins with focal endo phlebitis	Not done	Recovered
	40	Female	Post-COVID-19 cholangiopathy	Yes	Hepatomegaly, no dilatation	Peribiliary diffusion, moderate portal and periportal fibrosis	Yes, remains with tracheostomy & MV, and then off MV on day 63	Yes, recovered	Portal tract findings; Moderate duct paucity, moderate bile duct swelling & reaction; Severe portal tract inflammation; Endothelial hepatic artery swelling; Portal veins with focal endo phlebitis	Not done	Death, cardiac arrest
Faruqui *et al* [13], 2021	Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	U/S showed; extrahepatic bile duct dilatation and intrahepatic bile duct dilatation and periportal diffusion	MRI showed, beading of intrahepatic ducts (11/12, 92%); Peribiliary diffusion (10/12, 83%); Bile duct wall thickening (7/12, 58%)	Patients required MV	Yes, recovered	Large duct obstruction without clear bile duct loss	Done OLT	Had t successful recovery and rapid clinical improvement
	Mean age 58	Female	Post-COVID-19 cholangiopathy	Yes	Experiencing persistent	Beading of intrahepatic ducts;	Patients required MV	Yes, recovered	Large duct obstruction without	Highly recommended	Recovery with long-term

				jaundice, hepatic insufficiency, and/or recurrent bacterial cholangitis	Peribiliary diffusion; Bile duct wall thickening			clear bile duct loss	for OLT. Patient on transplantation waiting list, still not done OLT at time of study	liability and comorbidity
Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	Experiencing persistent jaundice, hepatic insufficiency, and/or recurrent bacterial cholangitis	Beading of intrahepatic ducts; Peribiliary diffusion; Bile duct wall thickening	Patients required MV	Yes, recovered	Large duct obstruction without clear bile duct loss	Highly recommended for OLT. Patient on transplantation waiting list, still not done OLT at time of study	Recovery with long-term liability and comorbidity
Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	Experiencing persistent jaundice, hepatic insufficiency, and/or recurrent bacterial cholangitis	Beading of intrahepatic ducts; Peribiliary diffusion; Bile duct wall thickening	Patients required MV	Yes, recovered	Large duct obstruction without clear bile duct loss	Highly recommended for OLT. Patient on transplantation waiting list, still not done OLT at time of study	Recovery with long-term liability and comorbidity
Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	Experiencing persistent jaundice, hepatic insufficiency, and/or recurrent bacterial cholangitis	Beading of intrahepatic ducts; Peribiliary diffusion; Bile duct wall thickening	Patients required MV	Yes, recovered	Secondary sclerosing cholangitis	Highly recommended for OLT, patient on transplantation waiting list, still not done OLT at time of study	Recovery with long-term liability and comorbidity
Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	Intrahepatic bile duct dilatation and periportal diffusion	Beading of intrahepatic ducts; Peribiliary diffusion; Bile duct wall thickening	Patients required MV	Yes, recovered	Secondary sclerosing cholangitis	OLT Not done	Recovery with long-term liability and comorbidity
Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	Intrahepatic bile duct dilatation and periportal diffusion	Beading of intrahepatic ducts; Peribiliary diffusion; Bile duct wall thickening	Patients required MV	Yes, recovered	Secondary sclerosing cholangitis	OLT Not done	Recovery with long-term liability and comorbidity
Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	Intrahepatic bile duct dilatation and periportal	Beading of intrahepatic ducts; Peribiliary diffusion	Patients required MV	Yes, recovered	Secondary sclerosing cholangitis	OLT Not done	Recovery with long-term liability and comorbidity

					diffusion						
	Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	Intrahepatic bile duct dilatation and periportal diffusion	Beading of intrahepatic ducts; Peribiliary diffusion	Patients required MV	Yes, recovered	Secondary sclerosing cholangitis	OLT Not done	Recovery with long-term liability and comorbidity
	Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	Intrahepatic bile duct dilatation and periportal diffusion	Beading of intrahepatic ducts; Peribiliary diffusion	Patients required MV	Yes, recovered	Secondary sclerosing cholangitis	OLT Not done	Recovery with long-term liability and comorbidity
	Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	Intrahepatic bile duct dilatation and periportal diffusion	Beading of intrahepatic ducts	Patients required MV	Yes, recovered	Secondary sclerosing cholangitis	OLT Not done	Recovery with long-term liability and comorbidity
	Mean age 58	Male	Post-COVID-19 cholangiopathy	Yes	Intrahepatic bile duct dilatation and periportal diffusion	MRI not available	Patients required MV	Yes, recovered	Secondary sclerosing cholangitis	OLT Not done	Recovery with long-term liability and comorbidity
Li *et al*[29], 2022	N/A	Two sample mendelian randomization	The autoimmune diseases showed not associated with COVID-19 infection	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hunyady *et al*[30], 2023	N/A	24 Patients	Post-COVID-19 cholangiopathy developed after a median of 91 d	Yes	N/A	N/A	Patients required MV, the median was 48 d among all patients	N/A	COVID-SSC and CIP-SSC share the same clinical phenotype	N/A	UDCA showed great improvement in patients without liver cirrhosis and reduced severity in patients with liver cirrhosis, while OLT showed significant improvement in patient with liver cirrhosis
Weaver *et al*[31], 2021	63	Male	Post-COVID-19 cholangiopathy	Yes	Sludge in the gallbladder, no biliary ductal dilation, and patent vasculature	N/A	Patients required MV	N/A	Filling defects in the common bile duct as well as an irregular and beaded appearance of the intrahepatic ducts	Not done	Recovered, after ERCP sphincterotomy followed by balloon sweep of the biliary ducts and removal of thick stone

Hartl *et al* [32], 2022	N/A	N/A	Post-COVID-19 cholangiopathy (65 patients with CLD of 496 patients included in the study, around 24.6% non-ACLD *vs* ACLD 10.6% associated with COVID	Yes. Alkaline phosphatase showed (pre: 91.0 *vs* T1: 121.0 *vs* last: 175.0 U/L) and gamma glutamyl transferase GGT (pre: 95.0 *vs* T1: 135.0 *vs* last: 202.0 U/L)	N/A	N/A	N/A	N/A	20% of patients with CLD developed progressive cholestasis post-COVID-19 cholangiopathy, and patients with NASH/NAFLD also have a risk of developing cholestatic liver failure and secondary sclerosing cholangitis post-COVID-19	N/A	N/A
Duengelhoef *et al*[33], 2022	N/A	N/A	Post-COVID-19 cholangiopathy, associated more with Autoimmune hepatitis AIH as well as post COVID vaccine than PBC and PSC patients	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A
John *et al* [34], 2023	N/A	N/A	Post-COVID -19 cholangiopathy study included 1607 patients with liver cirrhosis used UDCA	Yes	N/A	N/A	N/A	N/A	N/A	N/A	UDCA showed great improvement in patients with liver cirrhosis, by decreased symptoms and decreased COVID-19 infection
Heucke *et al* [35], 2022	N/A	48	Post-COVID-19 cholangiopathy 13% from 496 patients developed CLD; 23% of patients with CLD developed cholestasis/cholangiopathy	Yes (ALT & AST were elevated in 50 patients less than 5 times upper limit of normal. While in late-stage alkaline phosphatase and GGT were highly progressively elevated	N/A	N/A	Yes, require oxygen supply & some patients MV	Yes, some patients required dialysis for renal failure	The histopathology reported SARS-CoV-2 RNA and/or proteins in human liver tissue and bile samples, this SARS-CoV-2 RNA may lead to provoke a strong proinflammatory cytokine response (TNF, IL□1, IL□6) with hypercoagulation, endothelial damage, consecutive venous and arterial	9 patients listed for OLT and 6 patients done OLT with good recovery	16 patients died, and 24 patients were treated with ketamine during the acute phase of COVID-19 and around 28 patients with SSC from 48 were reduced after using UDCA treatment

									embolism, as well as secondary parenchymal damage		
Bazerbachi *et al*[36], 2022	56	Female	Post-COVID-19 cholangiopathy	Yes alkaline phosphatase 1574U/L, total bilirubin 11 mg/dL, ALT 88 U/L, AST 101 U/L	EUS showed a left hepatic duct stricture and heterogenous, non-shadowing cylindric objects in the main bile duct	N/A	Yes, require tracheostomy & MV	Yes, developed renal failure and required hemodialysis	LHD stricture with upstream dilation of the left ducts, and obliteration of right intrahepatic with secondary sclerosing changes	Not done	Improved, casts were swept and removed, and left lobe was stented with a 10 Fr 20 cm plastic stent improving bilirubin level to a baseline of 3 mg/dL
Cho *et al*[37], 2022	47	Female	Post-COVID-19 cholangiopathy	Yes, highly elevated ALP-positive ANA, anti-mitochondrial highly positive	N/A	N/A	N/A	N/A	N/A	N/A	Post-COVID-19 cholangiopathy may be due to direct cytotoxicity from SARS-CoV-2 active replication, hypoxia induced respiratory failure, drug induced liver injury, vascular coagulopathy, immune mediated liver damage
	57	Male	Post-COVID-19 cholangiopathy	Yes, hypogammaglobinemia, high GGT, elevated AST/ALT, positive anti-mitochondrial antibody, anti-smooth muscle antibodies, and anti-double stranded DNA antibodies	N/A	N/A	N/A	N/A	N/A	OLT Considered for some patients	
	N/A	N/A	Post-COVID-19 cholangiopathy	Yes, ALP > three times	N/A	MRCP showed dilatation of hepatic ducts with stenosis and beading of intrahepatic ducts	N/A	N/A	N/A		
	N/A	24 Patients	Post COVID-19 Cholangiopathy	Yes	N/A	N/A	N/A	N/A	N/A		
Yu *et al*[38], 2022	N/A	N/A	Post-COVID-19 cholangiopathy	Yes	N/A	N/A	N/A	N/A	N/A	N/A	The patients are not only related to liver disease, but also cholangitis may be due to viral cholangitis, systemic inflammation response, and hypoxic liver injury
Sanders *et al*	57	Male	Post-COVID-19 cholan-	Yes	Dilated CBD	N/A	Yes, required	Renal	N/A	N/A	Improved,

[39], 2021			giopathy		with a distal CBD stone		MV. (Tracheostomy & gastrostomy)	impairment required fluid resuscitation			biliary cast removed by ERCP, and bile duct stent and patient referred for cholecystectomy
López Romero-Salazar *et al* [40], 2022	76	Male	Post-COVID-19 cholan-giopathy	Yes, elevated ALT & AST developed AIH and complicated to liver cirrhosis secondary to primary biliary cholangitis (PBC) igg positive, ANA	U/S showed hepatic fibrotic inflammation, dilated lobes, and biliary ducts	N/A	N/A	N/A	Biopsy showed lobular hepatitis, with intense interface, centrilobular necrosis with lymphoplasmacytic inflammation	N/A	The patient has poor prognosis due to liver cirrhosis, the study emphasizes the hypothesis that AIH induced due to or post COVID-19 vaccination. Patient given UDCA and obeticholic acid
Wall *et al* [41], 2022	N/A	N/A	Post-COVID-19 cholan-giopathy	Yes	N/A	N/A	N/A	N/A	N/A	N/A	The study showed to avoid using SARS-CoV-2-positive donors for liver transplantation unless there is a justifying indicator such as recipient illness severity
Ghafoor *et al* [42], 2022	Mean Age 60.5	15 Male patients	Post-COVID-19 cholan-giopathy	Yes	N/A	All patients had intrahepatic bile duct strictures and 10 patients had associated upstream dilatation. Fourteen patients showed intrahepatic bile duct beading. One patient had extrahepatic bile duct structuring; 9 patients showed high signal on T2 and diffusion weighted images & 7 patients showed	N/A	N/A	N/A	N/A	The post-COVID-19 cholangiopathy patients showed on MRI/MRCP multiple intrahepatic bile duct strictures with intrahepatic bile duct beading

						patchy arterial phase hyperenhancement; 2 patients showed biliary casts. Vascular complication, and periportal lymphadenopathy were not seen on MRI/MRCP					
Singh *et al* [43], 2021	57	Male	Post-COVID-19 cholangiopathy	Yes, elevated ALT, AST, GGT, hypergammaglobulinemia and anti-mitochondrial antibody, anti-smooth muscle antibody and anti-double stranded DNA antibodies	N/A	N/A	N/A	N/A	N/A	N/A	The patient diagnosed with auto immune hepatitis with primary biliary cholangitis overlap syndrome triggered by COVID-19
Seifert *et al* [44], 2023	N/A	7 patients (3 males & 4 females)	Post-COVID-19 cholangiopathy among 7 patients of 544 patients with cholangitis. 4 patients had SSC due to other reasons	Yes, elevated GGT, Alkaline phosphatase ALP among 7 patients more than 4 patients non COVID-19	N/A	N/A	N/A	N/A	N/A	N/A	The 7 patients with post-COVID-19 cholangiopathy showed more hepatitis and cholangitis than other group non-COVID cholangitis most probably due to direct cytopathologic effect of COVID virus
Lee *et al*[45], 2021	64	Male	Post-COVID-19 cholangiopathy	Yes	U/S intrahepatic bile ducts loss	MRI not available	Required MV	Yes, Recovered	Diffuse hepatic injury, onion skinning of the bile ducts and bile duct loss in scattered portal tracts	OLT not done; patient need to be stable for the operation	Not recovered
Cunha-Silva *et al*[46], 2023	45	Male	Post-COVID-19 cholangiopathy	Yes, elevated in the first 2-wk AST, ALT, GGT, Alkaline phosphatase post SARS-CoV-2 infection: ANA and anti-smooth muscle-positive. Negative viral hepatitis & anti-mitochondrial antibodies	N/A	No dilatation of biliary ducts	N/A	AKI after recovering 2 wk from COVID-19	Numerous foci of lobular necrosis but with no ductopenia or portal biliary reaction. After 2 mo: Biopsy showed: extensive areas of confluent necrosis,	N/A	The patient is given prednisolone in the first phase, then after 2 mo added azathioprine and UDCA to management

									hepatocytes regenerating into pseudorosettes and numerous plasma cells, non-suppurative cholangitis all these features diagnosed by PARIS Criteria as AIH-PBC-OS		and showed great response and recovery
Hamid *et al* [47], 2021	N/A	N/A	Post-COVID-19 cholangiopathy	Yes, elevated AST, ALT, low albumin, and low platelet	N/A	N/A	N/A	N/A	Endoscopy and ERCP are recommended by WGO	N/A	OLT is advised to be postposed till SARS-CoV-2 infection treated and patient recovered
Kroepfl *et al* [48]	N/A	2 patients	Post-COVID-19; cholangiopathy	Yes	N/A	N/A	N/A	N/A	ERCP biopsy showed severely destructed biliary mucosa with ischemia and epithelial roughness	N/A	N/A, early cholangioscopy can confirm the diagnosis
Mayorquín-Aguilar *et al* [24]	3 Cases 45 52 46	 Male Male Female	Post-COVID-19 cholangiopathy	Yes	Not available	Mild intrahepatic; Biliary ductal; Dilatation with; Multifocal strictures or; Beading without; Extrahepatic biliary; Dilatation	Yes, required MV	Yes, recovered	SSC-CIP beading of intrahepatic ducts, bile duct wall thickening with enhancement, and peribiliary diffusion high signal	2 Done OLT, 1 Not done	2 males death; 1 female recovered
Graciolli *et al* [49]	63	Male	Post-COVID-19 cholangiopathy	Yes	Not available	Dilations with intercalated stenotic segments in intra and extrahepatic bile ducts and edema of the bile ducts corresponding to inflammation of the adjacent parenchyma	Yes	Not available	Intrahepatocellular cholestasis	Not done	Death, infected ulcer, palliative care
Keta-Cov research group[50]	Median Age 59 (35-65)	Male Male Male Female	Post-COVID-19 cholangiopathy	Yes, elevated AST, ALTGGT, ALP, total bilirubin all elevated	N/A	Aspects of sclerosing cholangitis, with strictures and dilatations of intrahepatic bile ducts, peribiliary	All patients required M/V	All patients developed acute kidney injury required renal replacement therapy	ERCP showed filling defects in the common bile duct and rarefication of the intrahepatic biliary tract and biopsy showed	N/A	Intravenous ketamine is dose dependant and used for maintenance sedation of patients required

Zdanowicz *et al*[51], 2022	Paediatric patient	Female	Post-COVID-19 cholangiopathy	Yes	N/A	cysts and multiple biliary casts	N/A	N/A	biliary obstructions, including cholangiolar proliferation, biliary plugs, portal inflammation with neutrophil infiltrates, extensive biliary fibrosis and cirrhosis	N/A	M/V for acute respiratory distress syndrome ARDS, and showed associated with biliary obstructions, cholestatic liver injury, biliary cirrhosis, and end-stage liver disease, that's the reason the new guidelines is not recommend ketamine especially if prolonged or at higher dose
Schwarz *et al* [52], 2022	N/A	Male	Post-COVID-19 cholangiopathy	Yes, GGT is elevated in 15 patients with SSC-CIP after lung transplantation out of 40 patients in the study. ALP is elevated after lung transplant	N/A	N/A	15 patients out of 40 developed SSC-CIP underwent lung transplant	N/A	N/A	N/A	Patient developed autoimmune hepatobiliary diseases, autoimmune sclerosing cholangitis ASC which required long-term liver function monitoring
Keskin *et al* [53], 2022	N/A	15 patients	Post-COVID-19 cholangiopathy	Yes	N/A	N/A	N/A	N/A	N/A	N/A	GGT showed to be a sensitive parameter to predict severity in SSC-CIP
Bartoli *et al* [54], 2021	44	32 patients	Post-COVID-19 cholangiopathy	Yes, AST, ALT elevated and GGT, ALP elevated more ANA positive, anti-mitochondrial-positive, anti-smooth muscle negative	U/S showed slightly enlarged liver with moderate steatosis and a mildly enlarged spleen	N/A	Yes, required intubation and MV	N/A	N/A	Not done	Technical problems with ECRP were more common in biliary patients with delay group than in those without delay, while 7 pancreatic patients showed

											no difference in ERCP with or without delay of intervention. Technical issues considered such as abundant stone sludge in bile duct, stent migration, *etc*
Ferreira *et al* [55], 2022	N/A	Female	Post-COVID-19 cholangiopathy	Yes	N/A	N/A	N/A	N/A	Florid ductal lesions, moderate peri-portal fibrosis, portal chronic inflammatory infiltrate	N/A	Patient treated with UDCA and discharged and breathing normally, also treated from Guillain barre syndrome GBS by intravenous immunoglobulin
		4 cases				N/A			ERCP showed beaded appearance of intrahepatic bile ducts and bile casts		One patient undergone stone removal, and one patient complicate with liver cirrhosis, the other two progressed to advanced chronic liver disease
Bütikofer *et al*[56], 2021	N/A	20 Cases	Post-COVID-19 cholangiopathy	Yes 9 patients with severe cholestasis 11 patients with mild cholestasis	N/A	N/A	N/A	N/A	Ischemic changes to the perihilar bile ducts	N/A	SSC is more common and severe in critically COVID-19 patients, with prolonged ICU period
Zafar *et al* [57], 2022	N/A	2 Cases	Post-COVID-19 cholangiopathy	Yes	N/A	N/A	N/A	N/A	N/A	N/A	Both patients developed SSC post-COVID-19 vaccination, which lead to hepatitis and eventually cholangitis
Otani *et al* [58], 2022	N/A	N/A	Post-COVID-19 cholangiopathy in some cases of	Yes	N/A	N/A	N/A	N/A	N/A	N/A	166 cases for endoscopic

			166 cases								procedures for causes; Cholangitis, GI bleeding, Obstructive jaundice, neoplasia, COVID-19 led to delay in endoscopic procedures which led to delayed diagnosis of cholangitis, cancers, *etc*.
Cesar Machado *et al*[59], 2022	66	Male	Post-COVID-19 cholangiopathy	Yes	Ultrasound showed slight hepatomegaly and no bile duct dilatation	MRI showed biliary cast, also revealed. Diffuse irregularity of intra- and extrahepatic bile ducts, with multiple focal strictures alternating with mild focal dilations of the biliary tree, suggesting a sclerosing cholangiopathy	Yes, required MV	Yes, required haemodialysis	Biopsy showed a prominent bile ductular reaction, cholangiocyte injury, inflammatory infiltrate rich in neutrophils, biliary infarctions, marked cholestasis, and portal fibrosis	Not done OLT, due to poor clinical condition	Slight recovery, under observation & follow-up
Steiner *et al* [60], 2022	33	Female	Post-COVID-19 cholangiopathy	Yes, elevated liver enzymes AST, ALT, marked elevated GGT, ALP	N/A	MRCP done showed cholangiopathy	Yes hypoxia required intubation and MV, patient developed respiratory distress syndrome in which she was given veno-venous extracorporeal membrane oxygenation	Yes renal failure, and went through haemodialysis frequently	ERCP done showed cholangiopathy	OLT not done	Patient passed away, her clinical condition deteriorated, with severe hypoxia, renal failure, and multi-organ failure
Gourjault *et al*[61], 2021	55	Male	Post-COVID-19 cholangiopathy	Yes, elevated AST, ALT high GGT, ALP, elevated bilirubin, LDH	N/A	Periportal hypersignal without hepatic biliary dilatation	Yes, Required intubation& MV for 20 d with four sessions prone position	N/A	Interlobular biliary lesions with cholestasis	Waiting list for OLT	Discharged home, he had sphincterotomy and stone removal, planned for OLT

	45	Male			Hepatic steatosis without hepatomegaly or biliary dilatation	Diffuse intra-hepatic dilatation and liver steatosis without any focal obstructing lesion	MV for 26 d and sedated with ketamine for 24 d then he was on ECMO for 18 d	Fifteen sessions of hemodialysis			Discharged home, improved, not done OLT
	30	Male			US normal	Progressive irregular intrahepatic ductal dilatation	MV for 12 d with ketamine sedation, then replaced by ECMO for 29 d with 6 sessions of prone position	30 sessions of hemodialysis	Biopsy showed cholestatic hepatitis, bile ducts dystrophy	OLT done 11 mo after his admission	Developed liver failure with ascites, prolonged prothrombin, OLT done
Tafreshi *et al* [62], 2021	38	Male	Post-COVID-19 cholan-giopathy	Yes, mildly elevated AST, ALT and GGT mild bilirubin level	Intrahepatic biliary ductal irregularity and a markedly thickened common bile duct	Diffuse mild intrahepatic biliary distention, marked beading and irregu-larity& mild irregu-larity of the extra hepatic common bile duct	Required intubation & MV	N/A	Biopsy showed cholestatic hepatitis with cholangiocyte injury, bile ductular proliferation, canalicular cholestasis	Waiting list for OLT	Improved by treatment, waiting list for OLT
Leonhardt *et al*[63], 2023	N/A	N/A	Post-COVID-19 cholan-giopathy	Yes	N/A	N/A	Yes. Intubated on MV	N/A	N/A	N/A	One patient developed SSC-CIP in every 43 invasive ventilated COVID-19 patients (total 1082 patients)
Zengarini *et al*[64], 2022	30	Female	Post-COVID-19 cholan-giopathy	Yes	N/A	N/A	N/A	N/A	N/A	N/A	Patient developed subacute cutaneous lupus erythematosus post COVID-19 vaccination in patient with PBC
Wendel-Garcia *et al* [65], 2022	N/A	N/A	Post-COVID-19 cholan-giopathy	Yes. High total bilirubin	N/A	N/A	N/A	N/A	N/A	N/A	The study showed 243 patients; 170 Patients infused with ketamine developed post-COVID-19 cholangiopathy while other patients received propofol,

											fentanyl were not associated with cholestatic liver injury
Morão *et al* [66], 2022	46	Female	Post-COVID-19 cholangiopathy	Yes	N/A	MRCP; liver abscesses, intrahepatic bile duct dilation with multiple strictures and some linear repletion defects at the bifurcation of the common hepatic duct	Intubation with MV 12 d	N/A	ERCP Showed; biliary casts	N/A	N/A
Lee *et al*[67], 2022	56	Female	Post-COVID-19 cholangiopathy	Yes, hepatitis C, AST, 243, ALT 630, ALP 449, GGT 2765	N/A	N/A	N/A	N/A	Granulomatous cholangitis, nonsuppurative with destruction and proliferation of bile ducts with PBC Also immune infiltrations of CD3 T-cells, CD8 T-cells	N/A	Patient improved and discharged after high dose UDCA treatment, liver enzymes become normal
Nikoupour *et al*[68], 2020	35	Male	Post-COVID-19 cholangiopathy	Yes	N/A	N/A	N/A	N/A	N/A	OLT done before 3 yr from COVID-19 infection	Two identical twins had COVID-19 infection, both developed PSC, one of them who had OLT showed improvement with mild symptoms, while the other twin had more severe symptoms
	35	Male								Did not have OLT	
Arnstadt *et al* [69], 2021	62	N/A	Post-COVID-19 cholangiopathy	Yes	Echogenic intraductal longitudinal structures characteristic for intraductal casts and for SSC-CIP	MRCP showed irregular intrahepatic bile ducts	Yes, need long-term ventilation	N/A	Necrotic bile ducts	N/A	N/A
Meersseman *et al*[70], 2021	Mean age 48-68	Male	Post-COVID-19 cholangiopathy	Yes, elevated GGT, ALP, AST, ALT	N/A	MRCP showed focal strictures in intrahepatic bile ducts with	Yes, intubated & MV then VV-ECMO	Yes, required renal support	ERCP: Patient 1 diffuse beading of the intrahepatic biliary system,	OLT done for patient 1 and 2patient 3 & 4 did not	Patient 1 is doing well, patient 2 died due to septic

						intraluminal sludge and casts			patient 2 & 3 diffuse beading of the intrahepatic biliary ducts, patient 4 focal strictures on the right hepatic duct	undergo OLT	shock and pneumonia, patient 3 have mild SSC-CIP, patient 4 died due to lethal liver hemorrhage
Durazo *et al* [5], 2021	47	Male	Post-COVID cholangiopathy	Yes	Cholelithiasis without evidence of acute cholecystitis	Mild intrahepatic biliary ductal dilatation with multifocal strictures and beading with intra hepatic dilatation but without extrahepatic biliary dilatation	Yes, off MV on day 29	Yes, recovered	Liver abscess; Bile collection associated with bile duct dilatation with vacuolization and neutrophilia. Endothelial hepatic arteries swelling. Severe portal tract inflammation with Obliterative venopathy	OLT done	Recovered
Raes *et al* [71], 2022	64	Male	Post-COVID-19 cholangitis	Yes	N/A	N/A	Yes, MV then venovenous ECMO VV-ECMO	N/A	N/A	N/A	Passed away; patient having CAHA, progressive liver failure, secondary to ischemic cholangitis
Fajardo *et al* [72], 2021	24	Female	Post-COVID-19 cholangitis	Yes, GGT, ALP, AST, ALT, bilirubin	US: thickening of the gallbladder without stones	MRI: showed normal biliary tree and wall oedema of the gallbladder	N/A	N/A	Cholangitis of the small bile ducts consisting of a mixed inflammatory infiltrate with lymphocytes, plasma cells and neutrophils, accompanied by eosinophils, localized around and within the bile ducts	Not done OLT	Improved, patient discharged after laparoscopic cholecystectomy and liver biopsy
Pizarro Vega *et al*[73], 2023	63 66 60 65 44	Male Female Male Male Female	Post-COVID-19 cholangiopathy	Yes, GGT high in all patients especially in patient NO. 3 to 143 U/L then reached to 1130 U/L and patient 4 reached 3550 U/L. AST is high and higher in patient 4 to 82 U/L and patient 5 to 85 U/L then reached	N/A	MRI showed intrahepatic duct dilatations, stenosis without lithiasis, no extrahepatic duct alteration	Yes, required intubation, MV. Pronosupination	Yes, impaired renal function, required vasoactive drugs	No liver biopsy	One patient planned for OLT	All patients treated with UDCA and discharge. 3 patients re-admitted due to complication, patient 4 had pleural

Knooihuizen *et al*[74], 2021	68	Male	Post-COVID-19 cholangiopathy KISC	maximum 250 and 148, respectively. And patient 1 reached 1520 U/L. High tot. Bilirubin, ALT, ALP	N/A	MRI showed intrahepatic biliary dilatation with a beaded appearance & dilated common bile duct with distal narrowing	Yes	Yes	Liver biopsy showed minimal infiltration of neutrophils in the portal tract and lobule without cholestasis, also showed portal tract with bile duct injury	Not done	empyema. Patient 5 had cholecystectomy, patient 6 readmitted for acute cholangitis without lithiasis, no patients died during follow up
Zhou *et al* [75], 2022	54	Female	Post-COVID-19 vaccination leading autoimmune hepatitis	Yes, ALP peaked 2239 U/L, GGT 773 U/L, AST 1260 U/L, ALT 1729 U/L	N/A	N/A	N/A	N/A	Liver biopsy showed interface hepatitis with portal infiltration and discrete presence of rosette formation and apoptotic hepatocytes	Not done	Patient have KISC during intensive sedation, then ceased the KISC is transient, patient for repeat MRCP
Muehlenberg *et al*[76], 2021	36	Female	Post-COVID-19 cholangiopathy	Yes, AST 581, ALT 588 elevated, GGT, ALP slight elevation, bilirubin 1.4	US of liver and bile duct were normal	N/A	Yes, intubation and MV with antibiotics and catecholamine treatment	N/A	N/A	N/A	Patients have Autoimmune hepatitis AIH post vaccination (Moderna mRNA), treatment given after 2nd dose vaccine with prednisolone PSC treated with UDCA and ERCP
Soldera and Salgado[77], 2021	80	Female	Post-COVID-19 cholangiopathy	Yes, AST 100 U/L, ALT 113 U/L, bilirubin 12 mg/dL	Not Available	Diffuse irregularity of the intrahepatic bile ducts associated with sacular dilations suspicious for cholangiolithic abscesses	Yes	Not available	Intense cytoplasmic vacuolization of cholangiocytes and microvascular alterations	OLT done	Patient done ERCP with papillotomy and foreign body extraction
Rojas *et al* [78], 2021	62	Male	Post-COVID-19 cholangiopathy	Yes	Resemble SSC (secondary sclerosing cholangitis) but no portal inflammation, dilatation, or fibrosis)	MRI is negative	Yes, off MV on day 30	Yes, recovered	Low periportal inflammatory infiltrate without necrosis but with a severe obstructive cholestatic pattern	Not done	Recovery
Dhaliwal *et*	29	Female	Post-COVID-19 cholan-	Yes	Not Available	Mild intrahepatic	Not required	No	Filling defects	OLT Done	Not recovered

al[23], 2022			giopathy			biliary ductal dilation. With subtle central biliary enhancement concerning for. Cholangitis along with hypodense material hin extrahepatic. Biliary system likely representing transiting gallbladder. Sludge	MV		secondary to multiple large biliary casts (Biliary case syndrome)		
	42	Female		Yes							Recovery with long-term liability and comorbidity
Caballero-Alvarado *et al*[79], 2023	7 cases	7 cases	Post-COVID-19 cholan-giopathy	Yes	Not available	Not available	Not available	Yes, recovered	Secondary sclerosing cholangitis	1 done OLT 6 send for consideration of OLT	One recovered, 6 no data available
Soldera *et al l* [26], 2023	50	One male	Post-COVID-19 cholan-giopathy	Yes	Not available	MRI showed intra-hepatic sclerosing cholangitis and a dilated chilidium, with no signs of lithiasis (11 mm)	Yes, required MV	Yes, required haemodialysis	ERCP which showed a cast in the format of the external biliary tract, which was removed	Not done OLT	Recovered post cast removal
Franzini *et al* [80], 2022	65	Male	Post-COVID-19 cholan-giopathy	Yes	U/S showed no abnormalities	MRI Not available	Yes, required MV; under Fentanyl, Midazolam, and Ketamine sedation	Yes, required haemodialysis	ERCP revealed rarefaction of intrahepatic bile ducts, and removal of biliary casts	OLT Not done	No improvement
Roda *et al* [81], 2022	63	Male	Post-COVID-19 cholan-giopathy	Yes	Ultrasound results was inconclusive	MRI not done	Yes, required MV, and veno-venous extracor-poreal membrane oxygenation support (VV-ECMO). And eventually done bilateral lung transplant	Acute renal failure (AKI III); chronic illness neuropathy; several episodes of bacterial superinfections and lastly, PLS, characterized by severe haemolysis	Transjugular hepatic biopsy was performed with histopathological evidence of portal and periportal fibrosis, and intraparenchymal cholestasis with cholangiopathy and vasculopathy	OLT not done, patient did bilateral lung transplant	Not recovered, patient passed away due to Multiorgan failure MOF due to septic shock
Tebar *et al*	43	Male	Post-COVID-19 cholan-	Yes	Ultrasound	MRI not done	Yes, required	Not available	ERCP, MRCP	Not available	Not available

[82], 2022			giopathy		Not available		MV		Showed: Bile cholestatic, toxic. Cause necrosis of cholangiocytes and stenosis, determining persistent and irreversible biliary obstruction, with rapid progression to liver cirrhosis		
Santisteban Arenas *et al* [83], 2022	6 cases 55 54 62 56 73 34	 Male Male Male Female Female Male	Post-COVID-19 cholan-giopathy	Yes	Ultrasound not available	Destruction and curling of the pathway, beading of the intrahepatic bile duct	Yes, all 6 cases required MV	1 male not having renal failure or haemodialysis. All other 5 cases have renal failure; 2 females not required haemodialysis; 2 males required haemodialysis; 1 male have renal failure but not required haemodialysis	MRCP/ERCP showed destruction of biliary tract. In three of the six patients underwent liver biopsy, the most frequent findings were the presence of a reaction. Ductular, proliferation of cholangioles, infiltrate. Inflam-matory associated with the biliary epithelium with component. Lymphoplasmocyte and polymorpho-nuclear neutrophils	Not available	1 patient died, 5 other survived with severe comorbidities such as pneumonia, tracheal stenosis, pressure ulcers *etc*.

ACLD: Advanced chronic liver disease; AIH: Autoimmune hepatitis; AIH-PBC-OS: Auto-immune hepatitis-primary biliary cholangitis overlap syndrome; AKI: Acute kidney injury; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; ANA: Antinuclear antibodies; AST: Aspartate aminotransferase; CAHA: Cold agglutinin hemolytic anemia; CBD: Common bile duct; CBD: Common bile duct; CIP: Critically ill patients; CLD: Chronic liver disease; COVID-19: Coronavirus disease 2019; EUS: Endoscopic ultrasound; ECMO: Extracorporeal membrane oxygenation; ERCP: Endoscopic retrograde cholangiopancreatography; GI: Gastrointestinal; GGT: Gamma-glutamyl transpeptidase; IL: Interleukin; KISC: Ketamine-induced sclerosing cholangitis; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; MV: Mechanical ventilation; N/A: Not applicable; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; OLT: Orthotopic liver transplantation; PBC: Primary biliary cirrhosis; PLS: Passenger lymphocyte syndrome; PSC: Primary sclerosing cholangitis; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SSC: Secondary sclerosing cholangitis; TNF: Tumor necrosis factor; U/S: Ultrasound; UDCA: Ursodeoxycholic acid; WGO: World Gastroenterology Organization.

enzymes particularly alkaline phosphatase and gamma-glutamyl transpeptidase, and signs of liver dysfunction. Radiology showed bile duct thickening and enhancement, beading of the intrahepatic ducts, and peribiliary enhancement on diffusion. Additionally, every patient had severe respiratory distress syndrome and kidney failure reported as complications. Liver transplantation has been suggested as a potential management option for PCC, although its efficacy as a curative treatment requires further validation. Not all PCC patients require liver transplantation, as some may recover without undergoing this procedure. Studies have demonstrated that liver enzymes, especially alkaline phosphatase, total bilirubin, and gamma-glutamyl transferase, decrease after medical treatment of PCC. While liver transplantation is not suitable for all PCC patients, it remains the most effective option for select cases. Further research, clinical studies, and international collaborations are needed to gain a better understanding of this novel disease and

explore potential treatment avenues.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) pandemic, declared by the World Health Organization in March 2020, has had devastating global impacts, resulting in millions of deaths and significant economic and humanitarian losses. Despite vaccination efforts, new variants of the virus continue to pose a threat, hindering control measures. While respiratory symptoms are common in COVID-19, extrapulmonary manifestations and derangement of liver enzymes have been observed. One emerging complication is post-COVID-19 cholangiopathy (PCC), characterized by bile duct inflammation and damage in recovered individuals. PCC presents with symptoms such as abdominal pain, fever, and jaundice, affecting both severe and milder cases. The prevalence and potential drug associations with PCC remain uncertain.

Research motivation

Understanding post-COVID-19 cholangiopathy is crucial due to its novelty and potential impact on recovered patients. Exploring the clinical presentation and management of PCC can provide valuable insights into its diagnosis and treatment. By addressing the knowledge gaps surrounding this condition, future research can develop effective strategies for patient care and improve outcomes in clinical practice. The significance of solving these problems lies in advancing our understanding of this novel disease and facilitating evidence-based approaches to manage post-COVID-19 cholangiopathy.

Research objectives

The primary objectives of this systematic review were to comprehensively analyze and synthesize existing evidence on post-COVID-19 cholangiopathy, focusing on the clinical presentation and management approaches documented in reported cases. By realizing these objectives, we provide a comprehensive overview of the current understanding of post-COVID-19 cholangiopathy, identify knowledge gaps, and contribute to the development of effective diagnostic and therapeutic strategies for this condition. The findings from this study can guide future research endeavors, leading to improved patient care and outcomes in the field of post-COVID-19 cholangiopathy.

Research methods

The research methods employed in this study adhered to the guidelines for preferred reporting items for systematic reviews and meta-analyses protocols. A comprehensive search was conducted in electronic databases (Scopus, Web of Science, and Medline/PubMed) using specified search terms. The search was limited to English, Spanish, and Portuguese language publications without any date restrictions. In addition to database searches, the reference lists of identified studies were manually searched. The inclusion criteria encompassed clinical case reports or case series focusing on post-COVID cholangiopathy, with detailed information on clinical presentation, diagnosis, management, and outcomes. Studies that lacked relevant clinical information or were unrelated to the topic were excluded. Two independent reviewers performed data extraction using a standardized form, and any discrepancies were resolved through discussion or consultation with a third reviewer. The extracted data included variables such as age, sex, clinical presentation, liver and renal function tests, imaging findings, histopathology, liver transplantation status, and outcomes. Data analysis involved descriptive techniques, including frequencies, means, and medians.

Research results

This systematic review identified a total of 540 patients with post-COVID-19 cholangiopathy, predominantly male (12.7%) and over 50-years-old (12.2%). Elevated liver enzymes were observed in nearly all patients during the acute phase (93.8), persisting in the chronic phase. Total bilirubin levels were elevated in 63.5% of cases, while alkaline phosphatase was 488 (90.3%) and gamma-glutamyl transferase levels consistently exceeded 1000 U/L. Imaging findings revealed biliary ductal dilatation with fibrosis on ultrasound in 41.6% of patients and bile duct thickening with contrast enhancement on MRI in 47.7% of patients. Respiratory failure type 2, associated with acute respiratory distress syndrome, was observed in 41.3% of patients, with 1 patient undergoing lung transplantation. Acute renal injury requiring dialysis or renal transplantation was present in 65.7% of cases. Liver biopsy showed sclerosing cholangitis in 74.4% of patients. Sixteen patients (2.96%) underwent orthotopic liver transplantation, with successful outcomes observed in 93.75% of these cases. These findings provide important insights into the clinical characteristics and complications of post-COVID-19 cholangiopathy, highlighting the need for further research to elucidate its pathogenesis and optimal management strategies.

Research conclusions

This study proposes several new theories and methods in the field PCC. First, the study suggests that PCC is a serious systemic illness that affects not only the lungs but also the liver. It provides evidence that PCC is characterized by elevated liver enzymes, biliary ductal dilatation, and histopathological findings of secondary sclerosing cholangitis. The study highlights the importance of considering the differential diagnosis, as other diseases may present with similar symptoms, such as ketamine-induced cholangiopathy and ischemic cholangitis. The study emphasizes the diagnostic procedures for PCC. It recommends the use of cholangiography, endoscopic retrograde cholangiopancreatography, or

magnetic resonance cholangiopancreatography to visualize the biliary system and identify characteristic features of PCC, such as pruned tree appearance, beaded ducts, and band-like strictures.

Research perspectives

The future research in the field of PCC should focus on understanding its pathophysiology, including the mechanisms of bile duct paucity and unique microvascular features. Improving diagnostic procedures through novel imaging techniques and biomarkers is essential for early and accurate detection. Comparative studies with other cholangiopathies can enhance treatment approaches. Additionally, investigating the management and treatment of PCC, including the efficacy of liver transplantation, is crucial. Identifying predictive factors for transplantation and determining long-term prognosis are valuable areas of research. Overall, future studies should deepen our understanding, develop improved diagnostics, and explore effective treatments to enhance patient outcomes. Collaboration among researchers and international efforts will play a vital role in advancing knowledge and management of this disease.

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FOOTNOTES

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SYSTEMATIC REVIEWS

Potential long-term neurological and gastrointestinal effects of COVID-19: A review of adult cohorts

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Abstract

BACKGROUND

The respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved into a multi-organ disorder, with long-term effects known as post-acute sequelae of SARS-CoV-2 infection or long coronavirus disease (COVID).

AIM
To examine the current knowledge and outcomes of long-term neurological and gastrointestinal (GI) symptoms in adult cohorts, including United States minority populations.

METHODS
PubMed and Google Scholar were searched using relevant terms, and data from five studies were analyzed, comprising 27383 patients with persistent neurological and GI sequelae.

RESULTS
The main symptoms included anxiety, depression, dysphagia, headache, vomiting, nausea, gastroesophageal reflux, fatigue, and abdominal pain. Patients with comorbidities and metabolic syndromes were at higher risk for long COVID. While most patients were European Americans, there was a need for further study on African Americans.

CONCLUSION
The underlying causes of these symptoms remain unclear, warranting more investigation into the long-term impact of the SARS-CoV-2 on different populations.

Key Words: Angiotensin converting enzyme; Long coronavirus disease; Post-acute sequalae of SARS-CoV-2 infection; Neurological; Gastrointestinal; Post-viral syndromes

Core Tip: Long coronavirus disease (COVID) or post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection (PASC) can lead to prolonged and debilitating symptoms beyond 30 d after infection. Neurological manifestations are prevalent, with encephalopathy, myalgia, headache, and anosmia being common symptoms. Females seem to be more susceptible to long COVID, and severe disease is associated with longer or more frequent neurological symptoms. Gastrointestinal (GI) sequelae are also reported, with symptoms like difficulty swallowing, nausea, vomiting, and abdominal pain being common. Anxiety, depression, dysphagia, headache, and fatigue are among the top symptoms observed, with potential neurological and GI associations. However, there is a need for further research to explore the underlying causes and potential discrepancies in symptom reporting among different populations affected by long COVID/PASC.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is not only a respiratory illness; it can lead to multi-organ complications. Studying the long-term effects helps identify the post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC) or long COVID (LC), which may involve neurological and gastrointestinal (GI) symptoms. Recognizing these sequelae is vital for developing targeted interventions and treatments. Among the wide range of COVID-19 patients who experience mild or severe symptoms, there is a subset that sustains a prolonged residual illness that lasts beyond 4 wk. Barring the lack of accurate diagnostic or reporting methods and normalized data for age and sex across countries, global estimates of LC or PASC patients vary widely between 15% to 76% depending on the preexisting medical conditions and geographical locations. Irrespective of acute COVID-19 severity and age, reports from the globally affected populations show that neurological and GI[1] dysfunctions remain as the most significant alterations. Post-infectious fatigue syndrome linked to brain fog and post-exertional malaise is not rare. Most well-studied viral or bacterial pathogens have been connected to the development of chronic symptoms in a subset of infected patients such as myalgic encephalomyelitis/chronic fatigue syndrome and postural orthostatic tachycardia syndrome[2-5].

LC or PASC is a multifactorial condition that lingers in many COVID-19 patients for more than 30 d following the initial viral infection that precipitates COVID-19. This residual illness displays over 200 symptoms and affects multiple tissues, organs, and biological systems including neuropsychiatric and GI systems to varying degrees[6-8]. The major symptoms of PASC are fatigue, brain fog (cognitive dysfunction), post-exertional malaise, and shortness of breath (dyspnea) that can last for months and can debilitate normal daily activities. There are several hypotheses that attempt to explain the underlying mechanisms that propel these multifaceted symptoms. Some of the leading theories include viral persistence, chronic inflammation, autoimmune dysfunction, and microclot formation[9]. In most of the tissues and organs affected by LC/PASC including the neurological and GI disorders, there is evidence of endothelial dysregulation.

This has prompted some scientists to declare that PASC is a vascular disease.

There are no universal case definitions of PASC. The National Institute of Health (NIH) defines PASC as "the failure to recover from acute COVID-19, or those persistently symptomatic for > 30 d from onset of infection, with any pattern of tissue injury that remains evolving including the nervous system" (www.NIH.gov). The Centers for Disease Control defines PASC as a condition marked by the continuation of COVID-19 symptoms for four or more weeks after infection with SARS-CoV-2 (www.CDC.gov). The SARS-CoV-2 has been detected in brain tissue and the GI tract. Early research indicates that the virus enters the brain through the nose, and *via* the olfactory bulb invades the brain cells (neurons) where it prowls unchecked, conceivably leading to lasting neurological symptoms, such as cognitive impairment and brain fog[2,10-15]. The virus can also invade the GI system through angiotensin-converting enzyme 2 (ACE2). Understandably, the GI infiltration of the virus begins in the oral route and may precede the brain invasion. It is not clear, however, how the virus precipitates the neurological or GI symptoms that are common in LC patients. The postulation, although not universally accepted by researchers or scientists, is that neuronal inflammation resulting from the viral invasion and persistence in these biological systems may be the trigger for the GI and neurological symptoms[2,10-13,16].

Understanding the full spectrum of COVID-19 is essential to provide appropriate medical care and support to patients as the disease is relatively new and its long-term effects are still being discovered. By reviewing the existing literature, scientists can gain a comprehensive understanding of the various neurological and GI symptoms that can persist after the acute phase of the infection. In the general COVID-19 population of the United States, those with neurological and GI symptoms experience viral invasion in the central nervous system through vascular and lymphatic systems or the vagal nerve[17]. SARS-CoV-2 or its viral particles including the RNA or the associated proteins can infect leukocytes and migrate into the brain or can be directly transported across the blood-brain barrier (BBB) to the brain. Furthermore, ongoing research reports that the virus can invade the peripheral lymphatic vessels that connects the glymphatic system of the brain[18]. The sequential correlation between neurological and GI symptoms or disorders lends credence to the vascular system as being the primary culprit. But the lymph vessels around the GI tract, or the gut-brain axis or the enteric nervous system may also facilitate entry for SARS-CoV-2 to the brain[19,20].

Minority patients including African Americans and Hispanic Americans have been disproportionally affected by COVID-19. These two population groups share common symptoms with most of COVID-19 patients. However, there is a dire need to characterize the long-term effects and impact of these neuropsychiatric and GI symptoms as a significant proportion of these populations usually are socially and economically poor, and medically underserved. African Americans and Hispanic Americans have a higher disease burden and fatality rates from COVID-19 than the general population. Studies regarding LC sufferers in these communities are rare and the long-term outcomes are difficult to gauge based on the available public data. It is even rarer to assess the neurological and GI tract symptoms in such patients because their asymptomatic and mild cases are scarcely documented. Therefore, although the neurological and GI symptoms may be shared by most SARS-CoV-2-infected long haulers, there must be particular attention afforded to those disproportionally affected patients to truly understand the underlying biological and pathophysiological mechanisms of PASC under a different social construct.

In the United States, there is a high frequency of neurologic involvement in 82% of hospitalized COVID-19 patients [21]. However, most neuro-COVID-19 clinic population consists of individuals who were never hospitalized for respiratory complications resulting from COVID-19, and this includes primarily minority populations. Studying the enduring neurological and GI symptoms in minority LC patients who suffered disproportional affliction during the pandemic, which received scant research in the literature, is crucial. Although other combinations of symptoms such as neurological and pulmonary symptoms or their variations are also apparently important to study, there are numerous reviews on this subject. Comprehensive research in various symptom domains contributes to a holistic understanding of COVID-19 and its effects on human health. In this retrospective review, we will characterize the cardinal symptoms shared or exhibited by PASC patients particularly from communities that are underserved and disproportionally affected by the coronavirus pandemic.

MATERIALS AND METHODS

Search strategy and selection criteria

We conducted a systematic literature search of published articles using PubMed and Google Scholar databases from December 2019 to September 30, 2022. We used the following search terms: COVID-19, ACE2, angiotensin converting enzyme, and SARS-CoV-2, long COVID or PASC (post-acute sequalae of SARS-CoV-2 infection), neurological, GI, gastric sequelae of SARS-CoV-2, COVID-19, and post-viral syndromes in the United States. The protocol of this systematic review and analysis of COVID-19 patients' data is in accordance with the PRISMA Statement guidelines (https://prisma-statement.org) (Figure 1).

Inclusion and exclusion criteria

We first sorted the LC/PASC studies by title and abstract; then, we compiled the papers by relevance and conducted a new selection process by thoroughly reviewing the data. We incorporated studies that reported GI and neuropsychiatric findings in COVID-19 patients and long-haulers. From the selected papers, tables were generated for each data set in Microsoft Excel. These tables included the following information for each study (when available): General information about the study (year, location, hospital or city, state and country, and publication date), confirmed cases, GI/neuropsychiatric manifestations, symptoms involving other organ systems, comorbidities, hospitalization, outcome measurements, and PASC duration. We compared clinical manifestations, comorbidities, prevalence, and significant outcomes of the

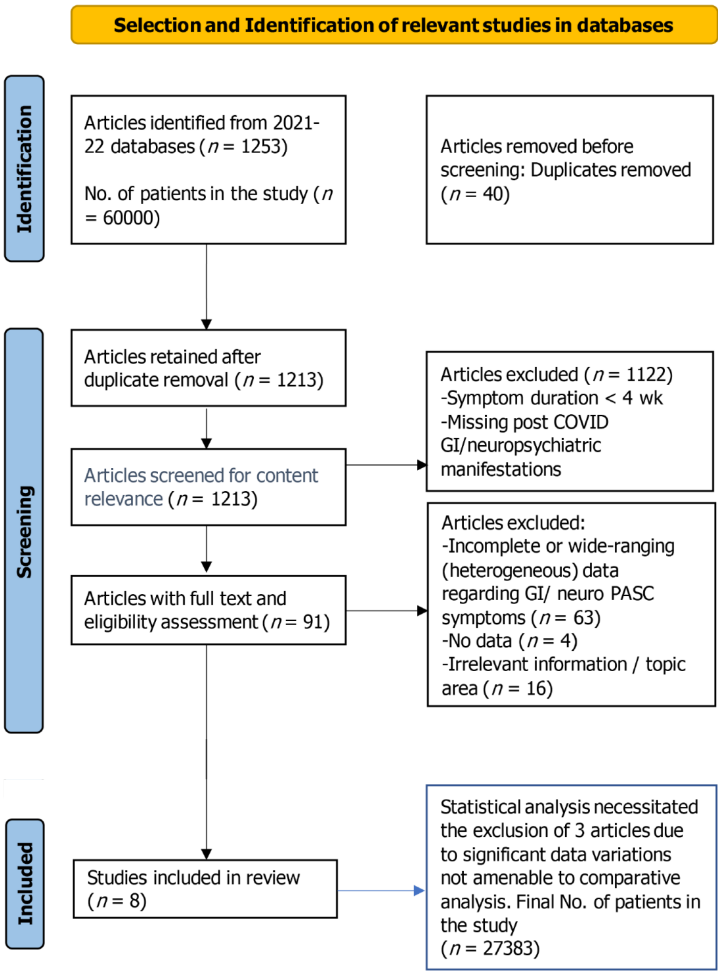

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Figure 1 Selection and identification of relevant studies in databases. COVID: Coronavirus disease; PASC: Post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection; GI: Gastrointestinal.

long-term neurological and GI sequelae of COVID-19 symptoms. We particularly attempted to include United States minority populations where available.

Inclusion criteria

The following inclusion criteria were adopted to validate article selection: Any study including patients with confirmed previous COVID-19 diagnosis with specified post-COVID neurological and GI sequelae of COVID-19 findings; any study with five or more patients; any study with all or most patients from Western countries including United States minority populations with no distinction regarding sex, age, severity of disease, inpatient or outpatient management, treatment, and outcome. Data on neurological and GI symptoms after 4 wk of SARS-CoV-2 infection were collected and presented.

Exclusion criteria

The following exclusion criteria were adopted to filter out incomplete data: Studies whose duration of symptoms following SARS-CoV-2 infection lasted less than 4 wk were excluded. In addition, studies which did not include post-COVID GI/neuropsychiatric manifestations and studies from Eastern countries were also excluded to have a more homogeneous data source.

Statistical analysis

The potential studies were assessed for data homogeneity including demographics and LC symptoms. Finally, five studies were included in the analysis of this review. The statistical analysis was performed, as appropriate, by weighted analysis where the weights were associated with the size of the study and the inverse of the variance of the main outcome. Descriptive, parametric, and non-parametric correlation, Chi-square tests, and *t*-tests, were performed using SPSS and Excel as appropriate. The primary limitation of this review, as our biostatistician has determined, is that the data are aggregated and confined to a small number of papers. Therefore, correlation between GI and neurological symptoms may not be robust.

RESULTS

Baseline patient characteristics and symptoms

More than 60000 COVID-19 patients of aggregate studies with various COVID and LC symptoms were initially screened for this review. Dozens of papers were sorted out for specific data on LC or PASC symptoms lasting more than 30 d. After excluding duplicates and unrelated studies by screening the title, abstract, or main text, a total of five published studies were included in this review containing a total of 27383 patients with long-term neurological and GI sequelae of COVID-19 symptoms. The mean age of these cohorts is 55.76 years. Females outnumber males by 1.6 to 1.0 as shown in Table 1 and Figure 2.

The baseline demographics of the aggregate study cohorts include European Americans (66.5%), African Americans (9.9%), Asian Americans (3.0%), Hispanic Americans (0.5%), and persons with undeclared (or unrecorded) racial or ethnic identities (20.0%), which made up the second largest group (Figure 2).

Table 2 and Figure 3 show PASC patients harboring GI or neurological symptoms, or both as documented in the five articles selected for this systematic review.

The papers did not single out PASC patients with overlapping GI and neuropsychiatry symptoms. Table 2 also displays the minimum and maximum numbers of each symptom reported among the five studies. Sometimes, only one or two papers reported certain symptoms. For example, among the GI symptoms, dysphagia (*i.e.*, difficulty swallowing) was the number one cited symptom (self-reported by 6114 PASC patients) in one of the studies (Table 2, Figure 3). However, this symptom was cited in only two of the three papers. Similarly, anxiety, the highest-ranked neurologic symptom by 6749 PASC patients, was cited by only two of the papers (Table 2). The separation of GI and neurologic symptoms into Figure 4A and B, respectively provides a clearer picture of the most common symptoms associated with each disorder.

GI symptoms

Various GI symptoms to a different degree were reported in the five studies that are reviewed (Table 3, Figure 4A).

These common symptoms in order of descending rank in the aggregated data included abdominal pain (3718, 3 studies)[22-24], dysphagia (6114, 2 studies)[24-27], nausea/vomiting (5223, 3 studies), gastroesophageal reflux (4858, 1 study)[24], and constipation (3116, 2 studies)[23,24]. The remaining GI symptoms were diarrhea (2711, 4 studies)[22-24, 26], general GI (1290, 1 study)[24], anorexia (1259, 2 studies), and dyspepsia (5, 1 study).

Neurological symptoms

There are more neurologic symptoms reported than GI symptoms. The five most common neurologic symptoms in the aggregated data of the studies are: Anxiety (6749, 2 studies), depression (6292, 3 studies), headache (5295, 5 studies), myalgia (5076, 4 studies), and fatigue (4038, 5 studies). These top five and the remaining neurologic symptoms are shown in Table 4 and depicted in Figure 4B.

Comorbidities

The five most reported pre-existing conditions or comorbidities by 1266 PASC patients in the study cohorts were documented by four of the five papers reviewed (Table 5). Females constituted about 61% of COVID-19 patients more likely to experience PASC than males. In the cumulative study cohort, those reporting PASC symptoms consisted of White/Caucasians at 66.54%, African Americans at 9.97%, and Asians at 3.0% (Table 1). The leading comorbidities are hypertension (617, 4 studies), diabetes (343, 4 studies), obesity (320, 3 studies), asthma (172, 4 studies), and hyperlipidemia (145, 2 studies)[23,26]. The remaining comorbidities are shown in Table 5 and Figure 4C.

General symptoms

In Table 6, various symptoms other than GI and neurologic were reported by all five studies to varying levels. Furthermore, in the same five study populations, a total of 57 clinical manifestations were also assessed. We divided these clinical manifestations into separate categories of organ systems such as neurologic/psychiatry, mental health, respiratory, cardiovascular, GI, dermatologic, and ear, nose, and throat. The highest ranked general PASC-associated symptom by far was weight gain at 11256 followed by dyspnea at 5638. The rest of these general symptoms are side effects of SARS-CoV-2 infection and are listed in Table 6.

DISCUSSION

COVID-19 patients experience a multitude of symptoms including respiratory, digestive, and neurological disorders. A subset of these patients experiences LC or PASC that prolongs the duration and the debilitating conditions of these symptoms beyond 30 d after infection. As there is no standard case definition for PASC, there are disparate PASC explanations ranging from a minimum of 30 d duration of symptoms to a maximum of 6 mo or 180 d in the study cohorts. Certain distinctive symptoms such as anosmia indicate a potential neurotropism of this virus. There are several pathways for the virus to enter the nervous system. One of these pathways proposed by Llorens *et al*[28], is a route to the brain from the infection of the gut *via* Toll-like receptor 4 and zonulin brain receptor. Other researchers proposed that the evolutionary similarity of SARS-CoV-2 with SARS-CoV makes it more likely that SARS-CoV-2 can invade the olfactory bulb and GI system through ACE2[18]. However, when the GI tract is invaded, the virus may enter the central nervous

Table 1 Baseline demographics of post-acute sequelae of severe acute respiratory syndrome coronavirus 2 study cohorts

Ref.	[22]	[23]	[24]	[25]	[26]	Aggregate	%
Female	236	174	16177	104	71	16762	61.21%
Male	294	190	9940	85	112	10621	38.79%
Mean age (SD), year	59.2	61.0	51.6	50.0	57.0	54.3	-
African American	62	76	2551	20	16	2725	9.97%
European American	155	74	17752	148	99	18228	66.54%
Asian American	79	6	704	14	16	819	3.00%
Hispanic	132	0	0	0	0	132	0.48%
Unknown	102	208	5110	7	52	5479	19.98%

Table 2 Gastrointestinal and neurological post-acute sequelae of severe acute respiratory syndrome coronavirus 2 symptoms

Symptom	Number of studies	Minimum number	Maximum number	Total of 5 studies
Anxiety	2	11	6738	6749
Depression	3	6	6268	6292
Dysphagia	2	3	6111	6114
Headache	5	6	5223	5295
Nausea and/or vomiting	3	3	5197	5223
Myalgia	4	11	4962	5076
Gastroesophageal reflux	1	4858	4858	4858
Fatigue	5	29	3839	4038
Abdominal pain	3	2	3682	3718
Dizziness or vertigo	2	7	3656	3663
Constipation	2	8	3108	3116
Stress	1	2925	2925	2925
Neuropathy	2	27	2794	2821
Paresthesia	2	2	2794	2796
Diarrhea	4	2	2690	2711
Abnormal gait	2	18	1540	1558
Brain fog	5	16	1410	1489
Smell & taste problems	4	8	1305	1356
General GI	1	1280	1280	1280
Anorexia	2	5	1254	1259
Dyspepsia	1	5	5	5

GI: Gastrointestinal.

system through vascular and lymphatic systems or the vagal nerve. SARS-CoV-2 can infect leukocytes and migrate with them into the brain, or the viral particles can be directly transported across the BBB to the brain.

At the beginning of the pandemic in 2019, there have been frequent neurologic manifestations and encephalopathy-associated morbidity in COVID-19 patients. In fact, more than 80% of hospitalized COVID-19 patients had neurologic symptoms during their disease course, and 82.3% at any time during the disease course according to a retrospective Chicago-area study[21]. In this study, in order of decreasing percentages of neurological symptoms, myalgia (44.8%), headache (37.7%), encephalopathy (31.8%), dizziness (29.7%), dysgeusia (15.9%), and anosmia (11.4%) were the most frequent neurologic manifestations[21]. These neurological symptoms were more prominent in the Chicago-area cohort than the COVID-19 symptoms observed in the adult cohort populations studied in the five papers reviewed in our study

Table 3 Gastrointestinal post-acute sequelae of severe acute respiratory syndrome coronavirus 2 symptoms

Symptom[1]	Number of studies	Minimum number	Maximum number	Total of 5 studies
Dysphagia	2	3	6111	6114
Nausea and/or vomiting	3	3	5197	5223
Gastroesophageal reflux	1	4858	4858	4858
Abdominal pain	3	2	3682	3718
Constipation	2	8	3108	3116
Diarrhea	4	2	2690	2711
General GI	1	1280	1280	1280
Anorexia	2	5	1254	1259
Dyspepsia	1	5	5	5

[1]Patients may harbor more than one symptom.
GI: Gastrointestinal.

Table 4 Neurological post-acute sequelae of severe acute respiratory syndrome coronavirus 2 symptoms

Symptom[1]	Number of studies	Minimum number	Maximum number	Total of 5 studies
Anxiety	2	11	6738	6749
Depression	3	6	6268	6292
Headache	5	6	5223	5295
Myalgia	4	11	4962	5076
Fatigue	5	29	3839	4038
Dizziness or vertigo	2	7	3656	3663
Stress	1	2925	2925	2925
Neuropathy	2	27	2794	2821
Paresthesia	2	2	2794	2796
Abnormal gait	2	18	1540	1558
Fever	3	2	1463	1478
Brain fog	5	16	1410	1489
Smell & taste problems	4	8	1305	1356

[1]Patients may harbor more than one symptom.

demonstrating that anxiety (Table 2) was the most prevalent GI-neuro symptom. In another cohort of LC sufferers reported by Nakhli *et al*[29], depression (65%), but not anxiety (48%), was significantly more common in those with post-COVID-19 disorders of gut-brain interaction.

The five studies in our report did not categorize PASC patients based on the timing of neurologic manifestations by COVID-19 severity. The mean age was 55 years included female cohort of 62% compared to 38% of the male PASC patients raising the question as to why females seem to be more susceptible to LC. Four of our five study cohorts also comprised 645 hospitalized COVID-19 patients who later developed PASC. The literature is replete with data of PASC patients who developed their various residual illnesses following a lengthy stay in intensive care units connected to ventilators.

As Table 4 summarizes, the neurologic manifestations that occurred at onset and any time during COVID-19 show that patients with severe disease had a longer duration or frequency of neurologic manifestations including encephalopathy than those with milder or no symptoms[21]. The severity of COVID-19 symptoms can be influenced by genetic factors such as variations in the expression of the ACE2 receptor in the body, as well as differences in the virulence and transmissibility of the virus strains[30]. It is also evident in the evolving PASC literature that among the most reported neurological symptoms is fatigue. However, in our limited systematic review, this common condition was not among the top five neurological symptoms. Fatigue is also a major symptom among COVID-19 patients regardless of whether the

Table 5 Comorbidities in post-acute sequelae of severe acute respiratory syndrome coronavirus 2 patients

Ref.[1]	[22]	[23]	[25]	[26]	Aggregate sum
Total (*n*)	530	364	189	183	1266
Hypertension	266	225	39	87	617
Diabetes	146	134	11	52	343
Obesity	158	-	72	90	320
Asthma	55	74	24	19	172
Hyperlipidemia	-	125	-	20	145
CAD	52	41	3	21	117
Heart failure	23	41	-	5	69
Anxiety disorder	-	-	54	-	54
Mood disorder	-	-	43	8	51
CVA	28	21	-	-	49
Cancer	15	32	-	-	47
Chronic kidney disease	-	29	-	-	29
Smoking	18	-	9	-	27
COPD	19	-	-	7	26
Other	-	-	15	-	15
HIV	10	-	4	-	14
Atrial fibrillation	-	-	2	9	11
Valvular heart disease	-	-	3	-	3

[1]Patients may harbor more than one symptom.
CAD: Coronary artery disease; CVA: Cerebral vascular accident; COPD: Chronic obstructive pulmonary disease; HIV: Human immunodeficiency virus infection.

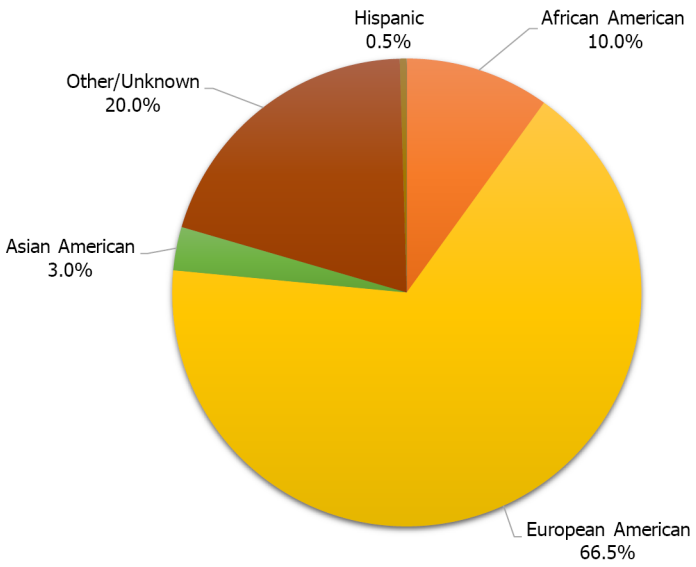

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Figure 2 Aggregate racial identities of the study cohorts.

Table 6 Other general symptoms associated with post-acute sequelae of severe acute respiratory syndrome coronavirus 2

Ref.	[22]	[23]	[24]	[25]	[26]	Aggregate sum
Total number	530	364	26117	189	183	27383
Weight gain	-	-	11256	-	-	11256
Dyspnea	55	58	5432	35	58	5638
Joint pain	-	-	5484	6	29	5519
Cough	10	37	4570	-	46	4663
Chills	-	-	3839	-	-	3839
Edema	-	-	3839	-	-	3839
Bleeding	-	-	3708	-	-	3708
Tachycardia	-	-	3264	16	-	3280
Pain	-	-	3212	-	-	3212
Wheezing	-	-	3108	-	-	3108
High BP	-	-	3108	-	-	3108
Skin lesion	-	-	2977	-	-	2977
Sleep disturbances	-	-	2925	17	-	2942
Swelling	-	-	2742	-	-	2742
Chest pain	7	30	2690	10	-	2737
Rash	-	-	2455	-	-	2455
Erythema	-	-	2403	-	-	2403
Urinary tract symptoms	-	-	2272	-	-	2272
Weakness	-	34	2167	1	-	2202
Peripheral edema	-	22	2063	-	-	2085
Weight loss	-	-	1906	-	-	1906
Erectile dysfunction	-	-	1854	-	-	1854
Sinonasal congestion	-	-	1671	-	-	1671
Respiratory distress	-	-	1515	-	-	1515
Sleep apnea	-	-	1410	-	-	1410
Throat pain	-	-	-	11	-	11
Tinnitus	-	-	5.2	-	-	5.2
Nasal congestion	-	-	-	3	-	3
Hearing loss	-	-	-	2	-	2
Sore throat	-	-	-	-	-	0
Alopecia	-	-	-	-	-	0

BP: Blood pressure.

disease progresses to LC or not. A notable factor is that the most frequently observed LC symptoms in our meta-analysis are anxiety and depression, which are also features of post-traumatic stress disorder (PTSD).

The GI sequelae of SARS-CoV-2 can affect any part of the digestive system, not only in the acute infection phase but also in the post-acute phase, leaving long-term sequelae to manifest frequently or sporadically. The main long-term symptoms that are reported, regardless of the presence of chronic diseases, are diarrhea, nausea, vomiting, abdominal pain, accompanied by increased liver enzymes[31]. In our retrospective study of 27383 PASC patients, the main GI symptoms experienced in decreasing order are difficulty swallowing, nauseas and/or vomiting, abdominal/or visceral pain, GI reflux, diarrhea, and constipation.

Wang *et al*[24] developed a broad post-acute sequelae of SARS-CoV-2 symptoms lexicon called PASCLex based on physician clinical notes and reviews to facilitate PASC symptom identification and research. There were multiple

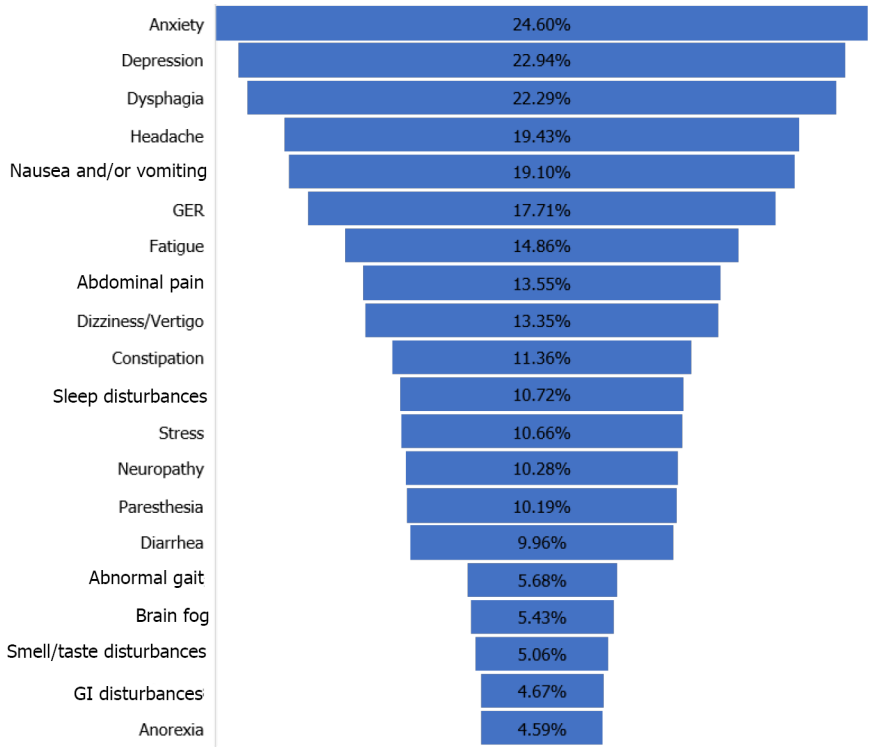

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Figure 3 Percentages of post-acute sequelae of severe acute respiratory syndrome coronavirus 2-gastrointestinal/neurological symptoms in all patients of the five studies reviewed. Patients with neurological or gastrointestinal symptoms may or may not harbor both symptoms. GI: Gastrointestinal; GER: Gastroesophageal reflux.

symptoms identified by the natural language processing tool that Wang *et al*[24] utilized to validate previously identified post-acute COVID-19 results recorded in meta-analysis studies of observational and survey data. Lopez-Leon *et al*[32] conducted a systematic literature review and identified more than 50 Long-term effects of COVID-19, with the most common being fatigue, headache, attention disorder, hair loss, and dyspnea. Halpin *et al*[33] identified fatigue, breathlessness, anxiety/depression, concentration problems, and pain among the five most common post-discharge symptoms in 100 patients hospitalized with COVID-19 (ward and ICU). A recent analysis of new ICD-coded outpatient symptoms among non-hospitalized COVID-19 patients 28-108 d post COVID-19 diagnosis lists that long-term symptoms such as throat and chest pain, shortness of breath, headache, malaise, and fatigue are the most common issues experienced by COVID-19 patients even after they have recovered from the initial infection[24]. We identified the most common ten GI and neurologic symptoms as anxiety, depression, dysphagia, headache, nausea and/or vomiting, myalgia, gastroesophageal reflux, fatigue, abdominal pain, and vertigo, highlighting symptoms common to both prior inpatient and outpatient-based studies and raising additional symptoms for consideration. Among the top 50 symptoms identified in our study, some have not been previously reported, or only reported in small series or single case studies. These include patient-level symptoms that may have previously been obscured in diagnoses or groups of symptoms, such as "cutaneous signs" like skin rash or lesion while our study captured individual symptom descriptors such as "erythema", "itching", and "rash". Similarly, our findings of "visual changes" and "abnormal gait"[34] have not been duly reported in most studies that we screened for this review. It is also interesting that in the general symptom category, both weight gain (11256) and weigh loss (1906) were reported in the same and only one paper among the five reviewed. It is therefore possible that obscure and uncommon symptoms are picked up by the questionnaires or survey questions posed by the investigators that are holistically conducting their research as opposed to selecting the most common symptoms to show in the analysis of their collected data.

The main limitation of our review is the small number of published papers that were used in collating the various common symptoms experienced by LC/PASC patients and the limited sources of data available exclusively in the GI and neurological category of symptoms. Based on our descriptive analysis of the symptoms and the varying degree of sample sizes in each cohort study from the five papers, there is a positive correlation between GI and neurological symptoms regardless of the significance level. It is important to point out that contrary to the published reports, fatigue was not a major symptom among those PASC patients experiencing the most GI or neurologic symptoms. Further work is needed in this area to clearly understand why such a discrepancy exists. It is important that future studies bring light and clarity to the underlying causes of the disproportionate infection, duration of symptoms, or mortality in minority populations. There may also be similarities in symptoms, in patients of other countries that could shed light on the long-term effects of COVID-19.

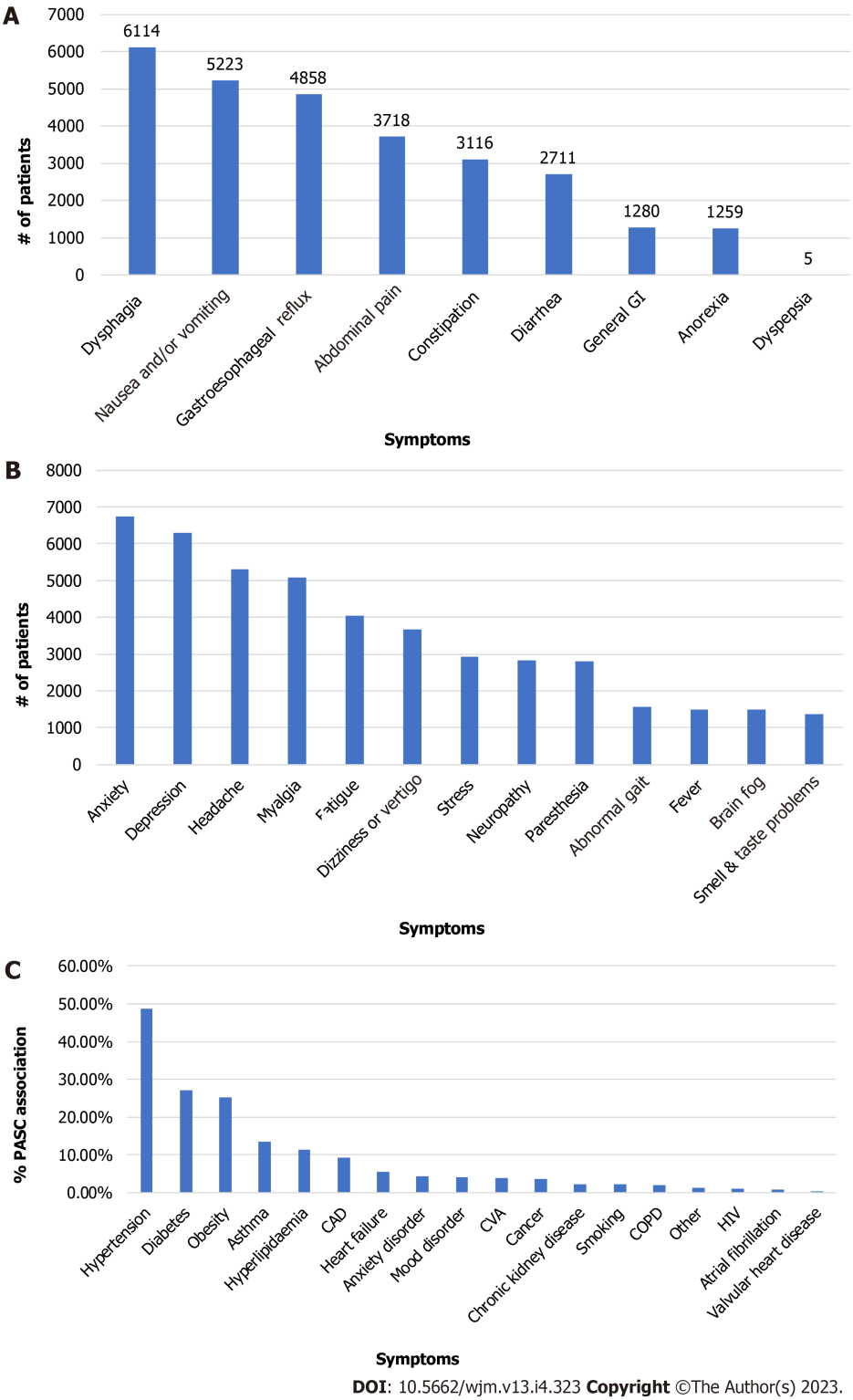

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Figure 4 Gastrointestinal, neurologic, and comorbidities post-acute sequelae of severe acute respiratory syndrome coronavirus 2 symptoms. A: Gastrointestinal post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection (PASC); B: Neurologic PASC; C: Comorbidities in PASC patients. GI: Gastrointestinal; CAD: Coronary artery disease; CVA: Cerebral vascular accident; COPD: Chronic obstructive pulmonary disease; HIV: Human immunodeficiency virus infection.

CONCLUSION

LC/PASC leads to prolonged and debilitating symptoms beyond 30 d after SARS-CoV-2 infection. Neurological symptoms, such as encephalopathy, myalgia, and anosmia, are common in LC/PASC patients. GI sequelae, including difficulty swallowing and abdominal pain, are frequently observed. Females may be more susceptible to LC/PASC. Anxiety and depression are prevalent, resembling features of PTSD. Fatigue's discrepancy in symptom reporting requires further investigation. More research is needed to understand the long-term effects and potential treatments for LC/PASC

patients.

ARTICLE HIGHLIGHTS

Research background

The respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for a global epidemic, extends beyond pulmonary issues. It induces multi-organ disorders, affecting cognition (neurological) and gastrointestinal (GI) function. Long-term repercussions of this infection are termed post-acute sequelae of SARS-CoV-2 infection (PASC) or long coronavirus disease 2019 (COVID) (LC). This review aims to analyze current knowledge and outcomes of long-term neurological and GI effects in adult cohorts, encompassing United States minority populations.

Research motivation

This research is motivated by the need to explore and understand the long-term neurological and gastrointestinal effects of COVID-19 in adult cohorts, with a particular focus on United States minority populations. By investigating these long-term sequelae, the study aims to contribute to the existing knowledge, provide insights into potential health impacts, and potentially lead to better management and care for individuals affected by PASC or LC.

Research objectives

To identify and document the neurological symptoms and cognitive impairments experienced by individuals who have recovered from COVID-19, as well as to examine and characterize the gastrointestinal symptoms and disorders observed in post-COVID-19 patients. The research seeks to determine the prevalence and severity of these long-term effects, considering the disproportionate affliction in United States minority populations. Furthermore, the study aims to investigate contributing factors, risk factors, comorbidities, and demographic variables associated with the development of long-term neurological and GI sequelae in post-COVID-19 individuals. We also wish to explore the underlying mechanisms and pathophysiological processes that may lead to these long-term effects. Future investigations might include a comparison with control groups to discern the specific impact of the virus on neurological and GI systems. Moreover, future research will analyze potential disparities in the prevalence and outcomes of long-term effects among different racial and ethnic groups. Ultimately, the study's findings will provide valuable clinical insights and contribute to public health knowledge, offering evidence-based information for improved assessment, management, and care of individuals experiencing long-term neurological and GI effects following COVID-19. The researchers will suggest recommendations for healthcare providers, policymakers, and future researchers to address the challenges posed by LC in diverse populations.

Research methods

PubMed and Google Scholar were searched using relevant terms, and data from five studies were analyzed, comprising 27383 patients with persistent neurological and GI sequelae.

Research results

The study revealed several prominent symptoms, such as anxiety, depression, dysphagia, headache, vomiting, nausea, gastroesophageal reflux, fatigue, and abdominal pain, among LC patients. Notably, individuals with comorbidities and metabolic syndromes faced an increased risk. While most patients were of European American descent, the impact on African American individuals requires more extensive investigation. The underlying reasons for these symptoms remain uncertain, emphasizing the necessity for further research into the long-term effects of the SARS-CoV-2 on diverse populations.

Research conclusions

The study concludes that LC is associated with a range of significant symptoms, including anxiety, depression, dysphagia, headache, vomiting, nausea, gastroesophageal reflux, fatigue, and abdominal pain. Patients with comorbidities and metabolic syndromes are at higher risk of experiencing these long-term effects. The research highlights the need for further investigation into the impact of LC on African American populations and emphasizes the uncertainty surrounding the underlying causes of these symptoms. Overall, the study underscores the importance of understanding the long-term consequences of SARS-CoV-2 infection in different populations.

Research perspectives

The study on LC symptoms reveals the importance of considering research perspectives that can enhance our understanding of the condition's impact on different populations. To achieve this, future studies should prioritize diverse and representative samples, particularly including African American populations and other minority groups. Exploring potential biological, socioeconomic, and cultural factors that influence LC symptoms in diverse communities can provide valuable insights. Additionally, investigations into health disparities and the intersectionality of comorbidities will aid in addressing specific challenges faced by various racial and ethnic groups. Culturally tailored interventions, improved healthcare access, and preventive measures are crucial for managing LC and ensuring better long-term outcomes for affected individuals from diverse backgrounds.

FOOTNOTES

Author contributions: Ashktorab H contributed to conception and design; Sherif ZA and Deverapalli M contributed to literature review, citation, and referencing; Ashktorab H, Brim H, Gholamreza O, and Sherif ZA contributed to data analysis & interpretation; Sherif ZA and Deverapalli M contributed to manuscript writing and editing; Brim H, Ashktorab H, and Gholamreza O contributed to manuscript reading and editing; Suryanarayana RC, Martirosyan Z, Whitesell P, Pizuorno AM, Naqvi Z, Tulloch IK, Ashktorab H, Brim H, and Sherif ZA contributed to proofreading; Sherif ZA contributed to manuscript revising and responding to the reviewers.

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SCIENTOMETRICS

Physician-scientists or celebrities? Kardashian-index of gastroenterologists

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Abstract

BACKGROUND

The coronavirus disease 2019 pandemic unleashed a flood of untrustworthy information on social media platforms, resulting in the unfortunate consequence of expert scientists' opinions getting lost amidst the chaotic sea of misinformation. The question of how much influence these esteemed scientists hold on social media platforms remains elusive. To address this scientific quandary, we sought to explore the concept of the Kardashian index (K-index), a term introduced by Hall in 2014. This metric provides a rudimentary means of evaluating whether a physician scientist's popularity on social media aligns with their significant scientific contributions.

AIM

To evaluate if a Gastroenterologist physician's popularity on social media is at par with their scientific contributions (research articles and publications).

METHODS

We conducted an extensive search to identify all gastroenterologists actively practicing and associated with the top 100 hospitals as reported by the United States News. We collected specific data on a sub-group including their names,

affiliations, degrees, and sub-specializations. To gauge their social media popularity, we utilized the K-index calculation which is determined by dividing the actual number of Twitter followers by the number of researcher's citations. The expected number of followers (F) is calculated using the formula F = 43.3 C ^ 0.32, where C represents the number of citations.

RESULTS

Physicians affiliated with the Mayo Clinic emerged as the most prominent presence on Twitter, constituting 16% of the total. They were followed closely by physicians from Mount Sinai Hospital (9%) and the University of Michigan Hospital (9%). Surprisingly, 76% of the physicians evaluated exhibited a low K-index, falling within the range of 0 to less than 2. This suggests that a significant number of highly influential physician-scientists are not receiving due recognition, as indicated by their relatively low number of followers. On the other hand, 24% of the physicians had an inflated K-index, exceeding 5, which positioned them as the "Kardashians". These individuals enjoyed greater social media popularity than their actual scientific contributions. Interestingly, our analysis revealed no discernible association between sex and K-index (*P* value of 0.92).

CONCLUSION

In the gastroenterology field, our study estimated that a majority (76%) of highly researched physicians are undervalued despite their significant scientific contributions.

Key Words: Kardashian index; Gastroenterology Twitter; Kardashian index of gastroenterology; Physician-scientists; Social media; Physician celebrities

Core Tip: Twitter has become the most used social media by physicians to connect with colleagues and disseminate health information. People are prone to believing any information posted on social media to varying degrees. Thus, when do we consider this information factual and the truth? In our study, we used the Kardashian index to estimate whether the Twitter followers of the top 100 gastroenterologists are relatable to their scientific contributions in terms of citation of their scholarly works, and we found the majority of the gastroenterology physician scientists scored < 2 because of inactivity on Twitter and very low number of followers. We postulated that an avenue to mitigate the prevalence of misinformation on social media could emerge by involving a greater number of physician-scientists on this platform. Their engagement, coupled with the dissemination of their research discoveries could contribute significantly to this endeavour.

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INTRODUCTION

The role of social media platforms in the promotion and exposure of medical literature has shown marked improvement in the last several years. Numerous societies and journals patronize Twitter, Facebook, and other platforms to bring their readership closer to their published articles. Twitter, with an estimated 300 million monthly users, has become a major nerve center between medical practitioners, patients, journals, and healthcare for discussion and transit of information. A directory of researchers on Twitter does not exist, hence it is difficult to estimate the percentage of researchers that patronize this popular media[1] A systematic review of scholars on Twitter by Costas *et al*[2] identified > 385000 scholars linked to a Twitter account, however, the number varies based on level of productivity, identifying scholars with a higher level of productivity to have a stronger presence on Twitter especially those in social science and humanities by discipline. The K-index was proposed by Neil Hall in 2014 to study the effect the number of Twitter followers a physician or scientist has on the degree of citation of their research publications[3]. It was inspired by a popular celebrity with millions of followers on social media, Kim Kardashian. Her status, though not related to academics galvanized a new index to measure the dissemination of research to reach millions of people. The concept of the K-index centers around the fact that the popularity of a clinician on Twitter depends on the number of followers. The more followers, the more fame and success which in turn increases a gastroenterologist's research visibility, thus increasing the likelihood of having more citations of research articles. A couple of studies have been published for other specialties correlating the effect of their social media influence on their scientific works. We, therefore, sought to evaluate that of gastroenterologists. Our study hypothesized that many high-impact gastroenterology (GI) physicians don't have a significant social media presence limiting their outreach and popularity among the public, despite significant scholarly work.

MATERIALS AND METHODS

We conducted an extensive search using usnews.com to identify all gastroenterologists currently practicing and affiliated with the top 100 hospitals as reported by the United States Health News and World Report. From this comprehensive search, we collected specific sub-group data including names, affiliations, degrees, and sub-specializations. Additionally, we collected other variables such as sex, title [Doctor of Medicine degree (MD) or Doctor of Osteopathic Medicine (DO)], and number of years in practice. We randomized the data using randomization software to ensure unbiased selection and selected the top 2000 gastroenterologists for our study.

Utilizing Twitter as our chosen social media platform, we evaluated the number of followers for each of these selected gastroenterologists, excluding those whose accounts were no longer active. It's important to note that we were unable to determine the occupation of each follower, thus we could not ascertain whether the majority were medical professionals or not.

To authenticate the number of citations, we utilized various publications and citation search engines, including Semantic Scholar, Scopus, ResearchGate, and Google Scholar. The K-index was then calculated using the formula K-index = $F_{(a)}/F_{(c)}$, where $F_{(a)}$ represents the number of Twitter followers and $F_{(c)}$ represents the number of followers based on citations. The actual trend of Twitter follows was described using the formula $F = 43.3\ C^{0.32}$, where F denotes the number of Twitter followers and C represents the number of citations.

A higher K-index suggests a lower proportion of actual scientific contribution in relation to the number of followers on Twitter. Demographic data were presented as mean or median values, and associations were assessed using appropriate statistical tests such as *t*-tests, chi-square tests, and Spearman tests. Further evaluation of significant results was performed using ordered logistic regression. All statistical analyses were conducted using STATA version 15.1.

RESULTS

A total of 1979 GI physicians had analyzable data. 98.8% (n = 1956) were MDs and 1.16% (n = 23) were DOs. Only 6.6% (n = 131) had an extra-degree. The mean years as faculty was 19.8 years (SD = 9.4). Only 16.6% (n = 330) had an active Twitter account and among them 66% (n = 218) were males, and 34% (n = 112) were females. Only 2.5% (n = 50) of Twitter-using physicians had an extra degree and their median years as faculty was 18 (SD = 8.6). The most dominant presence on Twitter was by physicians from Mayo Clinic (16%), followed by Mount Sinai Hospital (9%) and the University of Michigan Hospital (9%) (Figure 1, Table 1). Approximately 76% of the physicians studied exhibited a low K-index (ranging from 0 to less than 2), suggesting a significant under-representation of highly influential physician-scientists on Twitter. Conversely, 24% displayed an inflated K-index (> 5), classifying them as "Kardashians" or physician celebrities, implying that their popularity surpasses their actual scientific contributions. (Figures 2 and 3). We found no association between sex and K-index (P value = 0.92). There was a significant association between K-index and extra degree (P = 0.17). A higher K-index was associated with lower odds of an advanced degree [odds ratio (OR): 0.74, 95% confidence intervals (95%CI): 0.57-0.96, P value = 0.03] when adjusted for sex and years as faculty. There was a significant association between the number of years as faculty and K-index (P value = 0.008) but this association did not remain significant when adjusted for sex, years on Twitter, and extra degree (P value = 0.69). A higher number of years of Twitter use leads to higher K-index (OR: 1.39, 95%CI: 1.11-1.74, P value = 0.004) after controlling for sex, years as faculty, and extra degree.

DISCUSSION

Some gastroenterologists have utilized Twitter as a platform for sharing interdisciplinary discussions and raising awareness about their areas of expertise. Out of the 1979 GI physicians analyzed, only 16.6% maintained an active Twitter account. Among the Twitter users, 76% had a K index ranging from 0 to less than 2 depicting undervalued on social media, despite their scientific contribution. The adoption of social media among physicians significantly increased from 41% in 2010 to approximately 90% in 2011[4]. A study by Madde and Zickuhr[5] suggested that social media usage grew by 43% between June 2009 and 2010, becoming the most time-consuming internet activity[6].

Analysis of social media usage has revealed some notable trends. Twitter appears to be more popular among individuals aged 15 to 29, compared to only around 7% of those over 65-years-old[7]. According to a survey conducted by Woitowich *et al*[8] on sex differences in social media usage among physicians, the majority of respondents were women. However, men were found to utilize social media more extensively for building professional networks and staying updated on research and clinical topics[9]. Another study by Demailly *et al*[10] focused on anesthesia and critical care researchers reported lower visibility of women compared to their male counterparts on a scientific research-dedicated social network called ResearchGate. Similarly, our study found that male GI physicians had a higher prevalence of Twitter usage (66%) compared to females (33%).

Although our data analysis did not show a significant difference between sex and K-index (P value = 0.92), it revealed an association between years of experience as faculty and K-index. However, when adjusting for sex, years on Twitter, and additional degrees, this association no longer remained significant (P value = 0.69). It is important to note that the K-index, used as a measure of celebrity status, has been referenced to evaluate researchers in certain clinical specialties such as cardiology and interventional neuroradiology. The K-index studies conducted by Khan *et al*[11] and Vilanilam *et al*[12] on cardiologists and interventional neuroradiologists, respectively, demonstrated that most physicians on Twitter had a

Table 1 Top 15 hospitals contributing to most gastroenterology physician users on Twitter

	Frequency	Percent
Stanford Healthcare-Stanford Hospital	12	6.90
Baylor College of Medicine	13	7.47
Brigham and Women's Hospital	14	8.05
Cedars-Sinai Medical Center	10	5.75
Cleveland Clinic	13	7.47
Hospitals of University of Pennsylvania-Penn Presbyterian	9	5.17
Jefferson Health-Thomas Jefferson University Hospitals	10	5.75
Massachusetts General Hospital	9	5.17
Mayo Clinic	27	15.52
Mount Sinai Hospital	15	8.62
NYU Langone Hospitals	8	4.60
New York-Presbyterian Hospital-Columbia and Cornell	8	4.60
University of Chicago Medical Center	11	6.32
University of Michigan Hospital-Michigan Medicine	15	8.62

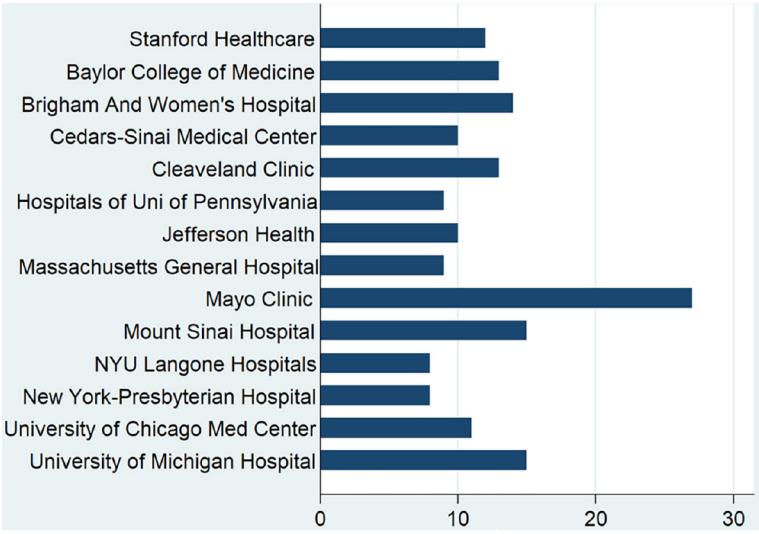

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Figure 1 Top 14 hospitals contributing to most gastroenterology physician users on Twitter.

low K-index between 0 and 2, while only a few were considered the Kardashians or physician-celebrities (K-index > 5), consistent with the findings of our study. However, it should be emphasized that the K-index formula has limited scientific value and may not accurately reflect a physician's true value and worth[3].

Nonetheless, spending more time on Twitter may have a positive impact on the citation of scholarly works. Recent studies have suggested a positive correlation between highly tweeted articles and increased citations. For instance, a study by Haustein *et al*[13] on tweeting biomedicine, demonstrated a positive correlation between tweeting and citation behavior across various specialties. Eysenbach[14] reported that highly tweeted articles were more likely to be cited than less tweeted articles, with statistically significant Pearson correlation coefficients ranging from 0.42 to 0.72 for log-transformed Google Scholar citations. Gunaratne *et al*[15] illustrated that articles tweeted by authors experienced a 3.08-fold increase in citations within a year and a 1.51-fold increase in total citations. Furthermore, a recent prospective randomized controlled trial study by Luc *et al*[16] found that tweeted articles achieved a significantly higher increase in altmetric scores compared to non-tweeted articles, along with a greater change in citations in 1 year.

The issue of information authenticity on social media is a contentious one, particularly since many individuals rely on social media instead of journals or guidelines. Our hypothesis is that if highly cited GI physicians become more active on Twitter, it may be possible to raise the K-index of a majority of physicians to 3. This would lead to more tweets on published research articles and guidelines, attract more followers, and potentially reduce the dissemination of

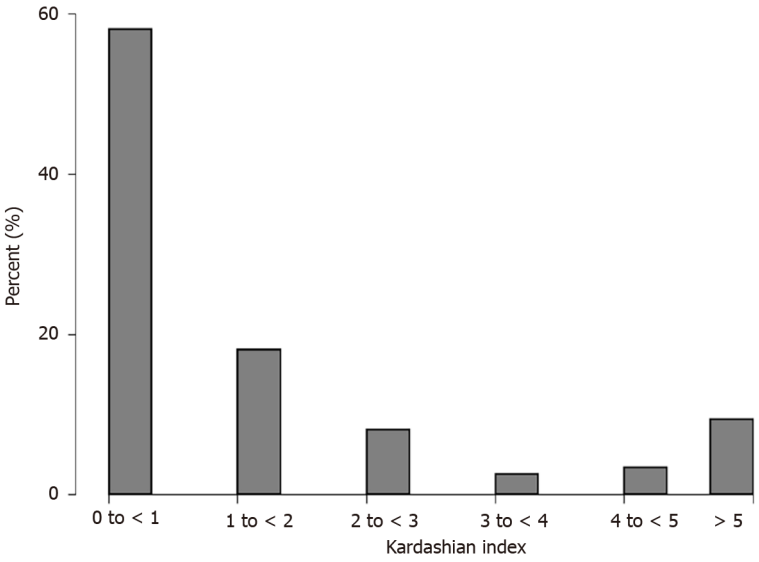

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Figure 2 Kardashian index of gastroenterology physicians on Twitter.

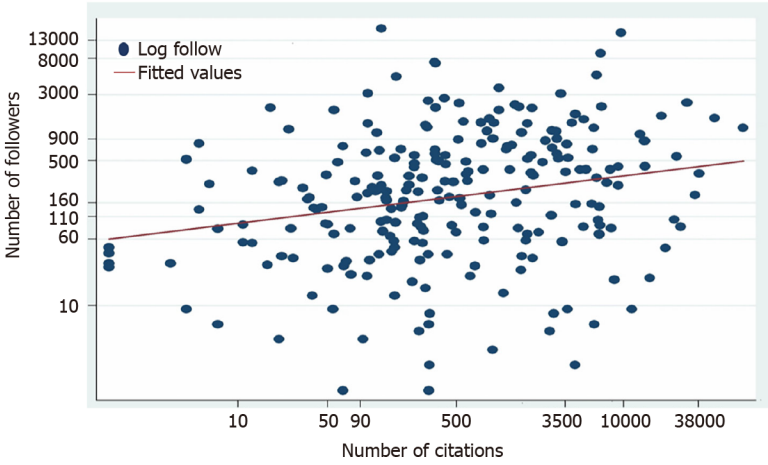

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Figure 3 Number of followers of studied gastroenterology physicians on Twitter *vs* the number of citations for their publications.

misinformation. Aside from increasing research citations and providing factual health information to the public, Twitter offers various other benefits. As a GI physician on Twitter, you have the opportunity to network with colleagues, recruit diverse applicants for fellowship programs, participate in discussions like the Monday night inflammatory bowel disease initiated by John Hopkin's GI physician, Dr. Charabaty, and engage in academic forums like Liver Twitter, which focuses on sharing contents related to chronic liver diseases with a global audience[9,17]. GI mentors with high Twitter impact who are advanced in their field can use this medium to promote the accomplishments of their mentees, increase their visibilities, and open up channels for additional career opportunities[18].

Certain limitations are associated with the K-index. Younger researchers tend to score higher due to a faster accumulation of Twitter followers compared to lifetime citations. Additionally, effective communication of scientific knowledge to attract a large audience is a necessary skill. Furthermore, researchers working in fields with highly ranked professionals are more likely to have their articles cited compared to those in smaller fields[19]. Our data analysis revealed that most GI physicians active on Twitter were affiliated with top-ranked hospitals, with Mayo Clinic having the highest percentage (16%) of physicians with an active Twitter presence, followed by Mount Sinai Hospital (9%) and the University of Michigan Hospital (9%).

It is important to acknowledge the limitations of our study. Firstly, our focus was solely on GI physicians on Twitter due to the original Kardashian study's emphasis on Twitter. We were unable to determine how many of the Twitter followers were medical professionals likely to retweet or quote articles. We also were not able to analyze the contents of the Tweets. Although we conducted a thorough search, there remains a chance that certain Twitter accounts might have eluded detection. Lastly, it is worth noting that the Kardashian formula lacks scientific validation to determine a physician's worth. It is common for celebrity physicians to forgo the humorous intent behind the creation of the K-index

by Hall and take it too seriously, misinterpreting it in a different light than it was created. Hall, 2014 advocated that physicians on Twitter may find it useful to calculate their K-index and attach it to their profile.

CONCLUSION

In conclusion, encouraging highly cited GI physicians to be more active on Twitter may have positive implications, including increased citation of research works and the availability of accurate health information. Twitter also offers opportunities for networking, recruitment, and participation in academic discussions. Nonetheless, the K-index has its limitations, and caution should be exercised when interpreting its results. By sharing and retweeting articles, fostering scientific discussions, forming professional connections, and potentially boosting the impact factor of journals through increased citations, Twitter can serve as a valuable platform. However, it is essential to remember that having an opinion on a subject does not automatically make one an expert. Increased participation of GI physician-scientists on Twitter, specifically in sharing new clinical guidelines and research findings, may help combat misinformation within the GI community.

ARTICLE HIGHLIGHTS

Research background

There is a growing recognition among certain physicians about the significance of social media in facilitating the dissemination of research findings. While some physicians are beginning to appreciate the usefulness of social media, a ton of others are yet to comprehend its importance. In 2014, Hall proposed the K-index as a scientific metric aimed at evaluating if a physician's celebrity status on Twitter (assessed by the high number of followers) is at par with their scientific contributions based on the number of cited research work.

Research motivation

The coronavirus disease 2019 pandemic brought about a lot of misinformation on social media relating to its treatment and prevention. Hence, there arose a need to measure the scientific contribution (number of cited research works) of physician celebrities on Twitter. A study on the K-index of cardiology showed that the majority of the cardiologists on Twitter had a K-index < 2 (indicating more research works compared to the number of social media followers). We were motivated to find out the K-index of gastroenterologists on Twitter.

Research objectives

Our objectives are: (1) To assess whether a gastroenterologist's celebrity status on Twitter equates to the number of published and cited research works; (2) to assess the Twitter activity level of the gastroenterologists in the Top 100 hospitals as reported by the United States World News; and (3) to determine the effect of high Twitter followers on the number of cited scholarly works.

Research methods

An extensive search was done to identify all gastroenterologists actively practicing and associated with the top 100 hospitals as the United States News reported. We collected specific data on a sub-group including their names, affiliations, degrees, and sub-specializations. To gauge their social media popularity, we utilized the K-index calculation which is determined by dividing the actual number of Twitter followers by the number of researcher's citations. The expected number of followers is calculated using the formula $F = 43.3\ C^{0.32}$, where C represents the number of citations.

Research results

We found that physicians affiliated with Mayo Clinic emerged as the most prominent presence on Twitter, constituting 16% of the total. They were followed closely by physicians from Mount Sinai Hospital (9%) and the University of Michigan Hospital (9%). 76% of the physicians evaluated exhibited a low K-index of 0-2 which suggested that a significant number of highly influential physician-scientists are not receiving due recognition, as indicated by their relatively low number of followers. However, 24% of the physicians had an inflated K-index of > 5, which positioned them as the "Kardashians" or physician celebrities. These individuals enjoyed greater social media popularity than their actual scientific contributions.

Research conclusions

Encouraging highly cited gastroenterology physicians to be more active on Twitter may have positive implications, including increased citation of research works and the availability of accurate health information and research findings for the public. Twitter also offers opportunities for networking, recruitment, and participation in academic discussions.

Research perspectives

Some physicians, though, may misunderstand the intent of creating the K-index measure. We have been able to determine from the literature review that active presence on Twitter as evidenced by increased tweeting and retweeting

of articles can help boost citation and the H-index of scientists. Physicians who are actively invested in research may find an alternative way to get the result of their research findings to the public and increase their visibility. Mayo Clinic has been at the forefront of utilizing socialmedia in health care, embarking on its journey with podcasting in 2005 and eventually expanding to various social media platforms like Twitter, YouTube, and Facebook. Their objective has been to disseminate the knowledge and expertise of their physicians to a wider audience while also providing a platform for patients to share their stories and experiences. By leveraging these channels, Mayo Clinic has effectively made healthcare information and personal narratives easily accessible to a diverse range of individuals. It is not surprising they ranked number 1 in our study. We hope that other programs will adopt and replicate this approach. In the future, we hope for a scientifically proven index or metric to assess a physician's impact and research influence.

FOOTNOTES

Author contributions: Malik US performed the analysis and wrote both the methods and results; Akbar AU and Zamani Z assisted in data analysis and findings; Ugonabo O performed a comprehensive literature review, wrote the introduction, discussion, and edited and merged all of the author's contributions to fit with the Journal's requirements; Akbar AU assisted in reviewing the manuscript; Frandah W did a final review of the manuscript and made significant contributions before submission to the journal.

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SCIENTOMETRICS

Mapping research trends of transarterial chemoembolization for hepatocellular carcinoma from 2012 to 2021: A bibliometric analysis

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the second leading cause of cancer-related deaths. Transcatheter arterial chemoembolization (TACE) is a therapy where drugs aimed to slow or halt tumor development are injected into the artery supplying for HCC tissues. A comprehensive analysis of all the articles on TACE for HCC can give us a general understanding of the progress in this field and provide guidance for future research.

AIM

To analyze and visualize scientific results and research trends in TACE treatment for HCC.

METHODS

The "Web of Science" database was used to identify articles regarding TACE for the treatment of HCC from 2012 to 2021. VOSviewer and CiteSpace were used to analyze the publications trends, collaboration between countries/institutions/authors, and the co-occurrence of keywords, keyword bursts, and references.

RESULTS
A total of 5728 original articles on TACE for HCC were retrieved. Regarding the volume of publications, the total number of yearly publications showed a generally increasing trend. China had the highest number of articles, while the United States achieved the highest Hirsch index and highest number of citations. The Sun Yat-sen University in China was most prolific institution. The most active author was Park, J.W from South Korea. The Journal of Vascular and Interventional Radiology (234 articles) was the most productive journal. There is a growing trend toward international collaboration in TACE for HCC. Cluster networks of co-cited references suggested that practice guidelines and targeted therapies are an essential theme in this field. In addition, cluster analysis based on keyword co-occurrence identified the research topic "prediction of TACE treatment" as a hotspot, and propensity score matching can be used to help investigators conduct innovative studies in the future.

CONCLUSION
The results of our bibliometric analysis provide the latest trends and hot topics in TACE therapy for HCC.

Key Words: Transarterial chemoembolization; Hepatocellular carcinoma; VOSviewer; CiteSpace; Bibliometrics

Core Tip: Transarterial chemoembolization (TACE) has been considered the standard of care for intermediate stage hepatocellular carcinoma (HCC). Bibliometric analysis assesses the scientific activity in a given field. Based on the assessment of database and literature characteristics, bibliometrics can estimate developing trends in a scientific manner and expose research frontiers to researchers. Knowledge of the literature in TACE treatment for HCC can lead to a better understanding of the research trends in the field. The results of this bibliometric analysis provided the updated trends and hot topics in TACE treatment of HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the second leading cause of cancer-related deaths[1]. Approximately 70% of patients with HCC are diagnosed at an intermediate to advanced stage, when curative treatment is no longer feasible[2]. Conventional transarterial chemoembolization (cTACE) is performed by injecting chemotherapeutic agents and lipiodol emulsion through a catheter into the tumor supply artery under the guidance of medical imaging, followed by the injection of gelatin sponge particles to embolize the tumor vessel[3]. According to the current guidelines[4,5], TACE is the recommended first-line treatment for patients with Barcelona Clinic Liver Cancer stage B (BCLC-B) disease, defined as a multinodal tumor burden, preserved liver function and good performance status.

Recent advances in TACE techniques, such as the well-known drug-eluting bead TACE (DEB-TACE), have demonstrated the potential to improve the overall survival of patients with intermediate to advanced HCC[6,7]. Studies on the combination of TACE with other treatment modalities, such as thermal ablation[8], radiotherapy[9] or systemic therapy[10], have been actively conducted and have achieved encouraging results. A comprehensive analysis of all the articles on TACE for HCC can give us a general understanding of the progress in this field and provide guidance for future research.

Bibliometric analysis assesses the scientific activity in a given field[11]. Based on the assessment of database and literature characteristics, bibliometrics can estimate developing trends in a scientific manner and expose research frontiers to researchers[12]. In recent decades, a large number of bibliometric analyses have been utilized in the medical field[13]. However, comprehensive bibliometric studies on TACE for HCC are still lacking. Therefore, the aim of this study was to systematically analyze studies on TACE for HCC to determine its current status and assess future trends.

MATERIALS AND METHODS

Data sources and search strategies

Ethics Committee approval was not required for this study as it did not involve intervention or data collection in animal or clinical trials. Articles were obtained from the Web of Science (WoS) with a time limit of January 1, 2012 to December 30, 2021, using the following search terms: TS = (Hepatocellular Carcinoma OR HCC OR Liver Cancer OR Liver

Neoplasms OR Hepatic Neoplasms OR Cancer of Liver) AND TS = (Chemoembolization OR Chemoembolisation OR Transcatheter Embolization OR Transcatheter Chemoembolization OR TACE OR Transarterial chemoembolization). Inclusion criteria included: articles from peer-review journals; written in English. We also excluded reports, books or book chapters, conference proceedings, dissertations, theses, expert opinion, commentaries, editorials, and letters. We excluded 102 studies from the list after removing duplicates because they failed all inclusion criteria or met at least one exclusion criterion. The complete screening process is shown in Table 1.

Data collection

Two reviewers selected the articles independently, and any discrepancy was solved through discussion. We used the bibliometric method, VOSviewer 1.6.13 and CiteSpace 5.8.R2 to identify the data, including authors, affiliations, countries/regions, journals, number of papers and citations, year of publication, Hirsch index (H index), keywords, and references. The H index is used to quantify an individual's scientific research output and measure the impact of his or her research[14]. In this study, journal impact factors (IFs) were collected from journal citation reports for 2021.

Data analysis

In this study, the following network graphs were constructed and visualized using VOSviewer: A network graph of co-cited authors and journals, and a co-occurrence analysis of keywords. According to the frequency of items appearing together, co-citation and co-occurrence analysis can reflect the relationship of the items[15]. Additionally, in the network visualization, each node represents a different item, such as author, journal, country/region, or keyword, and the different colors of the nodes indicate different classification criteria or frequency of occurrence. The size of the node represents the number of citations or occurrences, and larger nodes represent higher-level citations or occurrences[16]. The links between nodes demonstrate the relevance of the items' co-citation or co-occurrence, and the thickness of the lines represents the strength of the links.

In addition, another bibliometric software called CiteSpace is used to show new trends and developments in the scientific literature. It is multidimensional, time-shared, dynamic visual analysis software. Burst detection is used to detect abrupt changes in nodes (including authors, countries, keywords, *etc.*). In this study, we use CiteSpace 5.8.R2 to identify highly cited references and keywords with the strongest citation burst during a certain period.

RESULTS

An overview of publications

From 2012 to 2021, a total of 5728 articles from the last decade were retrieved from WoS, including 72,403 citations for the retrieved articles, with an average number of citations (Nc) per article of 20.67. The H-index for all publications was 111. Supplementary Figure 1 shows the geographical distribution of the total number of papers on TACE for HCC.

Annual trend of paper publication quantity

Figure 1 demonstrates the annual number of papers (Np) related to TACE for HCC. Overall, despite fluctuations over the decade, the number of annual papers increased from 440 in 2012 to 733 in 2021, while Np increased to a peak in 2021.

Analysis of the active countries, institutions and co-authors

The included studies were published in 77 countries and regions in the last decade. We ranked the 10 high-output countries for all authors according to Np (Table 2). China had the highest number of publications (2109), followed by the United States (USA) (1100) and Japan (746). According to the citation analysis, the USA had 31045 citations, followed by China (22453) and Japan (10739). In addition, the USA achieved the highest H-index (71), followed by China (61) and South Korea (49). Overall, 201 institutions contributed to this area. Table 3 displays the five most productive institutions, all of them from Asian countries. Sun Yat-sen University (from China) was the most productive institution, followed by Fudan University (from China) and Seoul National University (from South Korea). Figure 2A shows the trend of global collaboration. There is extensive collaboration among active countries. China has the closest cooperation with the USA and the United Kingdom. Three countries– China, the USA and the United Kingdom–have shown more active cooperation with each other. Figure 2B shows that the organizations are also interacting very closely. Sun Yat-sen University (China) and Johns Hopkins University (USA) are the principal institutions leading collaborative research. The co-author network knowledge map provides relevant links between authors to help researchers access potential collaboration opportunities. As shown in Figure 3, the top three prominent nodes include llovet, J. M., Lencioni R. and Kudo M.

Analysis of highly cited articles

Figure 4 Lists the number of the highest local citation score (LCS) per year for the top 20 articles. The paper is written by Park, J.W in 2015 had the highest LCS of 465 and was ranked first. This is a large multicenter, multinational collaborative retrospective study published in Liver International. The study concluded that TACE was the commonly usedin North America, Europe, China and Korea, regardless of disease stage. Most of the articles with high LCS were conducted in multicenter and international studies and focused on major issues in TACE for HCC. Supplementary Table 1 shows the study characteristics of the top 10 highly cited articles. When the threshold is set at 3, most studies focused on the clinical perspective and conventional TACE-based combination therapies.

Table 1 Topic search quires and refinement procedure

Step	Results	Refinement
1	13393	TS = (Hepatocellular Carcinoma OR HCC OR Liver Cancer OR Liver Neoplasms OR Hepatic Neoplasms OR Cancer of Liver) AND TS = (Chemoembolization OR Chemoembolisation OR Transcatheter Embolization OR Transcatheter Chemoembolization OR TACE OR Transarterial chemoembolization)
2	8530	Refined by publication years: (2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020 OR 2021)
3	5830	Refined by document types: Articles
4	5728	Refined by languages: English

TS: Topic; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization.

Table 2 The top ten countries/regions with the highest productivity

Rank	Country/Region	Np	Nc	Average per item	H-index
1	China	2109	22453	13.17	61
2	United States	1100	31045	30.41	71
3	Japan	746	10739	16.03	46
4	South Korea	595	10605	19.92	49
5	Germany	371	5529	16.04	37
6	Italy	279	9252	34.27	45
7	China Taiwan	244	5330	22.84	34
8	France	190	6609	35.97	35
9	Egypt	120	969	8.72	18
10	England	106	3554	34.74	29

H-index: Hirsch index; Np: Number of papers; Nc: Number of citations.

Table 3 The top five most productive affiliations

Rank	Affiliations	Country	Np	Nc	Average per item	H-index
1	Sun Yat-senUniversity	China	228	4360	20.53	34
2	Fudan University	China	146	2991	21.15	27
3	Seoul national University	South korea	112	1497	14.23	23
4	Ulsan University	South korea	111	2033	19.51	25
5	Yonsei University	South korea	109	2126	20.35	25

H-index: Hirsch index; Np: Number of papers; Nc: Number of citations.

Productive journals

A total of 1247 journals published articles in the field. Furthermore, we list the 10 most productive journals with their impact factors in Table 4, and provide a map of the most productive journal in Figure 5. According to statistics from the WoS, Journal of Vascular and Interventional Radiology ranked first with 234 publications in the last decade. Cardiovascular and Interventional Radiology ranks second (220 publications), followed by World Journal of Gastroenterology (143 publications), Medicine (118 publications), and PLoS One (113 publications).

Analysis of co-cited references

Unlike local citation analysis, co-citation networks emphasize research topics that are closely linked to a specific field. The reference co-citation relationship changes over time, and its study can explore the development and evolutionary dynamics of a particular study. Figure 6A shows the mapping of co-cited references based on TACE treatment. Figure 6B depicts the top 20 references with the strongest citation explosion. The most cited references and the highest concen-

Table 4 The top 10 most active journals

Rank	Journal	Np	Nc	Average per item	H-index	IF (2021)
1	*Journal of Vascular and Interventional Radiology*	234	3858	17.41	33	3.682
2	*Cardiovascular and Interventional Radiology*	220	2845	13.86	26	2.797
3	*World Journal of Gastroenterology*	143	3423	24.25	33	5.374
4	*Medicine*	118	1057	9.16	18	1.817
5	*PLoS One*	113	2108	18.94	26	3.752
6	*European Radiology*	108	1441	14.13	21	7.034
7	*Hepatology Research*	81	1434	18.32	21	4.942
8	*Frontiers in Oncology*	77	278	3.83	9	5.738
9	*Oncotarget*	75	1119	15.17	19	/
10	*BMC Cancer*	74	1487	20.18	23	4.638

H-index: Hirsch index; Np: Number of papers; Nc: Number of citations; IF: Impact factors.

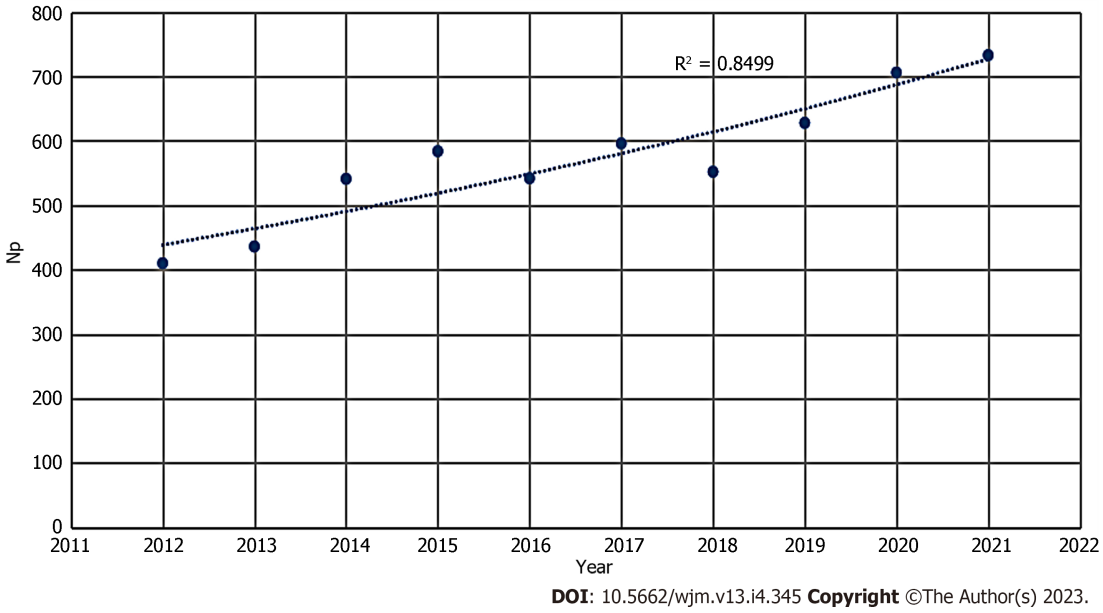

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Figure 1 Curve fitting of publications' overall yearly growth trend. Np: Number of papers.

tration of TACE treatment for HCC are "practice guidelines" and "targeted therapy".

Keywords co-occurrence analysis

The high frequency and centrality of keywords allows exploration of core issues and research hotspots of broad interest in the field. A total of 192 terms that appeared more than 20 times were grouped into five clusters. The top three clusters are as follows: Cluster 1 (red) mainly represented the prediction of TACE treatment, as shown in Supplementary Figure 2A. Cluster 2 (green) is focused on vascular endothelial growth factor (VEGF) expression and tumor angiogenesis. Cluster 3 (blue) was the drug-delivery method. The top frequent occurrences of keywords were "HCC", "survival", "management" and "prognosis", indicating that the main focus of research is placed on the prognosis of TACE treatment. Additionally, "drug-delivery method", "targeted therapy" and "response assessment" have long been a focus of research in the field, as shown in Supplementary Figure 2B. Additionally, we found that the propensity score matching was increasingly used to assess TACE safety/efficiency (Supplementary Figure 2C).

DISCUSSION

To the best of our knowledge, this is not the first but comprehensive bibliometric analysis of TACE management in HCC.

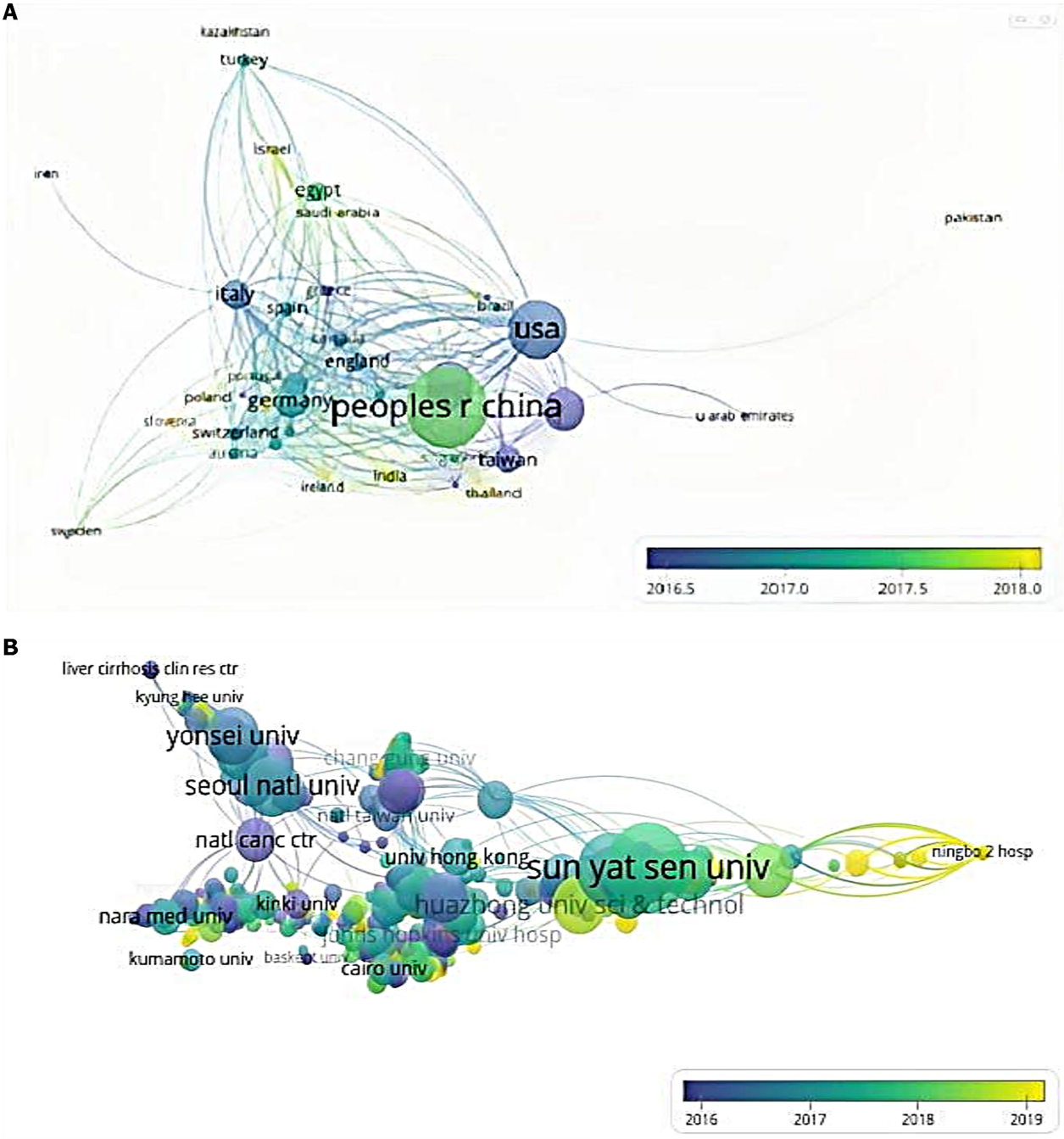

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Figure 2 Shows the trend of global collaboration, the organizations are also interacting very closely. A: Mapping of the main research countries in transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC). The minimum number of documents of a country was set at 5. Of the 80 countries that were involved in this field, 42 countries met the threshold; B: Mapping of the collaboration network of the main research organizations in TACE for HCC. The minimum number of documents of an organization was set at 15. Of the 2146 organizations that were involved in this field, 74 organizations met the threshold.

A unique database was created, duplicate articles were removed and then selected articles were analyzed along different dimensions: Bibliometrics, demographics, authors, and research trends. The overall increasing trend in the number of papers from 2011 to 2021 reflects a relatively promising research future for TACE in the coming years.

Among the most prolific countries/regions, China ranked first in Np, indicating that China is a highly productive country in this field. Two Chinese institutions and three South Korean institutions came in the top 5 affiliations in Np. According to the GLOBOCAN database, Asia accounts for nearly 72.5% of newly diagnosed cases and 72.4% of deaths from HCC[17]. The BRIDGE study in 2015 concluded that the survival times in South Korea and China were significantly less than that in Japan, which to some extent suggests that these two countries have invested significant resources in recent years. However, compared with China, the USA had a relatively high Nc and H-index. This is because the USA is undoubtedly the most impactful in scientific research fields. The USA has been at the center of academic publishing and has been supported by significant investments in academic research and technological innovation. In recent years, China has also invested heavily in innovative embolic materials for TACE. CalliSpheres® Beads are the first drug eluting beads

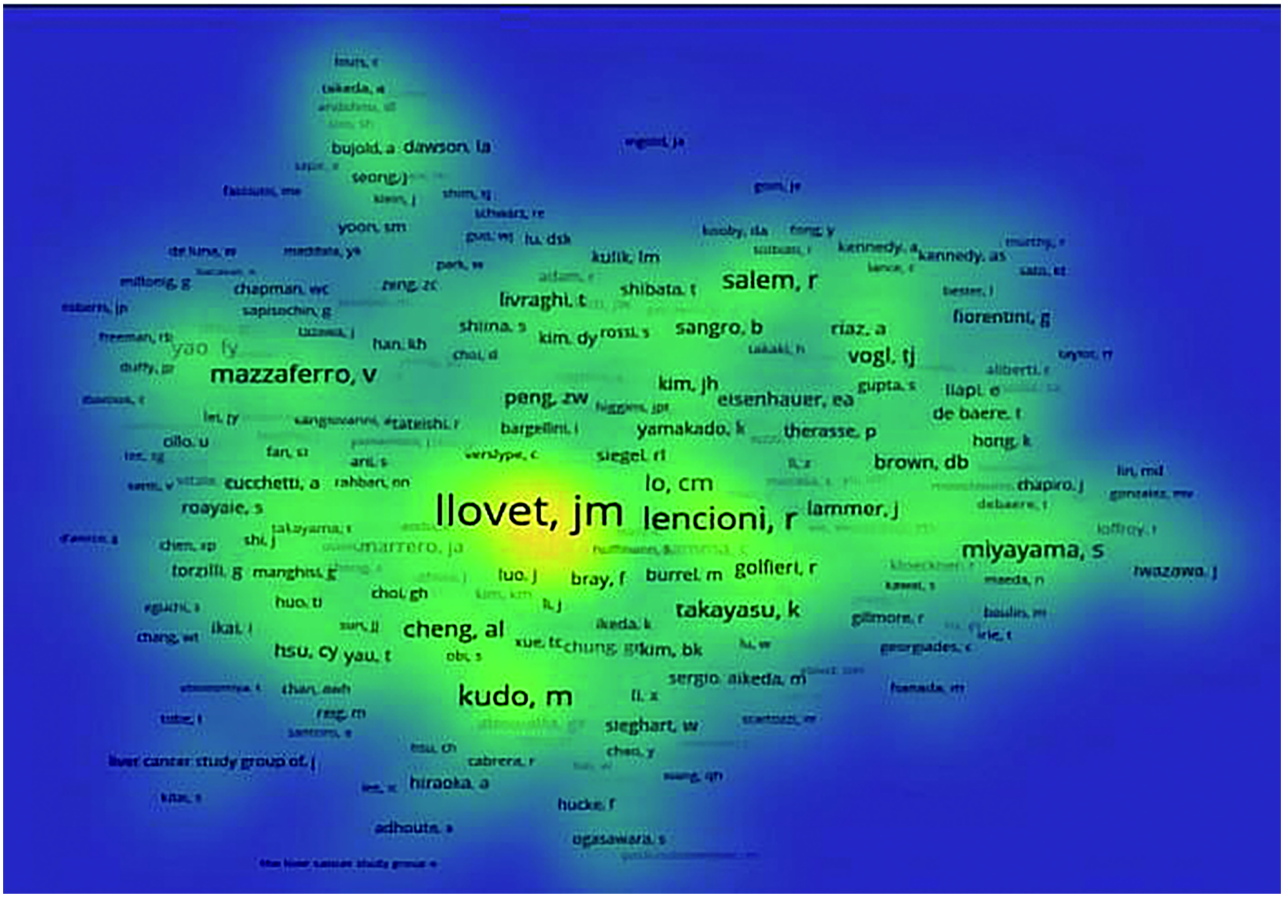

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Figure 3 Co-authorship network of productive authors conducting transarterial chemoembolization research. The minimum number of documents of an author was set at 5. Of the 8975 authors that were involved in the research field, 73 authors met the threshold. Yellow means appearing more frequently, while green means appearing less frequently.

(DEB) product available for HCC treatment in China, and studies have shown that HCC patients treated with CalliSpheres DEB-TACE have a better treatment response and safety than those treated with cTACE[18,19]. Notably, according to the global network of major research institutions and national collaboration, China could have a major impact on research in this area, and despite being a developing country, it has the strongest global collaboration. Large co-authorship nodes in the network diagram show llovet, J. M. occupying the central area, which is not surprising, as he has made significant contributions to this research. In terms of scientific influence a given field, co-authorship and researchers with a high H-index should be comparable, which helps researchers to understand the most influential authors and to seek potential collaboration opportunities with them.

Regarding the top 10 most productive journals, 7 journals have a relatively high IF score of more than 3. This shows that it is not hard to publish studies on TACE in high-quality journals. All of the top 10 high LCS articles were published in these journals with high IFs (IF > 5), including top journals in oncology and liver disease research, such as the Journal of Clinical Oncology and Hepatology. This implies that these journals have published potentially groundbreaking results in the field, which reminds researchers interested in the topic to pay more attention to these journals. We further analyzed the characteristics of the top 10 highly cited articles. In summary, these studies introduce the positive results of recent randomized clinical trials, and describe targeted therapy combination regimens for patients with intermediate stage HCC. Futhermore, we found that all of the studies were clinical studies, suggesting that the researchers in this field have a strong focus on the clinical perspective; however, basic/experimental research leading to major breakthroughs may have a good chance of being published in the top journals in the future.

Co-cited references show that the hotspots that have been of common interest are "practice guideline" and "targeted therapy". TACE is the only guideline-recommended standard of care for intermediate-stage HCC worldwide[20]. Therefore, relevant clinical guidelines are expected to be released every few years in both Western and Asian countries. Researchers have paid more attention to these clinical guidelines when conducting their studies. The explanation is that it is more standardized to conduct studies under clinical guidelines and that the guidelines provide us with possible next research hotspots. For example, the European Association for the Study of the Liver (EASL)-2018 clinical practice guideline sets the goal of treatment for HCC: Linking molecular subclasses in clinical trials to predict the treatment response and overall survival. Targeted therapy [tyrosine kinase inhibitor (TKI)] has been the main treatment for patients with advanced stage HCC for more than 10 years[21]. However, in 2019, lenvatinib was approved as an alternative to sorafenib for first-line targeted therapy for HCC[22]. Currently, studies have mainly focused on the molecular

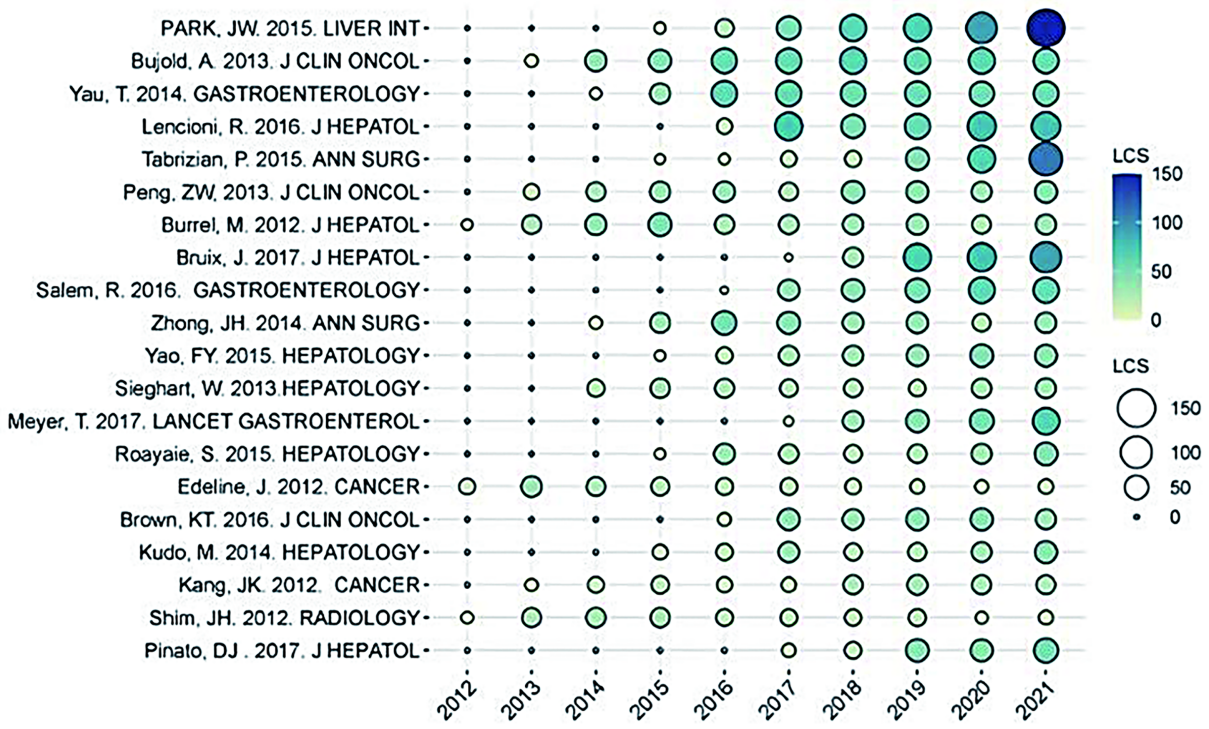

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Figure 4 The yearly number of local citations of papers with high local citations. The size and colors of the circle represent the high local citations of papers. LCS: High local citations.

mechanisms responsible for tumor progression and treatment resistance, the sequences and timing of drug administration, and which TKI drugs are most beneficial to patient survival from combination therapy[23,24].

Some emerging research on TACE is gradually becoming a research topic. Cluster 1 (red) primarily represented the prediction of TACE treatment. TACE benefits patients survival; however, repeated TACE therapy progressively impairs liver function. Careful evaluation of the risks and benefits of repeated TACE is needed to improve the long-term outcomes of TACE for HCC. Appropriate decision support has been established during TACE treatment, including the HAP (hepatocellular artery embolization prognosis) score and its modifications (mHAP-II and -III)[25]. A recent study by Wang *et al*[26] developed an easy-to-use model, referred to as the "six-and twelve" score, which stratifies ideal TACE candidates based on the sum of tumor size and number of lesions. Unfortunately, the results of some external validation studies suggested that the model only has a modest predictive ability[27,28]. More recently, Han *et al*[29] developed a survival prediction model that assesses patients prior to initial TACE. Although good results were obtained in the preliminary study, the utility of this model needs to be evaluated in future studies. Novel artificial intelligence approaches based on imaging data clearly hold great promise for the future. A study by Niu *et al*[30] demonstrated the feasibility of a CT-based radiomics model to predict the outcome of sequential TACE treatment.

Cluster 2 is involved in VEGF expression and angiogenesis in HCC. It has been demonstrated that both tumor progression and metastasis are closely related to tumor neoangiogenesis. VEGF is one of the most important angiogenic factors and is highly expressed in HCC tumors; it is associated with tumor angiogenesis, growth, recurrence, and metastasis[31]. Thus, studies on VEGF expression and angiogenesis may lead to novel therapeutic targets for HCC, particularly, in combination with TACE for HCC. Unfortunately, the ideal candidate for molecularly targeted drugs in combination with TACE remains uncertain. Currently, there are more than 1000 clinical trials enrolling patients, demonstrating a dedication to finding novel effective systemic therapeutics or targeting immune checkpoints for the treatment of HCC[32].

In terms of the "delivery method", conventional TACE using iodine oil loaded with anticancer drugs is less effective, and although DEB, including HepaSphere, CalliSpheres and TANDEM, are used, there are still problems of low response rates, as well as chemotherapeutic drug escape and tumor resistance[33]. Currently, the combination of nanodelivery systems with TACE is of interest. Due to the method of medication, the targeting effect of TKIs is poor, while nanodelivery systems can provide an opportunity to overcome the drawbacks and achieve good results[34]. Ding *et al*[35] developed peptide nanogels with a stimulatory response for the delivery of lenvatinib with good tumor suppression and few side effects. Although some nanoparticles (NPs) have been approved by the FDA for clinical use, the safety of NPs has been an unavoidable issue during human applications. Therefore, more in-depth experimental studies and clinical trials on various combinations of TACE and nanospheres are needed to explore the correlation between NP size and optimal drug loading and their impact on drug delivery properties.

In the last decade, technical improvements, mainly include: (1) The treatment should involve a water-in-oil emulsion, which maximize the propensity to target the tumor feeding arteries[36]; (2) improvement of imaging quality during

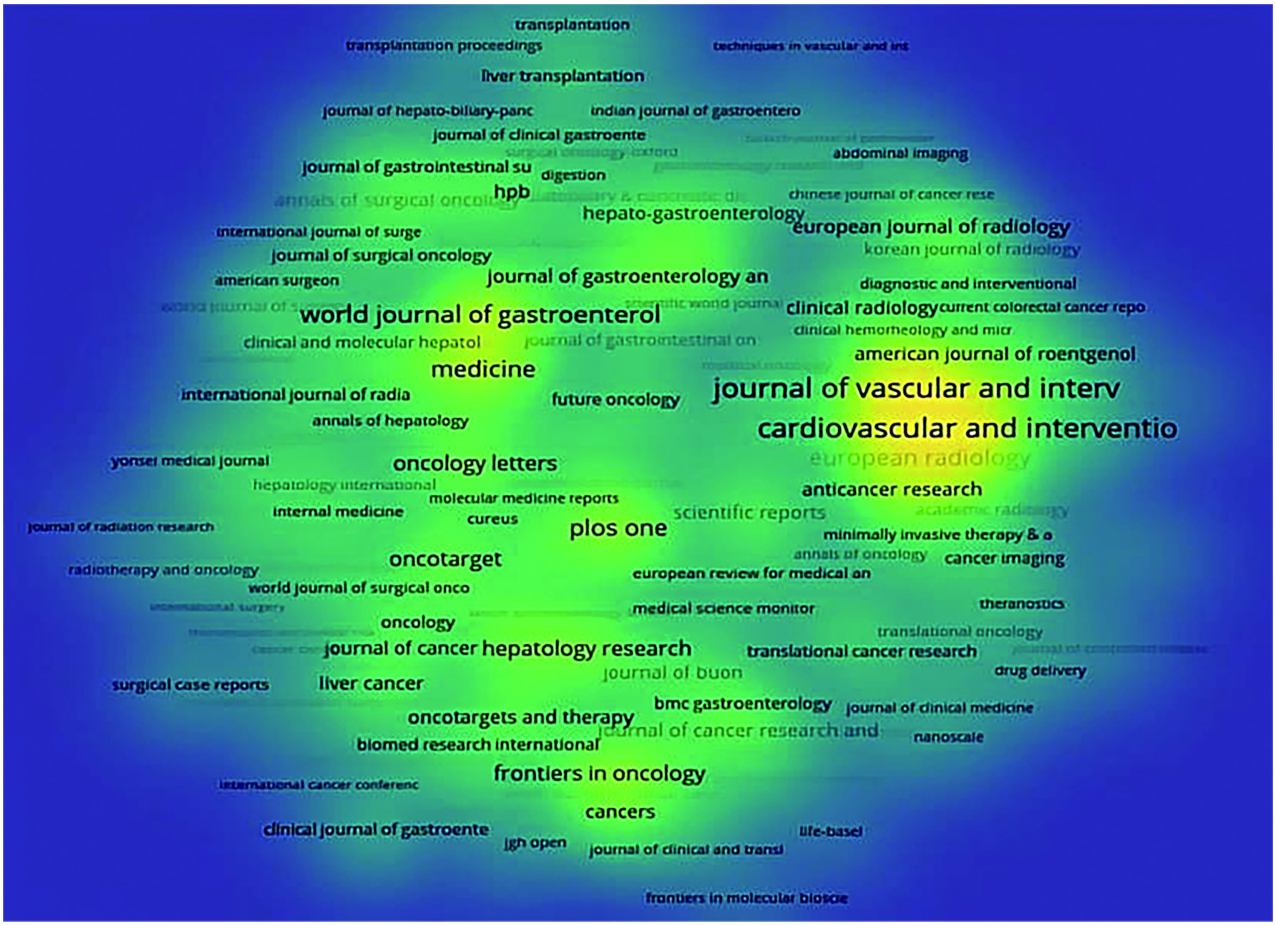

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Figure 5 Density visualization for the most prolific journals. The minimum number of documents of an organization was set at 5. Of the 857 journals that were involved in this field, 232 journals met the threshold. Yellow means appearing more frequently, while green means appearing less frequently.

fluoroscopy or digital subtracted angiography: Angio Cone-Beam Computed Tomography should be used to detect enhancing tumors, tumor feeders and guide tumor targeting[37,38]; and (3) whenever cTACE is proposed, it should aim at being supraselective-TACE. Regarding the most suitable and appropriate microcatheter for the procedures, 2.4 French (F) was recognized as the upper caliber limit accepted to perform supraselective-TACE. However, all experts agree that a lower microcatheter diameter, 1.5-2.0 F, should be preferred and recommended whenever possible. Recently, balloon occluded TACE (B-TACE), due to its ability to redistribute flow towards lower resistance vascular territories and allowing a pressure-gradient driven embolization, has been shown to improvedrug delivery to target lesion[39,40].The top co-cited reference with the most citation burstiness is "propensity score matching". Propensity score matching (PSM) is one of the most popular statistical methods used to process data from observational studies. In observational studies, there are various bias and confounding variables for some reasons, and the propensity score matching method is designed to reduce the effects of these bias and confounding variables to make a more reasonable comparison between control and experimental groups. PSM has been shown to be comparable to Randomized control trials in producing unbiased estimates of efficacy; however, the cost and research time are significantly reduced[41,42]. A recent study conducted by Marinelli *et al*[43] used propensity score matching and found that TACE can be safely combined with programmed cell death 1 blockers and may lead to HCC downstaging in selected patients.

TACE may also be used as a downstaging therapy prior to hepatectomy or as a bridging therapy prior to liver transplantation in patients with advanced tumors. However, before considering TACE as a treatment option for patients with unresectable HCC, the patient's risk profile, comorbidities, treatment prognosis, and benefits should be taken into account in order to improve overall survival and minimize the occurrence of adverse events. Notably, in addition to the traditional TACE monotherapy, some researchsrs are now focusing on TACE-based combination therapies, such as the combination of TACE and tumor thermal ablation, the combination of TACE and radiotherapy, and the combination of TACE and systemic therapeutic agents. However, further research is needed to determine which combination therapy is more cost-effective in prolonging patient survival.

The present study also has some limitations. First, we only included articles published in English in WoS; therefore, not all publications were considered and the number of citations may have been underestimated. Second, CiteSpace only analyzed the main findings of the studies rather than reviewing the full text; As a result, some important information may have been overlooked. Finally, our results reflect only the current status of TACE for HCC, as data usually change over time.

B

Top 20 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2012 - 2021
Lencioni R, 2010, SEMIN LIVER DIS, V30, P52, DOI 10.1055/s-0030-1247132, DOI	2010	89.99	2012	2015	
Llovet J, 2008, NEW ENGL J MED, V359, P378, DOI 10.1056/NEJMoa0708857, DOI	2008	81.96	2012	2013	
Cheng A, 2009, LANCET ONCOL, V10, P25, DOI 10.1016/S1470-2045(08)70285-7, DOI	2009	71.62	2012	2014	
Lammer J, 2010, CARDIOVASC INTER RAD, V33, P41, DOI 10.1007/s00270-009-9711-7, DOI	2010	48.86	2012	2015	
Llovet J, 2008, JNCI-J NATL CANCER I, V100, P698, DOI 10.1093/jnci/djn134, DOI	2008	41.06	2012	2013	
Eisenhauer E, 2009, EUR J CANCER, V45, P228, DOI 10.1016/j.ejca.2008.10.026, DOI	2009	32.85	2012	2014	
Salem R, 2010, GASTROENTEROLOGY, V138, P52, DOI 10.1053/j.gastro.2009.09.006, DOI	2010	31.02	2012	2015	
Bruix J, 2011, HEPATOLOGY, V53, P1020, DOI 10.1002/hep.24199, DOI	2011	128.91	2013	2016	
Jemal A, 2011, CA-CANCER J CLIN, V61, P69, DOI 10.3322/caac.20107, DOI	2011	51.82	2013	2016	
Forner A, 2012, LANCET, V379, P1245, DOI 10.1016/S0140-6736(11)61347-0, DOI	2012	50.18	2014	2017	
European A, 2012, EUR J CANCER, V48, P599, DOI 10.1016/j.ejca.2011.12.021, DOI	2012	108.14	2015	2017	
Torre L, 2015, CA-CANCER J CLIN, V65, P87, DOI 10.3322/caac.21262, DOI	2015	40.56	2016	2019	
Golfieri R, 2014, BRIT J CANCER, V111, P255, DOI 10.1038/bjc.2014.199, DOI	2014	30.04	2016	2019	
Ferlay J, 2015, INT J CANCER, V136, P0, DOI 10.1002/ijc.29210, DOI	2015	35.29	2017	2021	
European A, 2018, J HEPATOL, V69, P182, DOI 10.1016/j.jhep.2018.03.019, DOI	2018	101.94	2019	2021	
Heimbach J, 2018, HEPATOLOGY, V67, P358, DOI 10.1002/hep.29086, DOI	2018	68.85	2019	2021	
Forner A, 2018, LANCET, V391, P1301, DOI 10.1016/S0140-6736(18)30010-2, DOI	2018	54.63	2019	2021	
Kudo M, 2018, LANCET, V391, P1163, DOI 10.1016/S0140-6736(18)30207-1, DOI	2018	52.58	2019	2021	
Omata M, 2017, HEPATOL INT, V11, P317, DOI 10.1007/s12072-017-9799-9, DOI	2017	32.98	2019	2021	
Lencioni R, 2016, HEPATOLOGY, V64, P106, DOI 10.1002/hep.28453, DOI	2016	30.24	2019	2021	

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Figure 6 Shows the mapping of co-cited references based on transarterial chemoembolization treatment, depicts the top 20 references with the strongest citation explosion. A: Density visualization of co-cited references. Of the 68527 references, 1159 (divided into six clusters) were cited at

least 20 times. Yellow means appearing more frequently, while green means appearing less frequently; B: The top 20 co-cited references with the most citation burstiness. Years between "Begin" and "End" represent the period when the reference was more influential. Years in light green mean that the reference has not yet appeared, years in dark green mean that the reference is less influential, and years in red mean that the reference is more influential.

CONCLUSION

In conclusion, the results of our bibliometric analysis provide the latest trends and hot topics in TACE therapy for HCC. Based on the results found by CiteSpace and VOSviewer, we can conclude that current research in this field is focused on survival prediction and TACE-based combined therapies. These results can also help researchers in the field find relevant literature and stay informed about hot topics.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the second leading cause of cancer-related deaths. Transcatheter arterial chemoembolization (TACE) is a therapy where drugs aimed to slow or halt tumor development are injected into the artery supplying for HCC tissues. A comprehensive analysis of all the articles on TACE for HCC can give us a general understanding of the progress in this field and provide guidance for future research.

Research motivation

The bibliometric analysis can be an important tool to help quantify and evaluate productivity within a scientifc feld, while also providing a comprehensive overview of the literature for students, trainees and experts in addition to identifying potential future research directions.

Research objectives

The aim of this study was to systematically analyze studies on TACE for HCC to determine its current status and assess future trends.

Research methods

The "Web of Science" database was used to identify articles regarding TACE for the treatment of hepatocellular carcinoma (HCC) from 2012 to 2021. VOSviewer and CiteSpace were used to analyze the publications trends, collaboration between countries/institutions/authors, and the co-occurrence of keywords, keyword bursts, and references.

Research results

A total of 5728 original articles on TACE for HCC were retrieved. Regarding the volume of publications, the total number of yearly publications showed a generally increasing trend. China had the highest number of articles, while the United States achieved the highest Hirsch index and highest number of citations. The Sun Yat-sen University in China was most prolific institution. The most active author was Park JW from South Korea. The Journal of Vascular and Interventional Radiology (234 articles) was the most productive journal. There is a growing trend toward international collaboration in TACE for HCC. Cluster networks of co-cited references suggested that practice guidelines and targeted therapies are an essential theme in this field. In addition, cluster analysis based on keyword co-occurrence identified the research topic "prediction of TACE treatment" as a hotspot, and propensity score matching can be used to help investigators conduct innovative studies in the future.

Research conclusions

We found that current research in this field focuses on survival prediction and TACE-based combined therapies. These results can also help researchers in the field find relevant literature and stay informed about hot topics.

Research perspectives

High-quality international multicenter studies are needed to confirm how TACE-based combination therapies better improve patient survival.

FOOTNOTES

Author contributions: Zhang N and He XF contributed equally to this work; Niu XK designed the research study; Zhang N performed the research; He XF contributed analytic tools; Zhang N and Niu XK analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Chen YX

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CASE REPORT

Clinical, imaging, arthroscopic, and histologic features of bilateral anteromedial meniscofemoral ligament: A case report

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Abstract

BACKGROUND

The anteromedial meniscofemoral ligament (AMMFL) is a very rare entity, commonly unrecognized and underreported. Although it was not proved to be a cause of anterior knee pain, concerns have been raised on the relationship between the presence of this structure and medial meniscus injury secondary to its abnormal motion. Regarding histologic examination, some studies have shown meniscus-like fibrocartilage, while others have identified it as ligament-like collagenous fibrous connective tissue.

CASE SUMMARY

We report the case of a 34-year-old ballerina with an AMMFL associated with a torn medial meniscus of both knees. Surgery was performed to treat the meniscal injury and two biopsies of each AMMFL were taken in different locations to define the histopathological composition. Histologic examination revealed fibrocartilaginous tissue compatible with meniscus. Follow-up evaluation one year after surgery evidenced full remission of symptoms and the patient had resumed her athletic activities.

CONCLUSION

Clinical, magnetic resonance imaging, arthroscopic, and histological features have been carefully described to better characterize the AMMFL.

Key Words: Meniscofemoral; Ligaments; Knee arthroscopy; Histology; Case report

Core Tip: The anteromedial meniscofemoral ligament (AMMFL) is a very rare entity, commonly unrecognized and underreported. Concerns have been raised on the relation between the presence of this structure and medial meniscus injury. Regarding histologic examination, some studies showed meniscus-like fibrocartilage, while others have identified it as ligament-like collagenous fibrous connective tissue. We report the case of a 34-year-old ballerina with an AMMFL associated with a torn medial meniscus of both knees. Surgery was performed to treat the meniscal injury and two biopsies of each AMMFL were taken in different locations to define the histopathological composition. Clinical, magnetic resonance imaging, arthroscopic, and histological features are carefully described to better characterize the AMMFL.

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INTRODUCTION

Given the interest on meniscal preservation and transplantation, the insertion zones of the meniscus have been widely investigated. Recent anatomical studies have demonstrated several common patterns of attachment of the anterior horn of the medial meniscus (AHMM)[1-4]. According to Berlet and Fowler[3], there are four distinct insertion patterns based on bony landmarks. In type I (59%), the meniscus is inserted in the flat area between the articular surfaces (intercondylar region), providing a very firm attachment. In type II (24%), the meniscus is inserted medially, closer to the articular surface, also providing a strong tibial fixation. Type III insertions (15%) are very anterior and offer little resistance to anterior movement of the meniscus. Finally, type IV (3%) has no solid bony attachment and only the coronary fibers restrain the displacement of the anterior horn of the meniscus. Ohkoshi *et al*[2] subdivided type IV pattern based on the structure to which the AHMM is anchored: Transverse ligament (49%), anterior cruciate ligament (ACL) (38%), coronary ligament (11%), and infrapatellar synovial fold (2%). At last, Cha *et al*[5] subdivided the ACL type into ACL and intercondylar notch (ICN) type. McCormack and McGrath[6] named this ligamentous structure the anteromedial meniscofemoral ligament (AMMFL).

Several studies, mostly case reports, have documented the AMMFL with a wide variation in prevalence (1.2%-15%)[7, 8] and several characteristics of this structure are still not well understood. Although the AMMFL was not proved to be a cause of anterior knee pain, concerns have been raised on the relation between the presence of this structure and medial meniscus injury secondary to its abnormal motion[2,6]. Regarding histologic examination of the AMMFL, some studies showed meniscus-like fibrocartilage, while others have identified it as ligament-like collagenous fibrous connective tissue [8,9].

Our knowledge of the AMMFL is based on very limited data. The aim of our work was therefore to describe the clinical, magnetic resonance imaging (MRI), and arthroscopic findings, as well as the histological composition of the AMMFL, through the case of a bilateral AMMFL in a 34-year-old ballerina.

CASE PRESENTATION

Chief complaints

A 34-year-old ballerina presented to our clinic referring bilateral knee pain of 10 mo long. This pain impaired her performance and provoked symptoms during her daily activities.

History of present illness

A partial meniscectomy in the patient's right knee was performed 8 years ago in another hospital.

History of past illness

The patient denied any other medical history.

Personal and family history

There was no personal and family history.

Physical examination

The patient appeared to be in good physical condition, with a height of 1.68 meters and a body mass index of 23. Examination revealed pain and tenderness over the medial joint line of both knees. The McMurray and Appley tests were positive on the medial side. No restriction in range of motion or laxity was detected.

Laboratory examinations

No laboratory examinations were performed.

Imaging examinations

The MRI of both knees revealed a homogeneous low-signal linear structure on T1- and T2-weighted images, coursing anteriorly to the anterior aspect of the ACL and connecting the medial portion of the AHMM to the posterolateral ICN (Figure 1). This structure was best seen on sagittal view (Figures 1B and F). The MRI of the right knee also showed surgical traces of the previous partial medial meniscectomy together with a tear of the posterior horn of the medial meniscus (Figures 1C and D). The left knee showed a tear of the posterior horn of the medial meniscus (Figures 1G and H).

Further diagnostic work-up

Plain knee and long-leg X-rays did not show bony abnormalities or coronal alignment deformity.

FINAL DIAGNOSIS

Bilateral AMMFL combined with a torn medial meniscus.

TREATMENT

Diagnostic arthroscopy was performed together with a partial meniscectomy of both knees. Figure 2 shows the intraoperative findings of both knees. The AMMFL was visualized on both sides as an anomalous band-shaped structure covering the anterior portion of the ACL (Figures 2A and D). The band was originated at the AHMM and was attached to the posterolateral wall of the ICN. A fine band of synovial tissue engaged the AMMFL with the ACL. In both knees, the AHMM lacked a robust attachment to the tibia. Instead, it was connected to the tibia by meniscocapsular soft tissue. Therefore, the AHMM was noted to be abnormally mobile on palpation. No impingement of the AMMFL with the ICN was observed after mobilizing the knee through full range of motion. Therefore, we did not resect the AMMFL, preserving the structure. Two biopsies were taken from the AMMFL of each knee for histopathological examination, one proximal close to the ICN and one distal close to the AHMM (Figure 3). Histologic examination showed fibrocartilaginous tissue compatible with meniscus in all four biopsies (Figure 3). A complex tear of the body and posterior horn of the medial meniscus was corroborated arthroscopically, and a partial meniscectomy was performed in both knees (Figure 2).

OUTCOME AND FOLLOW-UP

The patient recovered favorably in the postoperative period. The use of crutches for 10 d and physiotherapy for 1 mo was indicated. After a period of strengthening, she returned to sports after 3 mo. Follow-up evaluation 1 year after surgery evidenced full remission of symptoms and the patient had resumed her athletic activities.

DISCUSSION

Variability of the AHMM patterns of insertion is relatively common according to cadaveric and arthroscopic studies[2,3,10]. However, abnormal insertion of the anterior horn into the ICN through the AMMFL is rare. The precise prevalence of this anatomical variation remains underestimated, as it may go undetected on preoperative MRI examination and is often only incidentally discovered during arthroscopy. One of the main issues in our knowledge of the AMMFL is a lack of high-level evidence studies. Our understanding on this topic is largely based on case reports[5,6,9,11-15] and there are only two case series available[7,8]. On the one hand, Kim and Joo[7] performed a retrospective review of 13 patients with an AMMFL with insertion at the ICN. In contrast to our report, all cases were diagnosed incidentally during arthroscopy. Although the AHMM had no bony attachment, they performed an MRI analysis and showed that there was no significant meniscal extrusion. On the other hand, Anderson *et al*[8] published a case series of 12 patients. Six patients were identified on a retrospective review of pictures taken during arthroscopies and the other six patients were identified prospectively. As in our case, all 12 patients had other abnormal conditions that were thought to be the cause of their symptoms.

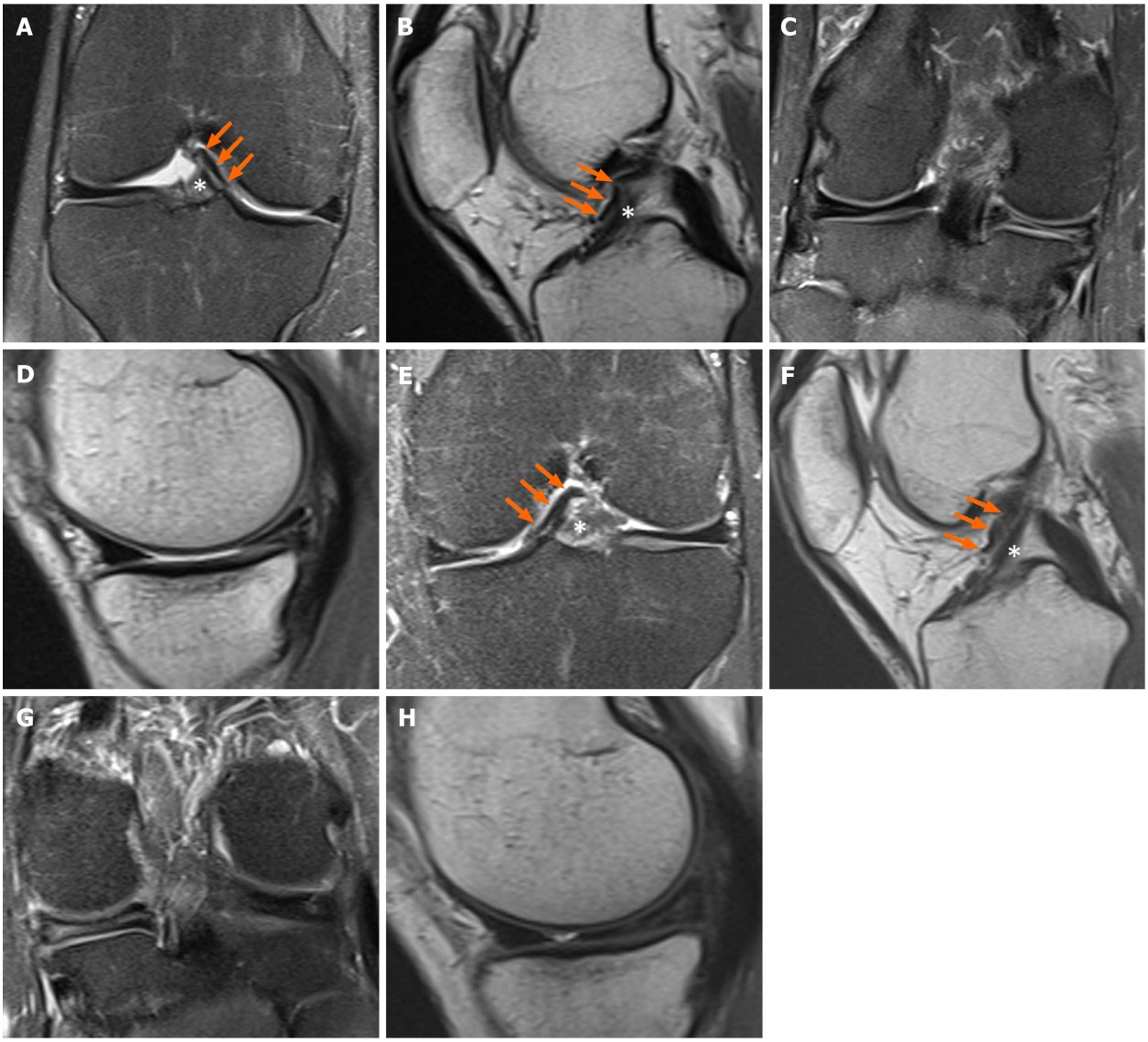

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Figure 1 Magnetic resonance imaging images of the knee. A-D: Magnetic resonance imaging (MRI) images of the right knee. Coronal T2-weighted fat-saturated image demonstrating the anteromedial meniscofemoral ligament (AMMFL) (green arrow) and the distal aspect of the anterior cruciate ligament (ACL) (white asterisk) (A); sagittal T1-weighted image showing the AMMFL (green arrow) running anteriorly to the ACL (white asterisk) (B); coronal T2-weighted fat-saturated and sagittal images showing the medial meniscus with a previous partial meniscectomy and tear of the posterior horn (C and D); E-H: MRI images of the left knee. Coronal T2-weighted fat-saturated image demonstrating the AMMFL (green arrow) and the distal aspect of the ACL (white asterisk) (E); sagittal T1-weighted image showing the AMMFL (green arrow) running anteriorly to the ACL (white asterisk) (F); coronal T2-weighted fat-saturated and sagittal images showing a tear of the posterior horn of the medial meniscus (G and H).

Without prior awareness, the AMMFL may not be identified on preoperative MRI. Our review of the MRI findings revealed comparable features to those previously reported[1,5,16]. The AMMFL was identified as a linear structure of low signal intensity anterior to the ACL on sagittal and coronal views of T1- and T2-weighted images. Among the differential diagnoses, an ACL tear or an infrapatellar plica may be misdiagnosed on sagittal projections and a displaced bucket-handle tear on coronal views[16]. The anatomy of the distal insertion of the AMMFL, along with its morphology and position, can be used to differentiate it from these other structures.

It is still unclear whether the AMMFL may have biomechanical significance. It has been suggested that it functions as an anchor of the AHMM and probably plays an important role in load transmission[8]. This is in good agreement with the results of Kim and Joo[7], in which no significant extrusion of the medial meniscus was observed. However, the lack of normal bony attachment to the tibia causes the meniscus to be hypermobile, resulting in meniscal tears. According to Ohkoshi *et al*[2], during knee flexion, the AMMFL tightens and pulls the AHMM backwards, causing abnormal hoop tension on the entire medial meniscus and potentially inducing progressive degeneration or tears. This is consistent with our finding that the patient had a bilateral AMMFL associated with a torn medial meniscus. There was no impingement against the ICN, therefore, we did not resect the AMMFL and tried to preserve the structure.

Finally, there has been some disagreement regarding histopathological examination of this structure in different studies. Anderson *et al*[8] reported a ligamentous nature in one case, with dense fibrous tissue and collagen interspersed with parallel rows of fibroblasts. In contrast, Nakajima *et al*[9] described the histological features of a meniscal structure.

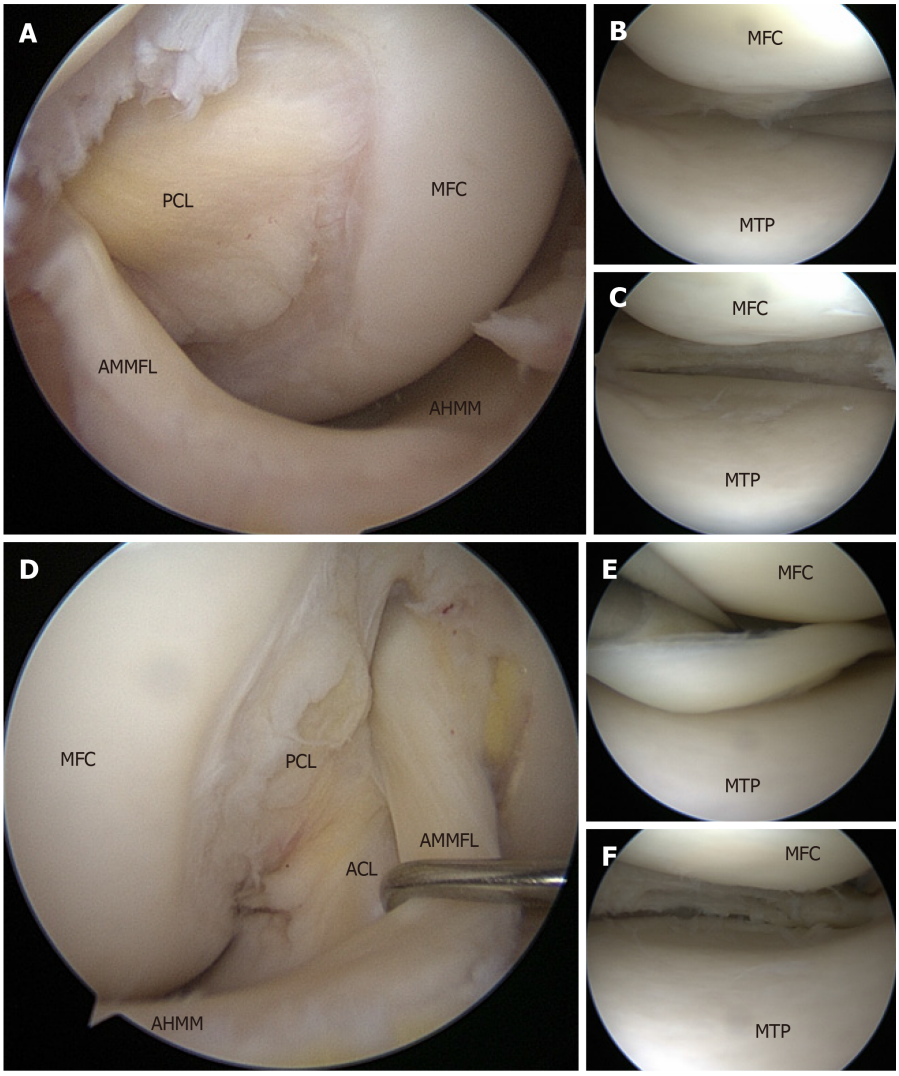

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Figure 2 Arthroscopic images of the knee obtained through the anterolateral portal. A-C: Arthroscopic images of the right knee obtained through the anterolateral portal. The anteromedial meniscofemoral ligament (AMMFL) can be seen coursing anteriorly to the anterior aspect of the anterior cruciate ligament (ACL) and connecting the anterior horn medial meniscus (AHMM) to the posterolateral intercondylar notch (A); tear of the medial meniscus (B); image of the medial meniscus after partial meniscectomy (C); D-F: Arthroscopic images of the left knee obtained through the anterolateral portal. The AMMFL can be seen coursing anteriorly to the anterior aspect of the ACL and connecting the AHMM to the posterolateral intercondylar notch (D); tear of the medial meniscus (E); image of the medial meniscus after partial meniscectomy (F). PCL: Posterior cruciate ligament; MFC: Medial femoral condyle; AMMFL: Anteromedial meniscofemoral ligament; AHMM: Anterior horn medial meniscus; MTP: Medial tibial plateau; ACL: Anterior cruciate ligament.

Some authors argued that this difference could be related to the different biopsy sites. Therefore, we decided to take two biopsies in each AMMFL, one proximal and one distal to study the presence of possible transition zones and be able to define its histological nature. According to our findings, fibrocartilaginous tissue compatible with meniscus was found in all four biopsies.

CONCLUSION

The AMMFL is a very rare entity, commonly unrecognized and underreported. According to our case, as well as other previously published cases, the AMMFL shows several common features that can help reach an accurate diagnosis: (1) The AMMFL is observed as a low signal intensity band-like structure on MRI and is best seen on the sagittal view; (2) It is asymptomatic and often related to meniscal tears; (3) If discovered incidentally during arthroscopy, it should not be removed routinely; and (4) Its histopathological structure is predominantly meniscal tissue.

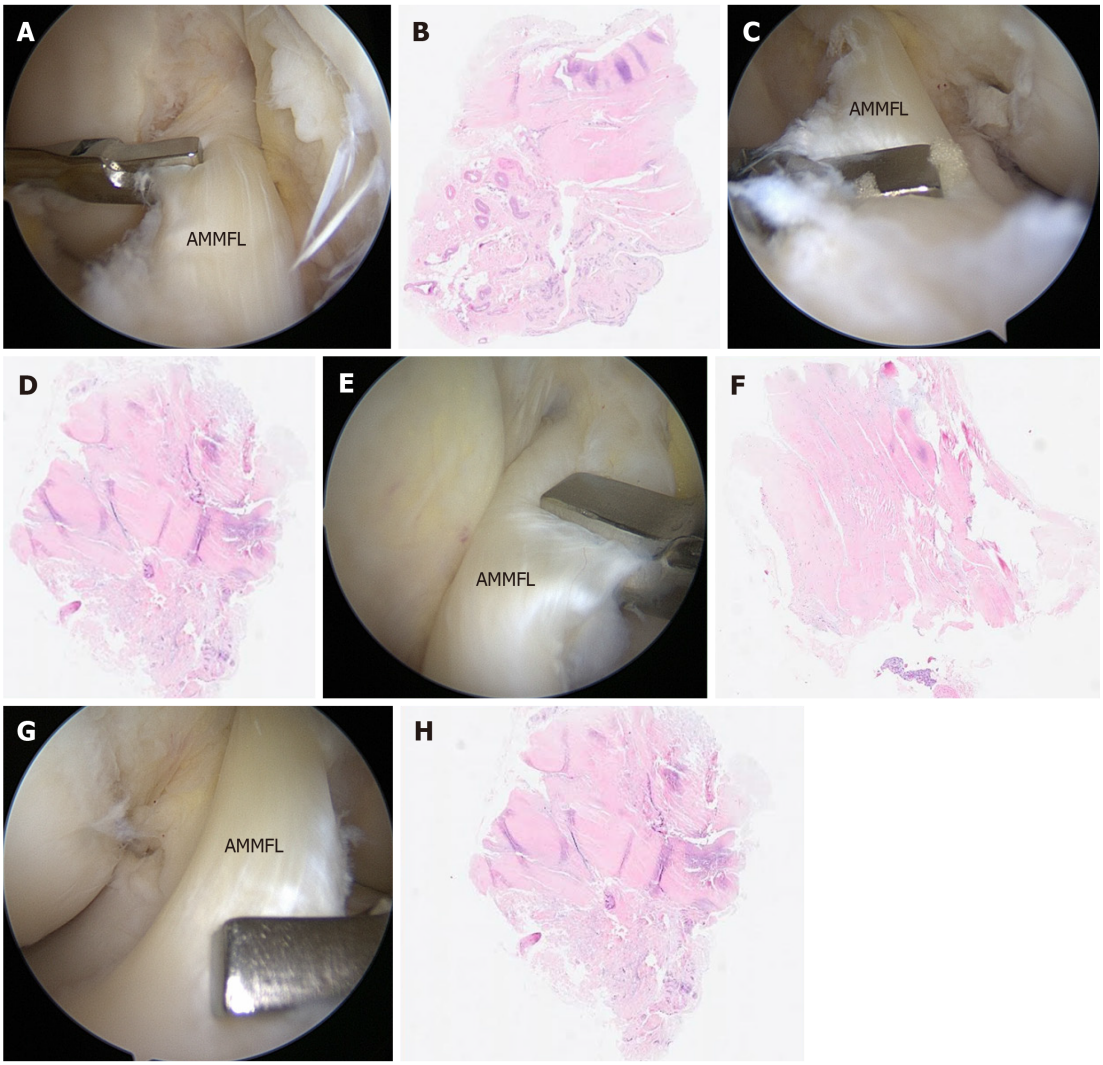

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Figure 3 Intraoperative images and histologic examination of the knee. A-D: Intraoperative images and histologic examination of the right knee. Arthroscopic images obtained through the anteromedial portal showing the biopsies performed through the anterolateral portal (A and B); hematoxylin and eosin staining of the meniscofemoral band reveals fibrocartilaginous tissue compatible with meniscus in both cases (C and D); E-H: Intraoperative images and histologic examination of the left knee. Arthroscopic images obtained through the anteromedial portal showing the biopsies performed through the anterolateral portal (E and F); hematoxylin and eosin staining of the meniscofemoral band reveals fibrocartilaginous tissue compatible with meniscus in both cases (G and H). AMMFL: Anteromedial meniscofemoral ligament.

FOOTNOTES

Author contributions: Luco JB, Di Memmo D, Nicolino TI, and Garcia-Mansilla I designed the research study; Astou J and Costa-Paz M performed the research; Luco JB and Garcia-Mansilla I analyzed the data and wrote the manuscript; Gomez Sicre V performed the histopathologycal analisis; and all authors have read and approved the final manuscript.

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CASE REPORT

Sclerotic marginal zone lymphoma: A case report

Zade Moureiden, Hammad Tashkandi, Mohammad Omar Hussaini

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Abstract

BACKGROUND

Marginal zone lymphoma (MZL) is an indolent non-Hodgkin B cell lymphoma with various architectural pattern including perifollicular, follicular colonization, nodular, micronodular, and diffuse patterns. A sclerotic variant has not been previously reported and represents a diagnostic pitfall.

CASE SUMMARY

A 66-year-old male developed left upper extremity swelling. Chest computed tomography (CT) in September 2020 showed 14 cm mass in left axilla. Needle core biopsy of axillary lymph node showed sclerotic tissue with atypical B lymphoid infiltrate but was non-diagnostic. Excisional biopsy was performed for diagnosis and showed extensive fibrosis and minor component of infiltrating B cells. Flow cytometry showed a small population of CD5-, CD10-, kappa restricted B cells. Monoclonal immunoglobulin heavy chain and light chain gene rearrangement were identified. Upon being diagnosed with MZL, patient was treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone and achieved complete remission by positron emission tomography/CT.

CONCLUSION

This is an important case report because by morphology this case could have easily been overlooked as non-specific fibrosis with chronic inflammation representing a significant diagnostic pitfall. Moreover, this constitutes a new architectural pattern. While sclerotic lymphomas have rarely been described (often misdiagnosed as retroperitoneal fibrosis), we do not know of any cases describing this architectural presentation of MZL.

Key Words: Sclerotic; Marginal zone lymphoma; Architecture; Pitfall; Diagnosis; Fibrosis; Case report

Core Tip: In the clinical context of suspicious lymphadenopathy, the presence of an extensive sclerosis on biopsy should not deter the clinician from a diagnosis of lymphoma, and careful evaluation and work up is needed to exclude covert lymphoma.

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INTRODUCTION

Marginal zone lymphoma (MZL) is an indolent B-cell non-Hodgkin lymphoma derived from marginal zone B cells within the lymphatic system[1]. The incidence of MZL, based on data from the United States SEER-18 program, is 19.6 per 1000000 person-years[2]. MZL is typically classified into extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (61%), nodal MZL (NMZL) (30%), and splenic MZL (SMZL) (9%). Other subtypes include pediatric MZL and immunoproliferative small intestinal disease[3]. 5-year relative survival rate for EMZL, NMZL, and SMZL are 88.7%, 76.5% and 79.7%, respectively with EMZL being most likely to transform to diffuse large B cell lymphoma[4,5].

Marginal zone B cells typically display a morphology of small to medium sized lymphocytes with somewhat irregular nuclei containing mature chromatin and relatively abundant pale cytoplasm. They may classically assume a monocytoid morphology[6]. In SMZL, villous lymphocytes can be seen in the periphery. MZL typically expresses an immunohistochemistry profile positive for B cell-associated antigens (CD19, CD20, CD22, CD79a) and complement receptors (CD21 and CD35). MZLs are usually negative for CD5, CD10, CD23, BCL6, and cyclin D1. Furthermore, SMZL has a high concentration of immunoglobulin D (IgD) cell surface antigens; whereas, EMZL and NMZL show expression of IgM and IgD [3]. MZL can assume various architectural patterns including perifollicular, follicular colonization, nodular, micronodular, and even diffuse patterns[7]. In the bone marrow, an intrasinusoidal pattern is often seen in SMZL[8].

We present a remarkable case of MZL masquerading in a sclerotic background as fibrosis with chronic inflammation. This constitutes the first report of this architectural pattern in MZL and represents a serious and important diagnostic pitfall in lymphoma diagnosis.

CASE PRESENTATION

Chief complaint

The patient is a 66-year-old male who developed left upper extremity swelling.

History of present illness

The patient had an episode of syncope of unclear etiology in January 2020. He started to have pain under his left arm in February that waxed and waned. Then over the course of a few weeks, he started having left upper extremity swelling. The patient had an ultrasound and mammogram that were reportedly negative. This was followed by a computed tomography (CT) of the chest without contrast on April 9, 2020 that showed a large, irregularly marginated mass arising in the left axilla.

History of past illness

Past medical history is notable for benign prostatic hyperplasia, chronic kidney disease stage III, type 2 diabetes, hypertension, hyperlipidemia, and pulmonary hypertension.

Personal and family history

The patient had a mother with history of breast cancer and colon cancer.

Physical examination

Temperature: 36.78 °C, heart rate: 93/min, respiratory rate: 16/min, blood pressure: 125/73 mmHg, SpO_2: 100%, weight: 104.5 kg, body mass index: 31.20 kg/m^2. General: Alert and oriented, no acute distress. Eye: Normal conjunctivae, anicteric. Head/ears/nose/mouth/throat: Normocephalic, no trauma, normal hearing. Neck: Supple, non-tender. Cardiovascular: Regular rate and rhythm, normal peripheral perfusion. Lung: Lungs were clear to auscultation, respirations were non-labored. Abdomen: Soft, nontender, nondistended, no splenomegaly. Hematological/lymphatics: No lymphadenopathy: Cervical, supraclavicular, axillary, inguinal. Extremities: Normal range of motion, normal strength, no deformity. Integumentary: Warm, dry, intact. Neurologic: Alert, oriented, no focal defects. Cognition and speech: Oriented, speech clear and coherent, functional cognition intact. Psychiatric: Cooperative, appropriate mood and affect.

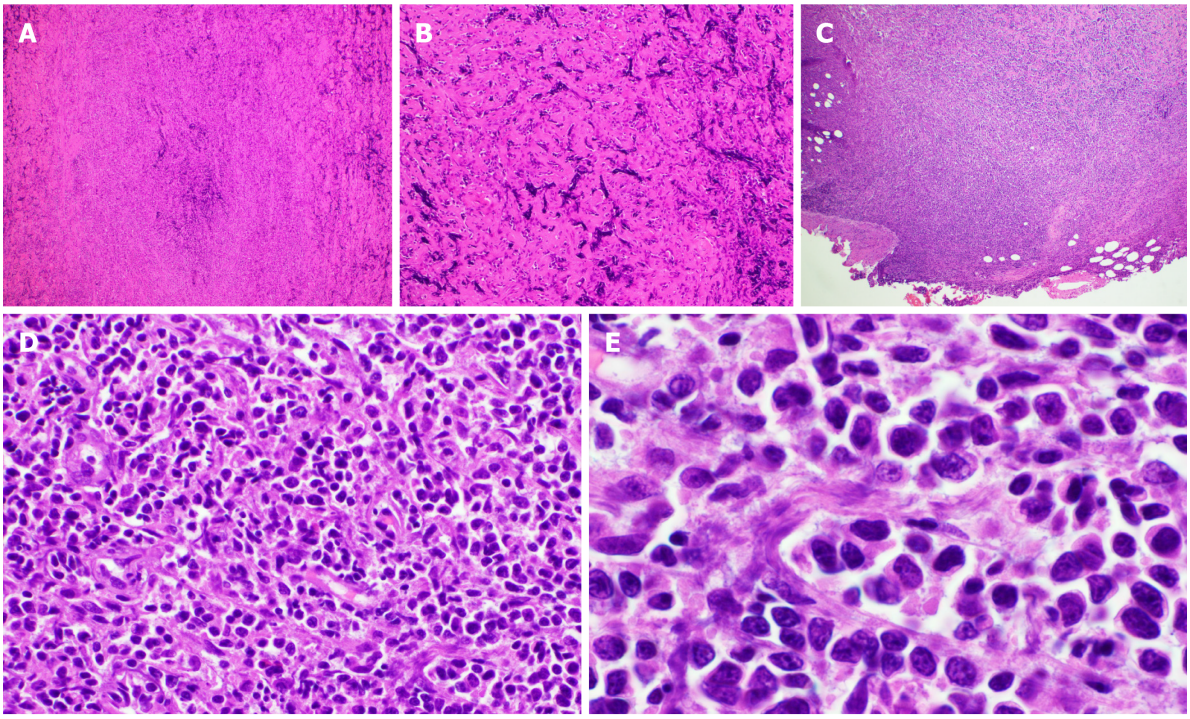

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Figure 1 Histology of sclerotic marginal zone lymphoma. A: Low power hematoxylin and eosin (H&E) section showing extensive fibrosis and crush artifact, 40 × (Olympus BX43); B: Low power H&E section showing extensive fibrosis and crush artifact, 40 × (Olympus BX43); C: More cellular area with small lymphocytes is seen focally (lower-left hand) compared with more sclerotic pattern (upper-right), 40 ×; D: High power H&E showing morphology of cells in cellular area (non-crushed), some have monocytoid features (400 ×); E: High power H&E showing morphology of cells in cellular area (non-crushed), some have monocytoid features (1000 ×).

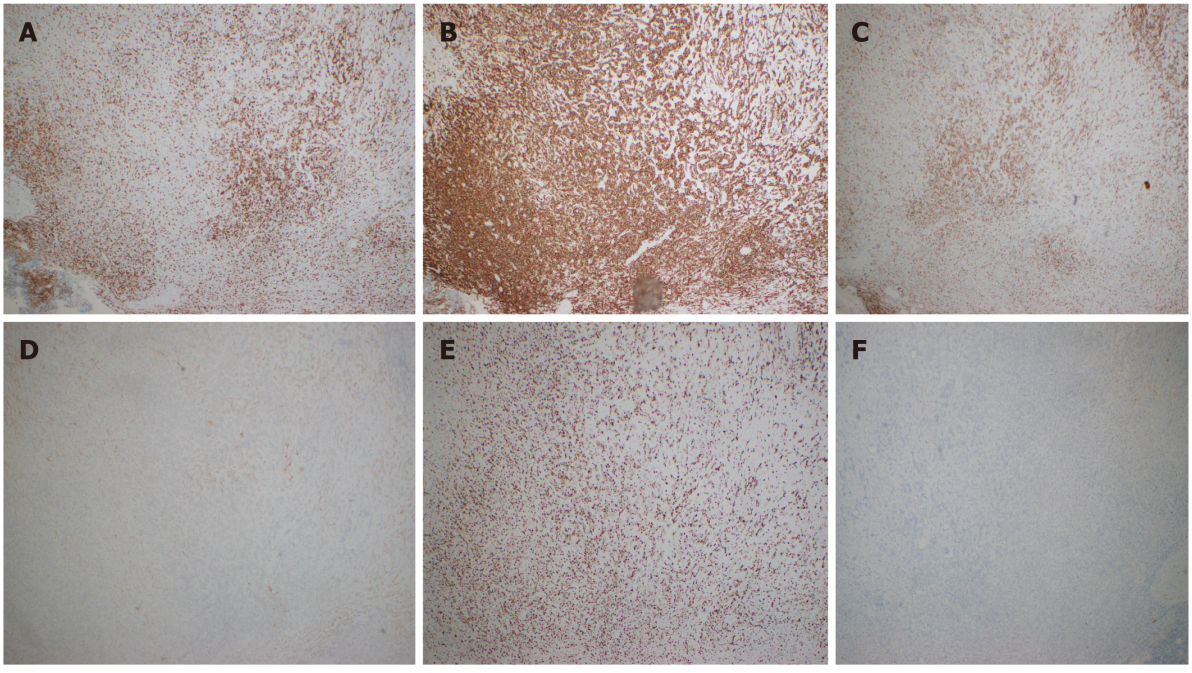

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Figure 2 Immunohistochemical profile of sclerotic marginal zone lymphoma. A: CD3; B: CD20; C and D: CD5; E: Ki67; F: BCL6.

Laboratory examinations

The specific examinations and results are listed in Table 1. Pathology results are provided in Figures 1-3.

Table 1 Laboratory examinations

	Value w/units	Normal range
CBC		
WBC	5.59 k/uL	4.00-10.90
Preliminary ANC	> 1.5 k/uL	
RBC	3.50 mil/uL	4.45-5.73
Hemoglobin	11.1 g/dL	13.4-16.9
Hematocrit	34.1%	40.0-48.0
Mean cell volume	97.4 FL	80.3-94.0
MCH	31.7 pg	27.4-33.4
MCHC	32.6 g/dL	32.0-36.8
RDW	50.6 FL	36.8-46.1
Platelet count	113 k/uL	143-382
MPV	10.1 FL	7.4-11.7
Differential		
Neutro auto	3.57 k/uL	1.80-7.80
Eos auto	0.37 k/uL	0.00-0.45
Basophil auto	0.04 k/uL	0.00-0.20
Immature Gran auto	0.03 k/uL	0.00-0.10
Mono auto	0.71 k/uL	0.30-0.80
Lymph auto	0.87 k/uL	1.10-3.50
Nucleated RBC	0.00 k/uL	0.00-0.10
Differential %		
Neutro auto %	63.9	
Eos auto %	6.6	
Basophil auto %	0.7	
Immature Gran auto %	0.5	
Mono auto %	12.7	
Lymph auto %	15.6	
Nucleated RBC %/100 WBC	0.0/100 WBC	0.0-1.0
Coagulation		
Prothrombin time	11.6 s	10.2-12.9
INR	1.0	0.8-1.1
APTT	27.0 s	25.1-36.5
Reticulocyte percent	1.78%	0.80-1.90
Reticulocyte number	0.0623 mil/uL	0.0360-0.1000
Immature retic fraction (%)	14.5	3.0-13.4
Eryth. sed rate	20 mm/hr	0-15
Metabolic panel		
Sodium	140 mmol/L	134-145
Potassium	4.0 mmol/L	3.4-4.5
Chloride	102 mmol/L	96-107
Total CO_2	26 mmol/L	22-30

Glucose level	111 mg/dL	70-110
BUN	13 mg/dL	6-23
Creatinine	1.5 mg/dL	0.7-1.3
Est. GFR	47 mL/min/1.73 m^2	
Est. GFR (Af-Am)	57 mL/min/1.73 m^2	
Uric acid	6.9 mg/dL	3.5-8.5
Calcium	11.3 mg/dL	8.6-10.2
Calcium corrected	11.2 mg/dL	8.6-10.2
Phosphorus	2.7 mg/dL	2.5-4.5
Total protein	6.8 gm/dL	6.6-8.7
Albumin	4.1 gm/dL	3.5-5.2
Total bilirubin	0.80 mg/dL	0.00-1.20
Alk. phosphatase	65 U/L	40-130
AST	34 U/L	10-50
ALT	25 U/L	0-41
LDH	158 U/L	135-225
Magnesium level	1.4 mg/dL	1.6-2.3

CBC: Complete blood count; WBC: White blood cell; ANC: Absolute neutrophil count; RBC: Red blood cell; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red blood cell distribution width; MPV: Mean platelet volume; INR: International normalized ratio; APTT: Activated partial thromboplastin time; BUN: Blood urea nitrogen; GFR: Glomerular filtration rate; AST: Aspartate aminotransferase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase.

Imaging examinations

Chest CT in September 2020 showed a 14 cm irregularly, marginated mass arising in left axilla. There was questionable invasion of the left subscapularis muscle and thickening the right pectoralis minor muscle. Positron emission tomography (PET) scan showed standardized uptake value (SUV) of 26.

FINAL DIAGNOSIS

The final diagnosis is MZL.

TREATMENT

Upon being diagnosed with lymphoma, patient was treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). More specifically, he received 6 cycles of R-CHOP, and doxo/cyclophosphamide 50% dose reduction starting cycle 4 due to severe cytopenias.

OUTCOME AND FOLLOW-UP

The patient achieved complete remission by PET/CT (July 20, 2021). He is under surveillance post treatment and 1-year post-treatment scans show no evidence of disease.

DISCUSSION

MZL can demonstrate a wide spectrum of clinical manifestations due organ-specific variability. Genomically, there is also heterogeneity, although dysregulation of B-cell receptor, nuclear factor κB, and NOTCH signaling pathways is typical[3]. Significant variation is also seen in the architectural patterns manifested by MZL[7]. This is complicated by the fact that there is no single universal biomarker for MZL, and the diagnosis is often only arrived at after integrating phenotypic,

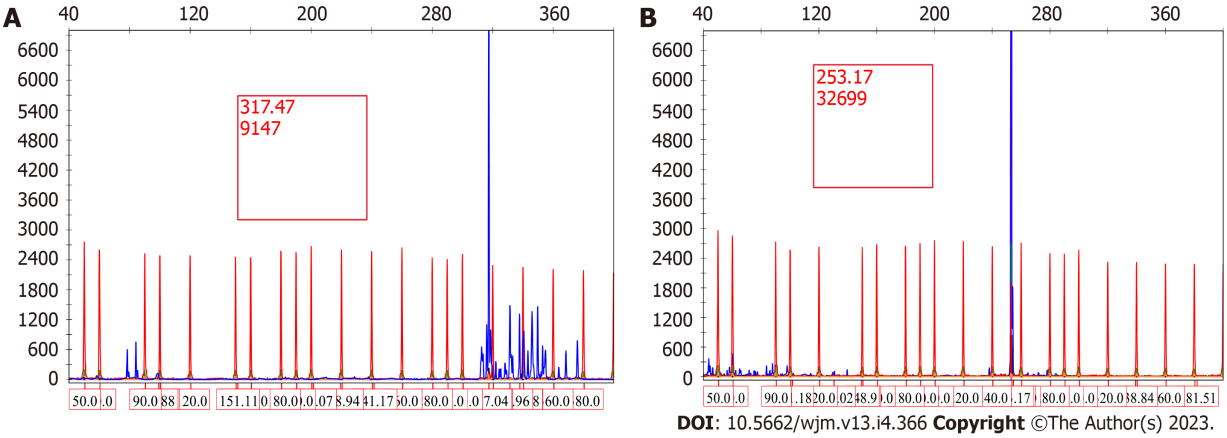

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Figure 3 Clonal peaks detected in immunoglobulin heavy chain. A: Framework 1 region; B: Framework 2 region.

cytogenetic, and molecular features[9].

There are a few studies that have cataloged the architectural patterns in MZL. Salama *et al*[10] evaluated 51 NMZL and found four major patterns, namely: Diffuse (75%), well-formed nodular/follicular (10%), interfollicular (14%) and perifollicular (2%). Interestingly, they noted compartmentalizing interstitial sclerosis in 28% of cases most commonly in the diffuse variant (12/15 cases). However, this was illustrated as relatively inconspicuous comprising of delicate tendrils of sclerosis which in no way resembles our case. Others have documented variable architectural patterns depending on the site of involvement: Spleen (nodular to diffuse), bone marrow (intrasinusoidal, interstitial, nodular, and even paratrabecular), lymph node (nodular to diffuse, liver (intrasinusoidal and portal tract lymphoid nodules), *etc*[9].

Rarely, lymphomas can present in a markedly fibrotic background or be clinically misdiagnosed as retroperitoneal fibrosis[11,12]. Sclerosing lymphomas are rare and typically of follicle center origin[13]. We do not know of any cases describing this architectural presentation of MZL. As such, this case could have easily been overlooked as non-specific fibrosis with chronic inflammation representing a significant diagnostic pitfall. Clues with regard to the diagnosis include the radiologic findings of a large (14 cm) mass with high SUV. Furthermore, the B cell predominance by immunohistochemistry was atypical. Flow cytometry and immunoglobulin heavy and light chain gene rearrangement studies were vital in order to arrive at the correct diagnosis. Response to R-CHOP further confirms the diagnosis clinically.

CONCLUSION

In summary, we present the first case report of sclerotic MZL which should be recognized as a rare architectural pattern in MZL and poses a diagnostic challenge, especially on limited fine-needle aspiration or needle core biopsy specimens. Integration of all clinical and pathological data is essential to arrive at the correct diagnosis.

FOOTNOTES

Author contributions: Moureiden Z, Tashkandi H, and Hussaini MO contributed to the conception and design of the study, acquisition and analysis of data; Moureiden Z and Hussaini MO drafted the manuscript or figures.

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