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EDITORIAL

Management of non-alcoholic fatty liver disease: Lifestyle changes

Hao Lv, Yang Liu

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Abstract

In this editorial, we commented on a recently released manuscript by Zeng *et al* in the *World Journal of Gastroenterology*. We focused specifically on lifestyle changes in patients with non-alcoholic fatty liver disease (NAFLD). NAFLD is a hepatic manifestation of the metabolic syndrome, which ultimately leads to advanced hepatic fibrosis, cirrhosis, and hepatocellular carcinoma and affects more than 25% of the population globally. Existing therapeutic strategies against NAFLD such as pharmacologic therapies focus on liver protection, anti-inflammation, and regulating disease-related metabolic disorder symptoms. Although several drugs are in late-stage development, potent drugs against the diseases are lacking. Additionally, existing surgical approaches such as bariatric surgery are not routinely used to treat NAFLD. Intervening in patients' unhealthy lifestyles, such as weight loss through dietary changes and exercises to ameliorate patient-associated metabolic disorders and metabolic syndrome, is the first-line treatment for patients with NAFLD. With sufficient intrinsic motivation and adherence, the management of unhealthy lifestyles can reduce the severity of the disease, improve the quality of life, and increase the survival expectancy of patients with NAFLD.

Key Words: Non-alcoholic fatty liver disease; Lifestyle; physical activity; Physical exercise; Low-calorie diet; Mediterranean diet

Core Tip: With a worldwide prevalence of 25%, non-alcoholic fatty liver disease (NAFLD) is a leading cause of cirrhosis and hepatocellular carcinoma. NAFLD is bi-directionally associated with the metabolic syndrome. Owing to the lack of specific drugs and conventional surgeries to treat NAFLD, correcting the unhealthy lifestyles of patients with NAFLD by opting for dietary changes and exercises is the first line of intervention to alleviate pain and improve the quality of life of the patients provided that the patients are intrinsically motivated and adherent.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), an epidemic liver disease of the 21st century, is manifested by metabolic disorders and is the leading cause of chronic liver disease, affecting more than 25% of the global population[1]. Additionally, NAFLD is associated with increased mortality owing to cardiovascular diseases (CVDs), diabetes, and pulmonary diseases, including obstructive sleep apnea[2]. Its exact pathogenesis has not been elucidated; however, risk factors associated with it include unhealthy lifestyle, insulin resistance (IR), type 2 diabetes mellitus (T2DM), increased hepatic lipogenesis, and intestinal dysbiosis[3]. Nevertheless, standard therapies for NAFLD are not available, and only a few pharmacologic options are available for these patients; currently, the European and American Association for the Study of the Liver recommend administering only vitamin E and pioglitazone (the proliferation-activated receptor γ ligand) to specific patients[4]. Additionally, bariatric surgery improves NAFLD in patients with NAFLD complicated with obesity[4,5]. This may be correlated to the higher remission rates of T2DM after bariatric surgery; however, NAFLD itself is not currently an indication for bariatric surgery[5].

Lifestyle changes, such as substantial weight loss by consuming low-calorie diets and engaging in physical activities, are considered first-line interventions for treating NAFLD because weight loss is correlated to liver fat reduction, which may reverse disease progression[6,7]. Consequently, the American Gastroenterological Association has provided recommendations for treating patients with obesity as well as for safe and effective weight control. These recommendations are based on four guiding principles, namely assessment, intensive weight loss interventions, weight stabilization, and weight loss re-enforcement if necessary, and weight rebound prevention, to achieve weight loss through low-calorie diets, physical activities, medications, bariatric endoscopy, and surgery[8]. However, medications, bariatric endoscopy, and surgery are primarily for patients who are severely obese and have concomitant diabetes mellitus (DM), biopsy-proven NAFLD, and at least stage 2 liver fibrosis[8]. NAFLD is not limited to patients with obesity, and the prevalence of normal-weight NAFLD in the general population may range from 4% to 10%[9]. However, depending on the number of metabolic disorders present, patients with NAFLD complicated with obesity carry a higher burden of morbidity and mortality[9]. Therefore, in the context of increased NAFLD, obesity, and metabolic syndrome incidence and prevalence, reducing body weight through lifestyle changes by consuming an appropriate diet and doing exercises remains the cornerstone of NAFLD treatment[8].

Finally, improving adherence and intrinsic motivation to make lifestyle changes is crucial from the viewpoint of patients with NAFLD. Scarce data exist on the persistence of the metabolic effects of diet and exercise; however, most patients with NAFLD cannot adhere to lifestyle changes to lose weight[10]. Zeng *et al*[11] developed and validated the Exercise and Diet Adherence Scale (EDAS) to rapidly assess adherence to lifestyle interventions in patients with NAFLD. Patients were grouped according to EDAS scores and received individualized treatment accordingly, which improved their adherence to lifestyle interventions[11].

PRACTICAL RECOMMENDATIONS FOR CHANGING LIFESTYLES

NAFLD is strongly correlated to obesity in most populations irrespective of histologic type, and lifestyle intervention aimed at weight loss and exercise are the mainstay of the treatment[1,6,12]. Weight loss reduces liver fat, improves glycemic control/insulin sensitivity, and reduces the risk of diabetes, CVD, and worsening liver disease[6]. Current guidelines from the American Gastroenterological Association recommend at least 5% weight loss to reduce hepatic steatosis and 10% weight loss to reverse liver fibrosis. Additionally, weight loss of ≥ 7% may regress non-alcoholic steatohepatitis[13]. For adults with NAFLD who are not overweight or obese, a weight loss of 3%-5% is recommended[6,13].

A low-calorie diet is critical in NAFLD treatment. A low-calorie diet is characterized by reducing calorie intake by 500-1000 kcal/d, resulting in intake of up to 1200 kcal/d for women and 1400-1500 kcal/d for men. Such a diet is associated with weight loss, improved IR, and reduced intrahepatic fats[2,14]. Improvements in intrahepatic fat levels persist after consuming a low-calorie diet, even when weight is regained after 2 years of weight loss[15]. Additionally, diets containing specific macronutrients are good options, including low-carbohydrate and Mediterranean diets (Med diet, MD)[16]. An MD is characterized by daily consumption of fresh vegetables, fruits, legumes, minimally processed whole grains, fish (rich in omega-3 fatty acids), olive oil, nuts, and seeds, which are the primary sources of fat[16]. As a primary

source of fat, minimize or avoid dairy products, red meat, and processed meats. The American College of Cardiology, the American Heart Association, and the Office of Disease Prevention and Health Promotion support the use of an MD in preventing and controlling CVDs, which is critical for patients with NAFLD, which is closely related to CVD occurrence. Moreover, MD consumption is associated with a reduced risk of hepatocellular carcinoma (HCC)[17]. In addition to DM, the consumption of a ketogenic diet (KD) is a recommended dietary intervention for NAFLD treatment. KD, which comprises a high proportion of fat and a low proportion of carbohydrates, proteins, and other nutrients, plays a positive role in NAFLD treatment owing to the extremely low proportion of carbohydrates. KD consumption markedly alters mitochondrial flux and hepatic redox status and promotes ketone body production without affecting intrahepatic triglyceride synthesis, thus considerably improving visceral fat content[18]. Although KD consumption exerts some therapeutic effects on patients with NAFLD, tests on animals and clinical studies have indicated some risks associated with it, and existing clinical trials suggest that the safety of KD in treating NAFLD should be investigated further[19]. Additionally, new dietary interventions have been used to progressively treat patients with NAFLD. For instance, high-protein (animal- or plant-based) diets can markedly decrease inflammatory marker levels[20]. An eight-week sugar-restricted diet reduced liver fat and improved liver steatosis in adolescent boys with NAFLD[21]. However, owing to the limited number of clinical trials on these dietary interventions, adequate conclusions are not drawn. Similarly, interventions such as intermittent fasting and time-restricted eating have limited clinical evidence and inconclusive results; thus, their safety and efficacy cannot be proven as of now.

Exercise improves impaired glucose and lipid metabolism and is an effective intervention for treating metabolic diseases[22]. Engaging in exercise may enhance the beneficial effects of a low-calorie diet on NAFLD. Furthermore, it may improve the course of NAFLD by reducing hepatic fat levels *via* increasing insulin sensitivity in the periphery of the body and decreasing hepatic neolipogenesis, lipolysis in adipocytes, and free fatty acid delivery to the liver. Physical activity can be achieved through aerobic exercise (*e.g.*, walking or bicycling), and resistance training can be achieved through weight-bearing exercise (*e.g.*, weight training on an exercise machine)[23]. Generally, 90-300 min of physical activity per week is beneficial for steatosis, and patients should consider 150-300 min of moderate-intensity exercise (3-6 metabolic equivalents) or 75-150 min of vigorous exercise (more than 6 metabolic equivalents). Compared with aerobic exercise, resistance training reduces steatosis; however, it is less intense and may be suitable for individuals with limited aerobic capacity[24]. However, a recent population-based study showed that walking more than 3 h/wk was correlated to reduced mortality from cirrhosis and HCC; thus, consideration should be given to encouraging aerobic exercise[24]. Exercise may enhance the effect of diet on weight loss; thus, moderate physical activity combined with an MD may result in weight loss and visceral adipose tissue and intrahepatic fat percentage reduction[22-24].

Lifestyle interventions for patients with NAFLD should include diverse general health-related behaviors. Smoking and alcohol consumption are risk factors that can accelerate liver disease progression and are synergistic with other risk factors[25]. Even light-to-moderate alcohol consumption (≤ 1 drink per day for women and ≤ 2 drinks per day for men; 1 drink is equivalent to 1 regular beer (12 ounces), 1 glass of wine (5 ounces), or 1 glass of white wine or spirits (1.5 ounces)) is associated with steatosis and hepatic fibrosis progression and exerts a synergistic effect on the risk of obesity and the development of numerous clinical liver diseases, including cirrhosis and liver cancer)[26]. Therefore, counseling and interventions should be considered to help smokers quit smoking and alcohol drinkers reduce or stop drinking, especially if they have liver fibrosis[27].

Adherence to lifestyle changes is crucial for patients with NAFLD as most of whom face challenges while sustainably changing their habits[10]. Zeng MH *et al*[11] provide important help on how to effectively improve the adherence of such patients to lifestyle modifications. They designed the EDAS for patients with NAFLD aged 18-70 years who were admitted to Tianjin Second People's Hospital from August 2013 to January 2014 (study subjects). They first identified factors affecting exercise and diet adherence in patients with NAFLD as well as analyzed and modified the EDAS using the Delphi method. After establishing the EDAS, patients with NAFLD were initially entered into the EDAS system as the target population for exercise and diet interventions and followed up for 6 months. The EDAS exhibited good item discrimination, internal consistency, reliability, retest reliability, content validity, structural validity, and criterion validity and could reliably measure adherence to exercise and dietary interventions in the patients. Thus, this scale allows patients to be grouped according to EDAS scores and helps recommend personalized treatments accordingly, thus improving adherence to lifestyle interventions[11].

CONCLUSION

Pharmacologic treatment options for patients with NAFLD are scarce, and surgery is not a routinely followed treatment modality[4]. Consequently, lifestyle modifications, including consuming a healthy diet and engaging in physical activity to lose weight and improve metabolic disorders, are the cornerstone of NAFLD treatment[6]. Furthermore, limiting or avoiding alcohol consumption and smoking is essential[26]. Additionally, some patients do not adhere well to the discussed lifestyle interventions; thus, improving their adherence to lifestyle modifications is equally important. Nevertheless, we should continue developing comprehensive interventions to help patients with NAFLD manage their lifestyles, improve nutrition, lose weight, and ultimately change their health trajectories to improve their quality of life and increase survival expectations.

FOOTNOTES

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EDITORIAL

Gastroesophageal reflux following per-oral endoscopic myotomy: Can we improve outcomes?

Inian Samarasam, Raj Kumar Joel, Anna B Pulimood

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Abstract

This editorial is an analysis the review article by Nabi *et al* recently published in this journal. Achalasia Cardia is a disease whose pathophysiology is still unclear. It is known that there is inflammation of unknown aetiology leading to loss of ganglion cells in the muscularis propria. The end result is lower oesophageal sphincter spasm, loss of receptive relaxation, decreased oesophageal peristalsis, all leading on to varying degrees of dysphagia. The treatment of this condition is palliative in nature, performed by myotomy of the lower oesophagus either surgically or endoscopically. Gastroesophageal reflux disease (GERD) has been associated with the myotomy performed, particularly with the Peroral Endoscopic Myotomy (POEM) procedure. Nabi *et al* have provided an excellent overview of the latest developments in predicting, preventing, evaluating, and managing GERD subsequent to POEM. Based on this theme, this review article explores the concept of using histology of the oesophageal muscle layer, to grade the disease and thereby help tailoring the length/type of myotomy performed during the POEM procedure. In the future, will a histology based algorithm available preoperatively, help modify the POEM procedure, thereby decreasing the incidence of GERD associated with POEM?

Key Words: Achalasia cardia; Peroral endoscopic myotomy; Laparoscopic Heller's myotomy; Histopathology; Histologic grading

Core Tip: Gastro Esophageal Reflux disease (GERD) is a side effect of the Peroral Endoscopic Myotomy (POEM) procedure done for Achalasia Cardia (AC). There is still lack of clear understanding of the histologic changes associated AC and its correlation with the natural history of the disease. The question put forward in this editorial is whether a histology based algorithm to modify the POEM procedure, will help decrease the incidence of GERD associated with POEM. This article is written to provide a deeper insight into the problem and provide thought for further research on this important, yet unexplored area in the management of AC.

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INTRODUCTION

First described by Inoue *et al*[1] in 2008, Per-Oral Endoscopic Myotomy (POEM) has been proven to be an effective treatment for Achalasia Cardia. However, the 'Achilles heel' of the procedure is the occurrence of Gastro Esophageal Reflux disease (GERD) postoperatively and the solution for this problem has still been elusive. In this current issue of the journal, Nabi *et al*[2] have presented an excellent overview of the latest developments in predicting, preventing, evaluating, and managing GERD subsequent to POEM. Their review article looks into the various modifications of the POEM procedure and into the future perspectives for improving outcomes in relation to GERD.

Anatomically, there are two factors which are crucial in maintenance of the anti-reflux barrier of the Lower esophageal Sphincter (LES) – firstly, the intrinsic factor consisting of the oblique sling muscle fibres and secondly the extrinsic factor consisting of the phreno-esophageal ligament, which is a membranous ligament between the abdominal esophagus and the diaphragm[3]. A lower oesophageal myotomy done surgically or endoscopically has the potential to adversely affect one or both of these barrier mechanisms.

The original surgical Heller's myotomy was a double-sided myotomy, by a transthoracic approach. This was later modified by Zaaijer[4], into a single-sided thoracic myotomy[4]. An anti-reflux procedure (fundoplication) was not part of these original procedures. The inherent problem with the thoracic approach was the inability to perform an adequate myotomy on the stomach side. This therefore resulted in suboptimal dysphagia relief. Therefore, the abdominal approach was improvised, to address this issue and subsequently Laparoscopic Heller's myotomy (LHM) became the gold standard in the surgical management. When the myotomy was performed transabdominally, the dysphagia relief was much better, but GERD was inevitable as both the intrinsic and extrinsic anti-reflux barriers were at risk. However, the solution to this problem was relatively easy, by the way of addition of an anti-reflux procedure in the form of a fundoplication[5]. An anterior (Dor) fundoplication or a posterior partial (Toupet) fundoplication were added as an additional procedure to LHM. Thus, the current surgical guidelines clearly mention that LHM with fundoplication is superior to LHM without fundoplication in controlling distal oesophageal acid exposure[6].

What has changed with the advent of POEM? Although the approach of the POEM is different (being an endoscopic procedure), the principles of surgical myotomy remains the same. Since POEM is an endoscopic procedure, the extrinsic anti-reflux barrier is less affected, but the intrinsic anti-reflux barriers are compromised, resulting in the GERD. The addition of an anti-reflux procedure endoscopically as in the NOTES-F procedure is much more technically demanding when compared to the LHM. Although shown to be feasible, this modification of the NOTES procedure requires quite advanced endoscopic skills and its safety, efficacy and durability of the wrap are yet to be proven[7,8].

The EndoFLIP seems to be an attractive option to assess intraoperative LES distensibility during POEM, thereby enabling the tailoring of myotomies, with a view to possibly decrease the risk of postoperative reflux. The short term outcomes of this procedure have been looked at and have been favourable[9]. However, the available literature on the intraoperative use of EndoFLIP during POEM is still scanty and the procedure still under evolution.

The review article in this journal by Nabi *et al*[2], details the pros and cons of the various techniques of modification of the standard POEM procedure. The modifications focus on the location and length of the oesophageal and gastric myotomies and the techniques which allow preservation of the sling fibres of the Esophago-gastric junction (EGJ). However as mentioned in the article, the results of these techniques have not been consistent, with studies showing contrasting outcomes. Perhaps of the reasons for this paradox might lie in the fact patients with AC present at different stages of the evolution of the disease. Therefore a 'one size fits all' option may not be suitable for all patients with AC and a more personalised approach may be the way forward. Are there unexplored options available, to modify the POEM procedure and tailor it to every patient?

There have been significant advances in the techniques of management of AC, but there is still lack of clear understanding of the histologic changes that are associated with the condition and the correlation with the natural history of the disease. Histologic examination of the oesophageal mucosal specimens obtained at esophagectomy have shown lymphocytic infiltration, muscle hypertrophy, interstitial fibrosis, ganglion cell loss, ganglionitis[10,11]. The study by Sodikoff *et al*[12] looked at surgically obtained muscularis propria biopsy specimens from patients with achalasia cardia. The spectrum of histopathologic findings included complete aganglionosis, lymphocytic inflammation, to almost normal histopathology[12]. This again underlines the fact that patients with AC represent a pathogenically heterogeneous group,

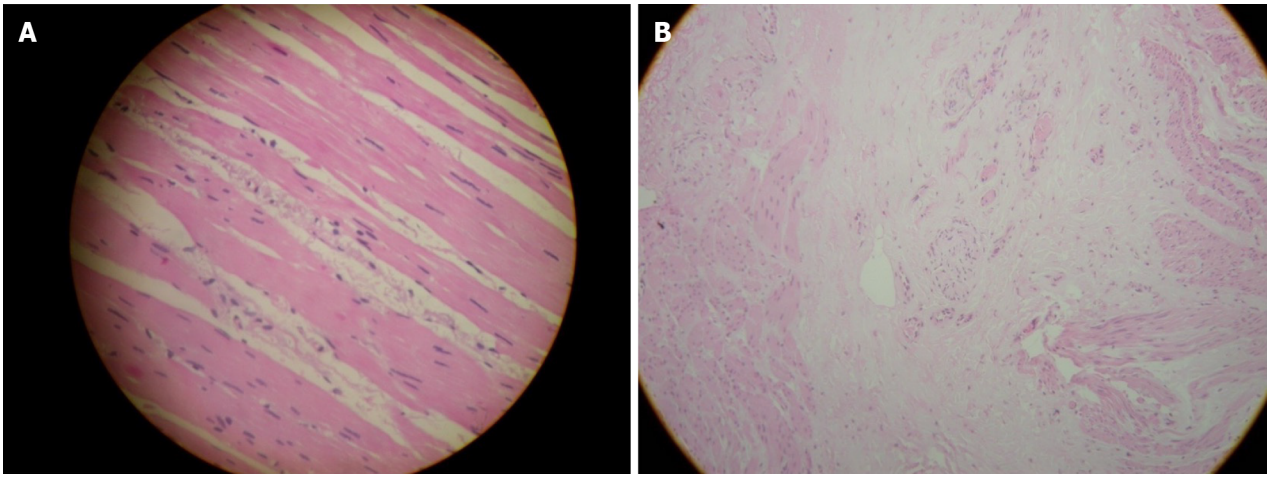

Figure 1 Mild fibrosis, in a patient with achalasia cardia. A: Mild fibrosis, in a patient with early stage of achalasia cardia (AC); B: Severe fibrosis and muscle atrophy, in a patient with late stage of AC.

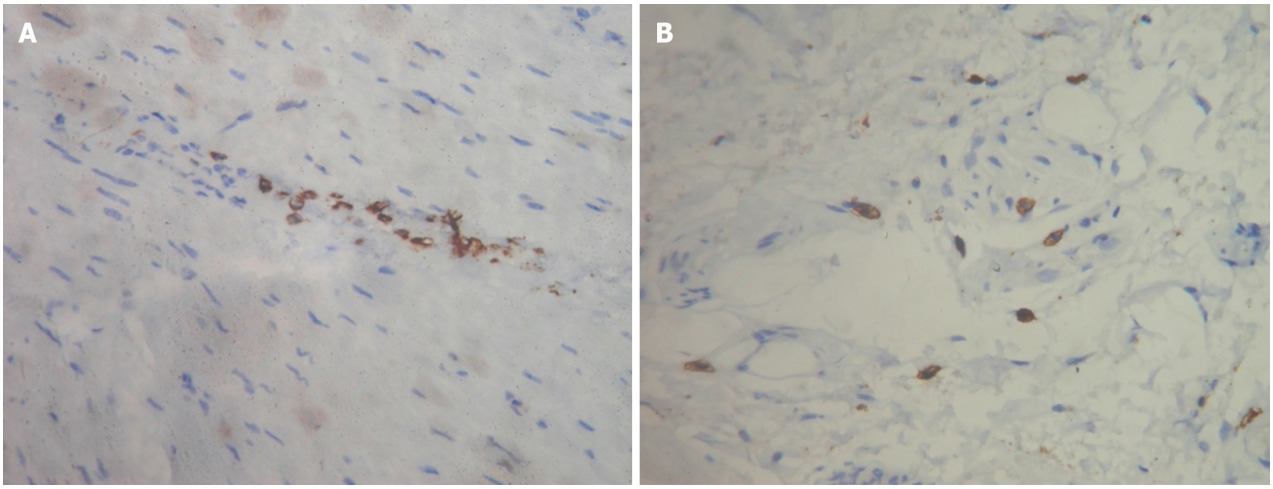

Figure 2 Immunohistochemistry. A: Lymphocytes seen by CD3 immunohistochemistry; B: Mast cells seen on immunohistochemistry (CD117).

with symptoms of EGJ outflow obstruction.

We have conducted a prospective observational study in our centre, involving 21 patients who underwent LHM for AC (unpublished data). The study included taking two small bits (0.5 cm × 0.5 cm each) of oesophageal muscle from the cut ends of the myotomy at the lower esophageal muscle layer and the GEJ. Histopathological, immunohistochemical and ultrastructural analysis was performed. These pathology results were correlated with the clinical features, manometric features and post-operative outcomes**.** Post-operatively, these patients were monitored till discharge and followed up at 1 month, 3 months and 6 months in the surgery OPD. The short term surgical outcomes including complications and relief of dysphagia were recorded.

Specimens were graded on degree of neuronal loss, muscular damage, inflammation, and fibrosis. The spectrum of fibrosis and smooth muscle atrophy ranged mild to severe (Figure 1). The histology also demonstrated eosinophil and mast cell infiltration, indicating inflammation of the myentric plexus (Figure 2). Damage and demyelination of ganglion cells was a consistent finding (Figure 3). These histological changes were dependent on the disease duration, lower oesophageal sphincter dysfunction, degree of esophageal dilatation and the manometric subtype. The study also showed histologic changes starting with myenteric inflammation, and damage to the ganglion cells and neuronal fibrosis (early disease). This then progresses to total absence of ganglion cells (aganglionosis), severe fibrosis and varying degrees of smooth muscle atrophy/hypertrophy (late disease).

Liu *et al*[13] have described the Histologic Findings in Mucosa and Muscularis Propria Biopsied during POEM, in patients with AC. The study has described the feasibility and safety of muscle biopsy during POEM. Again, there was again varying degrees of inflammation, neuronal loss, muscle fibrosis and atrophy the specimens examined[13].

Now that the safety of muscle biopsies during LHM/POEM procedures have been demonstrated, what we need are larger multicentre studies which can help grade the histological changes - namely ganglion loss, inflammation, muscle loss/hypertrophy and fibrosis. When the histologic pattern is available preoperatively, the POEM or the LHM procedure can be modified based on the severity of the disease and the symptom palliation required. For example, in a patient with early disease and lesser fibrosis, dysphagia relief may be obtained by even shorter myotomies, thereby offering protection

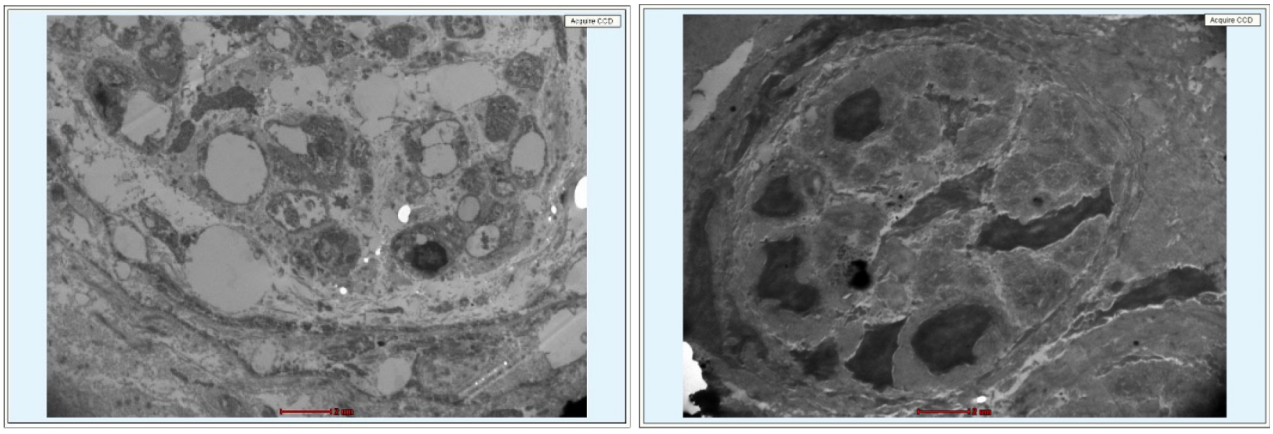

Figure 3 Degenerated pre and post ganglionic nerve cells on electron microscopy.

against future GERD. Whereas in a patient with end stage disease with severe aganglionosis and muscle atrophy/fibrosis, the focus of treatment must be to provide the maximum possible dysphagia relief and the side effect of GERD may be of secondary importance.

CONCLUSION

Will a pre operative, histology based algorithm help tailor the length/type of myotomy performed during POEM/LHM procedures, thereby minimising post procedural GERD? We leave this question in the minds of the readers of this article and hope this will provide fuel for further research on this important, yet unexplored area in the management of AC. This, along with the intraoperative use of EndoFLIP may offer a reasonable solution to the long debated issue of reflux following POEM.

FOOTNOTES

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EDITORIAL

Screening for metabolic dysfunction-associated fatty liver disease: Time to discard the emperor's clothes of normal liver enzymes?

Chen-Xiao Huang, Xiao-Dong Zhou, Calvin Q Pan, Ming-Hua Zheng

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) is the most prevalent chronic liver condition worldwide. Current liver enzyme-based screening methods have limitations that may missed diagnoses and treatment delays. Regarding Chen *et al*, the risk of developing MAFLD remains elevated even when alanine aminotransferase levels fall within the normal range. Therefore, there is an urgent need for advanced diagnostic techniques and updated algorithms to enhance the accuracy of MAFLD diagnosis and enable early intervention. This paper proposes two potential screening methods for identifying individuals who may be at risk of developing MAFLD: Lowering these thresholds and promoting the use of noninvasive liver fibrosis scores.

Key Words: Metabolic dysfunction-associated fatty liver disease; Non-alcoholic fatty liver disease; Alanine aminotransferase; Liver enzymes; Screening; Noninvasive liver fibrosis scores

Core Tip: Screening and risk assessment procedures for metabolic dysfunction-associated fatty liver disease by liver enzymes may result in underdiagnosis and treatment delays. To improve the screening methods, it is feasible to lower the normal thresholds for liver enzymes and promote the use of noninvasive liver fibrosis scores.

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INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD) is the most prevalent chronic liver condition worldwide. Current liver enzyme-based screening methods have limitations that may missed diagnoses and treatment delays. Regarding the article published in the *World Journal of Gastroenterology*, the risk of developing MAFLD remains elevated even when alanine aminotransferase (ALT) levels fall within the normal range. Therefore, there is an urgent need for advanced diagnostic techniques and updated algorithms to enhance the accuracy of MAFLD diagnosis and enable early intervention. This paper proposes two potential screening methods for identifying individuals who may be at risk of developing MAFLD: Lowering these thresholds and promoting the use of noninvasive liver fibrosis scores.

NEW PROSPECTIVE ON MAFLD SCREENING

MAFLD affects approximately 30% of the global adult population[1], contributing to a growing burden of multisystem disease and imposing substantial economic costs on society. Screening for MAFLD presents challenges, particularly during its early stages when it often manifests without symptoms. Therefore, healthcare providers must remain vigilant when evaluating liver disease in patients, particularly regarding the progression of liver fibrosis. Presently, liver disease screening primarily focuses on detecting abnormalities in liver enzymes or markers related to liver function, which can result in missed diagnoses and delays in treatment initiation. Unlike screening for conditions such as hypertension and diabetes, relying solely on a single parameter, using liver enzyme assessments for MAFLD is simplistic and commonly used but not ideal for monitoring liver disease progression.

Recent evidence indicates that MAFLD can be present even within the normal range of ALT values. In this context, Chen *et al*[2] conducted a retrospective analysis to explore the optimal ALT cut-off points for diagnosing MAFLD. Their findings revealed that a significant proportion of participants with MAFLD exhibited normal ALT levels, accounting for 83.13% of cases. Notably, the study identified a high-normal ALT level range of 18.6-40 U/L, emphasizing that sustained alterations in ALT levels can cumulatively increase the risk of new-onset MAFLD[2]. Large-scale epidemiological studies, such as the Dallas Heart Study, have reported normal ALT levels in 79% of MAFLD patients, while Gawrieh *et al*'s observational study[3] found that 43% of MAFLD patients had normal serum ALT levels[3]. Moreover, the risk of developing MAFLD remains elevated even when ALT levels fall within the normal range, as metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis can occur even when ALT levels are below the upper limit of normal, specifically in individuals with plasma ALT < 40 U/L[4]. Castera *et al*[5] conducted a prospective multicenter study and found a high prevalence of MASH (58%) despite a low ALT threshold[5]. Similarly, a meta-analysis by Li *et al*[6] revealed the unreliability of ALT in predicting liver injury in patients infected with hepatitis B. The meta-analysis found that about 1/3 of treatment-naïve chronic hepatitis B patients experienced significant histological changes with ALT levels at or below 40 IU/L. In contrast, only about 1/5 of patients showed significant fibrosis, even with ALT levels at or below 20 IU/L.

Two screening methods have been proposed for individuals at risk of MAFLD. The first method involves lowering the normal thresholds for liver enzymes, particularly ALT. By assembling a large-scale cohort of MAFLD patients from various nations, the upper threshold of normal ALT values can be reevaluated based on distinct age and gender characteristics, employing statistical methodologies such as performing receiver operating characteristic curve analysis. Lowering these thresholds enables the early detection of abnormal liver function, prompting further screening and facilitating earlier recognition of MAFLD, thus potentially reducing disease burden. However, this approach may result in some patients being inaccurately labeled as having abnormal liver function, leading to potential social implications. Additionally, clinicians may overlook certain beneficial medications, such as statins, due to concerns related to this label.

Promoting the use of noninvasive liver fibrosis scores may offer a more suitable and convenient method for assessing MAFLD. Analogous to the introduction of an age-adjusted estimated glomerular filtration rate (eGFR) in nephrology, which has become widely adopted for evaluating kidney function. This indicator has since been widely used in assessing renal function and determining appropriate medication dosages[7]. Various noninvasive scoring systems have been approved for accurate diagnosis and clinical monitoring of liver fibrosis[8,9]. Unfortunately, these noninvasive scoring methods were only discussed and used among hepatologists, and not widely used by other clinicians. Fibrosis-4 index (FIB-4) is a simple available blood-based marker of liver fibrosis that can be calculated using only commonly clinical parameters including age, platelet count, aspartate aminotransferase and ALT. Despite the similarity between

noninvasive scoring systems, such as the FIB-4, and the eGFR calculation, their use remains limited mainly to subspecialists[10]. A patient with an elevated FIB-4 index, even with normal liver enzymes, indicates a higher likelihood of advancing liver fibrosis, warranting further evaluation through techniques such as vibration-controlled transient elastography or liver biopsy[11]. However, promoting the use of liver fibrosis scoring systems faces significant challenges, including limited awareness among clinicians and the public, which necessitates additional efforts to facilitate their widespread adoption.

CONCLUSION

In summary, current screening and risk assessment procedures for liver enzymes are outdated, resulting in the underdiagnosis of a substantial number of patients with MAFLD. There is an urgent need for advanced diagnostic techniques and updated algorithms to enhance the accuracy of disease diagnosis and enable early intervention. The widespread adoption of noninvasive liver fibrosis scores should be prioritized as a crucial topic for discussion.

FOOTNOTES

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EDITORIAL

New challenges in hepatocellular carcinoma: A role for PIWI-interacting RNAs?

Domenico Tierno, Gabriele Grassi, Bruna Scaggiante

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Abstract

Hepatocellular carcinoma (HCC) is the most common and deadliest subtype of liver cancer worldwide and, therefore, poses an enormous threat to global health. Understanding the molecular mechanisms underlying the development and progression of HCC is central to improving our clinical approaches. PIWI-interacting RNAs (piRNAs) are a class of small non-coding RNAs that bind to PIWI family proteins to regulate gene expression at transcriptional and post-transcriptional levels. A growing body of work shows that the dysregulation of piRNAs plays a crucial role in the progression of various human cancers. In this editorial, we report on the current knowledge of HCC-associated piRNAs and their potential clinical utility. Based on the editorial by Papadopoulos and Trifylli, on the role and clinical evaluation of exosomal circular RNAs in HCC, we highlight this other emerging class of non-coding RNAs.

Key Words: Biomarker; Hepatocellular carcinoma; Liquid biopsy; Non-coding RNA; PIWI-interacting RNA; Next-generation sequencing

Core Tip: Hepatocellular carcinoma (HCC) is a worldwide clinical problem. Over the past decade, several papers have suggested that specific PIWI-interacting RNAs (piRNAs) may be useful as efficient HCC biomarkers at both tissue and serum levels. Interestingly, the piRNA expression profile changes dynamically over the course of the pathological stage from liver fibrosis to HCC development and progression. Knowledge of piRNAs may improve our understanding of HCC and open new clinical perspectives.

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INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for 80%-90% of all liver tumors and its incidence has increased in recent decades[1,2]. The risk factors are numerous, including hepatitis B or C infection, alcoholic and non-alcoholic fatty liver disease, and diabetes. In general, these pathological conditions lead to liver fibrosis, which develops into cirrhosis and eventually HCC. This tumor is extremely heterogeneous and aggressive, has a high recurrence rate and is often resistant to chemotherapy. For this reason, survival rates for HCC are poor despite improvements in diagnostic and therapeutic approaches[3]. Understanding the molecular networks underlying the development and progression of HCC is important for new biomarkers and therapeutic goals.

Non-coding RNAs (ncRNAs) account for 97% of total transcriptional output. Advancing technologies in the enrichment and sequencing of ncRNAs shed light on their active role in the regulation of biological processes and made them increasingly attractive. The ncRNAs can be classified according to their function, length and shape[4]. The most important classes are: (1) MicroRNAs (miRNAs): Small ncRNAs with a length of about 20 nucleotides (nt). Their primary function is the inhibition of mRNA translation by binding sequences with incomplete complementarity in the 3′-untranslated regions of the target mRNAs[5]; (2) PIWI-interacting RNAs (piRNAs): Small ncRNAs (mainly 24-35 nt long)[6,7], mainly found in germline cells. As the name suggests, they interact with proteins belonging to the PIWI family and regulate gene expression at transcriptional (through epigenetic chromatin modification) and post-transcriptional level (through RNA and protein interactions)[8]; (3) Long ncRNAs (lncRNAs): NcRNAs generated from pre-mRNAs. They are more than 200 nt long and are characterized by complex secondary/tertiary structures designated for interactions with their molecular targets (proteins or DNA/RNA). LncRNAs regulate many biological processes by acting as miRNA sponges, as recruiters of transcription factors to target promoters and as scaffolding meant to facilitate protein interactions[9]; and (4) Circular RNAs (circRNAs): NcRNAs which are similar in length and function to lncRNAs, except for their distinct ring-like shape. CircRNAs are formed by the circularization of exons, introns, or other ncRNAs by a non-canonical splicing event, so-called "back-splicing"[10].

Since ncRNAs play a crucial role in various biological processes, it is not surprising that evidence of their massive involvement in cancer is accumulating[11,12]. Accordingly, studying the biogenesis and functions of ncRNAs could be a valuable tool in deepening our knowledge of cancer. The editorial by Papadopoulos and Trifylli[13] in the *World Journal of Gastroenterology* discussed the role of exosomal circRNAs in HCC and proposed them as new therapeutic targets. In this editorial, we will extend the discussion to piRNAs, another class of ncRNAs, and their potential utility for the clinical treatment of HCC.

PIRNA

A brief note on the biology of piRNA: These ncRNAs are transcribed from specific loci, enriched with transposons, the so-called "piRNA clusters", which can be divided into single-stranded (ss) and double-stranded (ds) clusters. The ss-cluster generates a piRNA precursor with a 3′-polyadenylated tail and a 5′-methylguanosine-cap, similar to the canonical transcription of mRNAs. The ds-cluster can instead generate two non-polyadenylated piRNA precursors (sense and anti-sense) by means of a protein complex, including RNA polymerase II. Regardless of their origin, the piRNA precursors are exported to the cytoplasm, in particular to the outer membrane of the mitochondria, where the proteins involved in their maturation are located. The piRNA precursor is first cleaved at the 5′-end by an endonuclease called Zucchini to form a 5′-monophosphorylated pre-piRNA, which, in turn, is loaded into a PIWI protein (in a 1:1 ratio) and further cleaved at the 3′-end by the 3′-to-5′ exonuclease Nibbler. The new, truncated 3′-terminal end is finally methylated at the 2′-oxygen by Hen1, a 2′-O-methyltransferase, presumably to increase the stability of the piRNA. These primary mature piRNAs can trigger a secondary piRNA maturation cycle, called "ping-pong cycle", in order to exponentially increase the mature cellular piRNA pool. Basically, a mature anti-sense piRNA is loaded into the Aub protein to cleave the sense piRNA precursor into multiple sense piRNA precursors, which are fully processed and then finally loaded into the Ago3 protein. The mature sense piRNA-Ago3 complex cleaves the anti-sense piRNA precursor into multiple anti-sense piRNA precursors, which are loaded into Aub proteins to restart the cycle[14] (Figure 1). It is important to emphasise that our knowledge of the biogenesis of piRNA is still incomplete, and comes mainly from Drosophila melanogaster and mice-related studies. Despite the high degree of evolutionary conservation of this pathway, a deeper understanding of piRNA biogenesis, especially in humans, is crucial to assessing its importance for basic and translational research.

Functionally, the main role of piRNAs is to silence gene expression at the transcriptional level by recruiting DNA methyltransferase and histone methyltransferase to the target promoter and target histone, respectively. In addition, piRNAs protect the cells from transposons and prevent their amplification and mobilisation. The piRNA-mediated regulation of gene expression can also be observed at a post-transcriptional level: piRNA can inhibit mRNA translation and trigger the degradation of pseudogenic transcripts and lncRNAs by interacting with complementary sequences at the

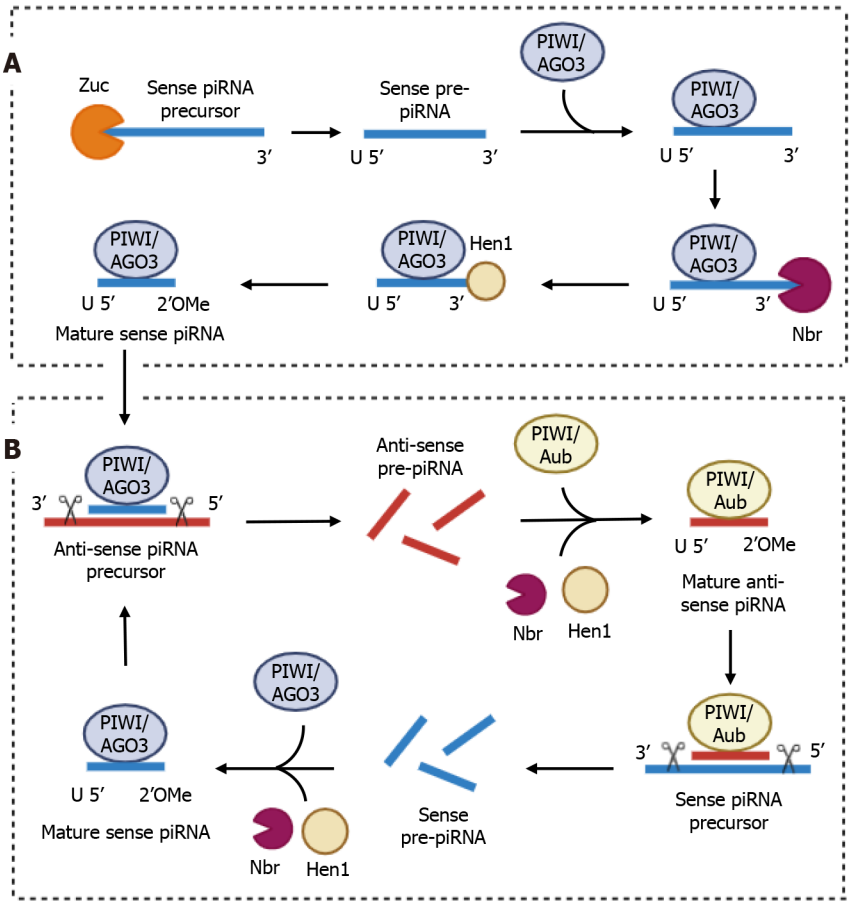

Figure 1 Schematic diagrams of the biosynthesis of PIWI-interacting RNAs. A and B: The primary (A) and secondary (B) cycles (also known as the "ping-pong cycle") are shown. Note that the PIWI-interacting RNA (piRNA) precursor that triggers primary biosynthesis can be either a sense or an anti-sense piRNA precursor. Image created by Biorender. Zuc: Zucchini; piRNA: PIWI-interacting RNA; Nbr: Nibbler.

5′-end. Finally, it has been reported that many piRNAs can act as scaffolding to facilitate interaction with multiple proteins, similar to circRNAs and lncRNAs[15]. In recent decades, increasing number of studies have reported the possible involvement of piRNA dysregulation in the development and progression of cancer. We provide a brief chronological overview of articles dealing with HCC-associated piRNAs.

PIRNA IN HCC

According to PubMed research, the paper by Law *et al*[16] is the first article to evaluate the clinical benefit of piRNAs in HCC. Using Illumina sequencing, they identified a novel piRNA, called piR-Hep1, which was significantly overexpressed in the tumour tissue of 73 HCC patients compared to adjacent normal tissue. Furthermore, inhibition of piR-Hep1 in HCC cell lines (HKCI-4 and HKCI-8) led to a reduction in cell viability, invasiveness, and phosphorylation levels of AKT, indicating a possible involvement of piR-Hep1 in the regulation of the AKT signalling pathway[16].

In 2016, Rizzo *et al*[17] used next-generation sequencing techniques to characterise the piRNA expression profile of the different pathological stages underlying the diagnosis and progression of HCC: (1) Cirrhotic nodules (CN); (2) Low-grade dysplastic nodules (LGDN); (3) High-grade dysplastic nodules (HGDN); (4) Early HCC (eHCC); and (5) Progressed HCC (pHCC). For this purpose, they obtained resection samples from 17 HCC patients with multiple nodules: (1) 17 CN; (2) 9 LGDN; (3) 6 HGDN; (4) 6 eHCC; and (5) 23 pHCC. Sequencing revealed a 125 piRNA expression signature specific for eHCC and pHCC, and a 24 piRNA expression signature specific for LDGN and HDGN[17]. Similar results were also obtained in 2018 by Koduru *et al*[18] through database screening and informatic analysis. The RNA-seq datasets analysed were from the NIH Short Read Archive and were from 14 CN, 9 LDGN, 6 HDGN, 6 eHCC, and 20 pHCC samples. They found a specific piRNA expression profile for each HCC-associated pathological stage (number of specific dysregulated piRNAs in round brackets): (1) CN (75); (2) LDGN (60); (3) HGDGN (49); (4) eHCC (56); and (5) pHCC (128). These results indicate dynamic changes in piRNoma during disease progression, which complicates their use as clinical tools.

In 2018, Tang *et al*[19] also investigated the role of piRNAs in those liver pathologies which will lead to the development of HCC in mice. They found that piR-823 was highly expressed in primary hepatic stellate cells (HSCs) and that its inhibition suppressed the activation of HSCs. In contrast, overexpression of piR-823 increased the proliferation of HSCs and the production of alfa-smooth muscle actin, collagen type I alpha 1, and transforming growth factor beta 1 (crucial genes for liver fibrosis progression). Accordingly, piR-823 could be an early therapeutic target to prevent liver

fibrosis and, subsequently, the progression of HCC.

In 2023, Wu *et al*[20] found that piR-017724 was significantly downregulated in 45 HCC tissues compared to adjacent normal tissues and that its downregulation was correlated with poor prognosis and advanced tumour stage. The oncosuppressive role of this piRNA was confirmed in HCC cell lines (SMMC-7721 and PLC/PRF/5), where silencing of piR-017724 resulted in the inhibition of cell proliferation and invasiveness but not apoptosis. Functional analyses suggested that piR-017724 could inhibit the expression of PLIN3, a member of the abdominal lipoprotein family involved in lipid droplet homeostasis, and plays a crucial role in the regulation of gene expression, protein degradation, signalling and membrane trafficking, particularly in the liver[20].

Rui *et al*[21] conducted a comprehensive characterisation of serum exosome piRNA levels in 125 HCC patients and 44 healthy controls in 2023, to assess their suitability as diagnostic biomarkers. They found 253 dysregulated piRNA in exosomes of tumour patients, compared to healthy controls. Then, Rui *et al*[21] selected the five most upregulated piRNA in HCC exosomes (piR-1029, piR-15254, novel-piR-35395, novel-piR-32132, and novel-piR-43597) and validated them in two different cohorts, confirming their overexpression in the tumour and, thus, their diagnostic potential.

CONCLUSION

As with the other classes of ncRNAs, the discovery of disease-associated piRNAs is highly dependent on building the pipeline of identification methods. Nowadays, piRNA identification methods include two approaches: Experimental and computational. The first method is based on common techniques for the isolation of protein-associated RNAs, such as RNA immunoprecipitation sequencing or cross-linking immunoprecipitation and high-throughput sequencing. However, these techniques are expensive, time-consuming, and not very sensitive for low expressed piRNAs. The computational approach to piRNA identification has attracted much attention in recent years as piRNA data has increased significantly. Essentially, it involves the application of various bioinformatics tools to specific piRNA databases [such as: (1) piRBase; (2) piRNAclusterDB; or (3) piRNAtarget] to identify novel piRNAs (*e.g.*, 2L-piRNA), piRNA clusters (*e.g.* protract), piRNA targets (*e.g.* miRanda), and disease-associated piRNAs (*e.g.*, WGCNA)[22]. Despite the promising performance, these computational methods have several issues that need to be addressed, such as standardising piRNA nomenclature, developing a gold standard for bioinformatics analysis pipeline and improving the quality and quantity of data in the current piRNA databases (especially regarding the data on healthy controls)[23]. Nevertheless, more and more studies show the involvement of piRNAs in the development and progression of pathological diseases in humans. It is expected that there will be a corresponding increase in high-throughput technologies for piRNA studies in the coming years.

In HCC, research into piRNAs is still in its infancy, and much still needs to be clarified about their involvement in tumour progression. The importance of piRNA mechanisms in HCC is also emphasised by the involvement of PIWI proteins. In 2015, Xie *et al*[24] demonstrated that Hiwi (or PIWIL1), a member of the PIWI family, is overexpressed at both mRNA and protein levels in HCC cell lines (MHCC97L and MHCC97H) compared to normal liver cell lines (L02), and in tumour tissues from 60 HCC patients compared to normal controls from 48 peritumour samples. Functional analysis showed that the silencing of Hiwi in HCC cell lines led to a reduction in cell proliferation and invasiveness. These results suggest that Hiwi is a potentially useful HCC biomarker and a valuable new therapeutic target[24]. Recently, Hammad *et al*[25] investigated the mRNA expression levels of PIWI family members [(1) PIWIL1; (2) PIWIL2; (3) PIWIL3; and (4) PIWIL4] in both tissues and serum of HCC patients. Their results showed significant overexpression of these mRNAs in 50 tumour tissues compared to adjacent normal tissues and in 50 HCC sera compared to those of 25 healthy controls. Furthermore, a significant correlation was found between PIWIL1-4 overexpression and advanced tumour stage, at least as far as the tissue samples are concerned[25]. With high-throughput technologies, it is now possible to extend the investigations to a large number of patients, as well as to deepen the molecular mechanisms in cellular models. All in all, these results suggest that piRNAs are attractive candidates in HCC research with the aim of expanding our knowledge of HCC development and progression, as well as opening up new potential applications in the screening and treatment of patients.

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FOOTNOTES

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EDITORIAL

Improving colorectal cancer screening programs

Oscar J Cordero, Lucia Mosquera-Ferreiro, Iria Gomez-Tourino

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Abstract

In this editorial we comment on the article by Agatsuma *et al* published in the *World Journal of Gastroenterology*. They suggest policies for more effective colorectal screening. Screening is the main policy that has led to lower mortality rates in later years among the population that was eligible for screening. Colonoscopy is the gold standard tool for screening and has preventive effects by removing precancerous or early malignant polyps. However, colonoscopy is an invasive process, and fecal tests such as the current hemoglobin immunodetection were developed, followed by endoscopy, as the general tool for population screening, avoiding logistical and economic problems. Even so, participation and adherence rates are low. Different screening options are being developed with the idea that if people could choose between the ones that best suit them, participation in population-based screening programs would increase. Blood tests, such as a recent one that detects cell-free DNA shed by tumors called circulating tumor DNA, showed a similar accuracy rate to stool tests for cancer, but were less sensitive for advanced precancerous lesions. At the time when the crosstalk between the immune system and cancer was being established as a new hallmark of cancer, novel immune system-related biomarkers and information on patients' immune parameters, such as cell counts of different immune populations, were studied for the early detection of colorectal cancer, since they could be effective in asymptomatic people, appearing earlier in the adenoma-carcinoma development compared to the presence of fecal blood. sCD26, for example, detected 80.37% of advanced adenomas. To reach as many eligible people as possible, starting at an earlier age than current programs, the direction could be to apply tests based on blood, urine or salivary fluid to samples taken during routine visits to the primary health system.

Key Words: Mortality rates; Colorectal cancer; Screening; Biomarker; Fecal hemoglobin immunodetection; Soluble sCD26; Colonoscopy; Immunoscores

Core Tip: Although cancer cases are increasing worldwide, the decline in cancer-associated deaths in middle-aged people in recent years has demonstrated progress in cancer treatment, detection, and prevention policies. Colorectal screening, one of those successful policies, however, has some drawbacks, such as low adherence to the fecal hemoglobin immunodetection. New ways to detect colorectal cancer are being discussed.

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INTRODUCTION

Cancer cases are increasing worldwide largely due to a growing population and lifestyle factors that impact people's cancer risk. The most recent study showed that in the United Kingdom cancer cases and death rates rose by 57% in men and 48% in women during the last 25 years[1], mainly for liver, mouth, and uterine cancers, all related with risk factors including ultraviolet exposure, alcohol, obesity, or smoking. The consequences for cancer patients, healthcare staff and for the economy in general are challenging.

However, there are good news too. Several advances in cancer treatment, detection, and prevention policies, conduced to a reduction in cancer-associated death in middle-aged people during the same period[1]. In data examined for 23 cancer types, overall mortality rates fell by 37% in men and 33% in women. Cancer prevention played an important role; for example, mortality rates from cervical cancer decreased by 54.3% due to the introduction of the human papillomavirus vaccine combined with cervical screening in health services. The reduction of risk factors in recent decades, such as smoking rates, contributed to lung cancer mortality rates falling by 53.2% in men and 20.7% in women. Other cancers with screening schemes also decreased, mainly breast and gastrointestinal cancer, highlighting that early cancer diagnosis dramatically improved survival rates, that is, it helped save lives[1]. Similar results can be expected not only in developed countries but also in developing countries that are investing in public health services.

Colorectal cancer (CRC) is one of the main causes of cancer-related and general causes of deaths worldwide. Early detection through screening could prevent more than 90% of deaths, which is why many countries have implemented, or are in the process of implementing, general age-based screening programs[2-4]. The gold standard tool for screening is colonoscopy, which has preventive effects by eliminating precancerous or early malignant lesions, that is, polyps, reducing the incidence of CRC, in addition to its therapeutic function. However, colonoscopy as a general tool for population screening faces many logistical and economic drawbacks, in addition to low participation rates as it is an invasive process.

One approach has been to find good, less invasive biomarkers for early detection that could select screening participants for colonoscopy. The main success so far has been the development of fecal tests such as the current hemoglobin immunodetection (FIT), followed by endoscopy. Still, these stool testing-based screening programs show low adherence, in some populations less than half of the people who were eligible for screening[2,4].

The study of Agatsuma *et al*[2] in Japan highlights that more than 70% of cases are diagnosed outside of screening and identifies specific subgroups of people in relation to the diagnostic routes they followed. They suggest policies for more effective and efficient counseling of the non-adherent population, for example paying special attention to populations who do not visit hospitals for comorbidities and lack access to healthcare centers.

As many people is reluctant about collecting stools and handling or storing them, researchers are looking for other minimally invasive and resource-effective tests such as blood tests, which could also be automated. These "liquid biopsy" tests are also being used for monitoring cancer recurrence in patients undergoing cancer treatment and for other emerging cancer screening tests. Offering different screening options and allowing people to choose the one that works best for them would increase participation in population-based screening programs[3,4].

An article published recently in the *New England Journal of Medicine* showed that a blood test can detect cell-free DNA shed by tumors called circulating tumor DNA (ctDNA)[4]. This retrospective study detected CRC in 83% of people with confirmed disease, an accuracy rate like that of stool tests, while 16.9% of patients with a ctDNA negative test did show CRC by colonoscopy. The test was most sensitive for CRC, including early stages of the disease (I to III), but was less sensitive for advanced precancerous lesions (only the 13.2%). Another sensitivity issue of the FIT, and ctDNA test, is the detection of sessile serrated adenomas/polyps, which are, in fact, difficult to find even by colonoscopy[5]. There are also false positives with FIT, for example in people with hemorrhoids[3], or the 10.4% with positive ctDNA with the blood test.

The serum protein biomarker we were studying, sCD26, decreased in patients' blood. sCD26 did not show any direct correlation with tumor location, degree of histologic differentiation, kind of metastasis or Dukes' stages, but it could be related to immune cell subsets[6]. At that moment, the crosstalk between the immune system and cancer was being established and we were one of the first groups to suggest that it was necessary to collect the patients' lymphocyte count

and other immune parameters. These biomarkers, sCD26 for example, will arise earlier in the adenoma-carcinoma development compared to the presence of fecal blood, and could be effective in the asymptomatic, pre-diagnostic window of opportunity for the early detection of CRC. In fact, in our latest work[3], 80.37% of advanced adenomas were detected. Our goal in that study was to reduce false positive rate with a sequential testing strategy for FIT positive individuals offering an alternative blood test with our biomarker for a confirmation prior to colonoscopy. This kind of markers, however, in comparison with tumor neoantigens, lack specificity, so immunoscores and pan-immune inflammation values are being used for tumor classification, prognostic information, or surveillance[7,8].

CONCLUSION

There are opportunities to optimize CRC screening programs. It has been recommended that people with average risk for CRC should begin regular screenings already at age 45, earlier than the standard age of screening programs (50-55)[1]. To reach as many eligible people as possible and reduce inequalities in access, the direction might be to have a blood or, better, urine or salivary, fluid-based test for samples taken during routine visits to their doctors. Cheap and easy to handle kits might follow a sequential testing strategy.

FOOTNOTES

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REVIEW

Enteric neuropathy in diabetes: Implications for gastrointestinal function

Mona Mohamed Ibrahim Abdalla

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Abstract

Diabetes, commonly known for its metabolic effects, also critically affects the enteric nervous system (ENS), which is essential in regulating gastrointestinal (GI) motility, secretion, and absorption. The development of diabetes-induced enteric neuropathy can lead to various GI dysfunctions, such as gastroparesis and irregular bowel habits, primarily due to disruptions in the function of neuronal and glial cells within the ENS, as well as oxidative stress and inflammation. This editorial explores the pathophysiological mechanisms underlying the development of enteric neuropathy in diabetic patients. Additionally, it discusses the latest advances in diagnostic approaches, emphasizing the need for early detection and intervention to mitigate GI complications in diabetic individuals. The editorial also reviews current and emerging therapeutic strategies, focusing on pharmacological treatments, dietary management, and potential neuromodulatory interventions. Ultimately, this editorial highlights the necessity of a multidisciplinary approach in managing enteric neuropathy in diabetes, aiming to enhance patient quality of life and address a frequently overlooked complication of this widespread disease.

Key Words: Diabetic neuropathy; Gastrointestinal; Insulin resistance; Diabetes; Enteric nervous system; Enteric neuropathy

Core Tip: Diabetic enteric neuropathy, an often-overlooked complication of diabetes, significantly impacts gastrointestinal (GI) functions and impairs patients' quality of life. This editorial examines the link between diabetes and enteric neuropathy, emphasizing its impact on essential GI functions. It discusses how diabetes-induced neuropathy leads to GI issues like gastroparesis and altered bowel habits and highlights recent advances in early diagnostic methods and management. The editorial reviews various treatment strategies, both current and emerging, addressing associated challenges and future directions. It stresses the importance of a multidisciplinary approach in managing this complication.

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INTRODUCTION

Diabetes, recognized as a global health challenge, affects millions and is increasingly prevalent. Among its myriad complications, enteric neuropathy emerges as a critical, yet often overlooked, condition[1]. Diabetic enteric neuropathy is a pathology impairing the enteric nervous system (ENS), essential for regulating gastrointestinal (GI) functions. This complication leads to various GI disturbances in diabetic patients, significantly impacting their quality of life[2-4].

The incidence of diabetic neuropathy, including enteric neuropathy, is rising in parallel with the escalating prevalence of diabetes. Epidemiological data indicate that a significant proportion of individuals with diabetes are likely to experience some form of neuropathy during their disease trajectory, with enteric neuropathy being a particularly concerning manifestation[5]. This form of neuropathy is characterized by diverse GI symptoms, adversely affecting patient health, and placing substantial strain on healthcare systems[6]. Notably, the International Diabetes Federation reports approximately 537 million adults globally diagnosed with diabetes, a number expected to reach 643 million by 2030[7]. This rising trend in diabetes prevalence correlates with an increased incidence of complications like gastroparesis, a common manifestation of enteric neuropathy[8]. Research indicates varying prevalence and incidence rates, with one study in Minnesota (1996-2000) reporting 9.8 cases per 100000 females and 2.5 in males[9]. In contrast, a 2020 United States survey found gastroparesis to be more prevalent in males across all age groups[10].

The pathophysiology of diabetic enteric neuropathy involves a complex interplay of hyperglycemic damage, autoimmune responses, oxidative stress, and vascular insufficiency, leading to ENS dysfunction. This dysfunction is not merely a peripheral complication but reflects systemic pathological changes in diabetic patients, necessitating an in-depth understanding of its broader implications[11,12].

Additionally, the socioeconomic and psychological impacts of enteric neuropathy on patients are considerable. The condition often leads to decreased work productivity, social withdrawal, and increased healthcare utilization, underscoring the need for urgent and precise management of this complication[13].

This editorial aims to bring into focus enteric neuropathy as a crucial aspect of diabetic complications, especially its impact on GI functions. It will examine the intricate pathophysiology underlying this condition and how diabetes-induced changes in the ENS modify GI processes. Additionally, it will explore the clinical manifestations, emphasizing the importance of accurate diagnosis and effective management strategies.

In integrating this information, the editorial seeks to bridge knowledge gaps, illuminate diagnostic challenges, and review the effectiveness of current treatment approaches. The goal is to enhance awareness and understanding of diabetic enteric neuropathy, guiding future research and informing clinical practice for improved patient outcomes.

The ENS, often hailed as the body's "second brain", is a key component of the autonomic nervous system (ANS), playing a crucial role in regulating GI functions. This complex neural network, embedded within the GI tract (GIT) walls and spanning from the esophagus to the anus, comprises two main plexuses: The myenteric (Auerbach's) plexus, positioned between the muscle layers, and the submucosal (Meissner's) plexus, situated in the submucosa[14-16].

The myenteric plexus primarily governs GI motility by regulating the rhythm and force of muscle contractions along the tract, thus ensuring the efficient movement of contents[17]. In contrast, the submucosal plexus plays an integral role in managing GI secretion, blood flow, and nutrient absorption[18]. The ENS, composed of diverse neuron types including sensory, interneurons, and motor neurons, forms complex circuits capable of autonomously mediating reflexes[19].

Functionally, the ENS utilizes a variety of neurotransmitters, such as acetylcholine, calcitonin gene-related peptide, tachykinin, serotonin, and nitric oxide, to modulate GI physiology[19,20]. It operates both independently and in concert with the central nervous system (CNS), responding to local environmental cues and coordinating with central inputs to maintain digestive homeostasis. Sensory neurons in the ENS detect changes in the gut's chemical composition and physical state, initiating appropriate reflexive responses[19].

Enteric glial cells, akin to astrocytes in the CNS, support the ENS, contributing to neuronal function maintenance, mucosal barrier integrity, and response to injury or inflammation[21]. This network's integrity is critical not only for normal digestive functioning but also in pathophysiological conditions, where its dysfunction can lead to various GI disorders[22].

In diabetes, both type 1 and type 2, enteric neuropathy manifests as a complication marked by ENS neuronal damage. While hyperglycemia-induced damage and microvascular complications are common pathological processes in both

diabetes types, specific manifestations and underlying mechanisms differ[23]. In type 1 diabetes, enteric neuropathy often associates with prolonged disease duration and suboptimal glycemic control, where hyperglycemia and autoimmune-related inflammation are primary contributors[24-27]. Type 2 diabetes, often linked with metabolic syndrome, brings additional factors like insulin resistance, obesity, and dyslipidemia, exacerbating enteric neuropathy[28]. This condition in type 2 diabetes forms part of broader metabolic dysfunction, including changes in gut microbiota, increased intestinal permeability, and chronic low-grade inflammation[24,29-31]. Moreover, lifestyle factors, notably dietary habits and physical activity, play a significant role in type 2 diabetes, influencing the severity and progression of enteric neuropathy [32]. Modifiable risk factors such as diet and exercise are thus crucial in managing GI complications in diabetic patients [28,33,34].

PATHOPHYSIOLOGY OF DIABETIC ENTERIC NEUROPATHY

The pathophysiology of diabetic enteric neuropathy is multifaceted, involving metabolic disturbances, vascular and autonomic dysfunction, immune responses, mitochondrial and neurotransmitter alterations, connective tissue remodeling, and shifts in gut microbiota[12,35,36]. Figure 1 summarizes the pathophysiology of diabetic enteric neuropathy. A comprehensive understanding of these mechanisms is vital for developing targeted therapies and improving management strategies for diabetic patients with GI complications.

Advanced glycation end-products-induced neuronal damage

Chronic hyperglycemia serves as a principal initiator in the pathophysiology of diabetic enteric neuropathy, primarily by inducing biochemical alterations within neurons. A key feature of this alteration is the accumulation of advanced glycation end-products (AGEs)[37]. These AGEs bind to their specific receptors (RAGE) on neuronal cells, leading to a cascade of oxidative stress and inflammatory responses[38,39]. This chain of reactions impairs neuronal function and promotes apoptosis, predominantly affecting neurons that regulate GI motility and secretion[40].

Mitochondrial stress and neuronal impairment

Furthermore, hyperglycemia-induced mitochondrial stress plays a significant role in this pathology. In enteric neurons, such stress leads to impaired energy production and an elevated generation of reactive oxygen species (ROS), which contribute to neuronal damage[41-43]. This mitochondrial dysfunction is a critical factor in the degeneration of neuronal health under diabetic conditions.

Oxidative stress, coupled with an imbalance in antioxidant defenses, constitutes another major factor in enteric neuronal damage. Chronic hyperglycemia exacerbates ROS production, overwhelming the body's inherent antioxidant systems. This suggests that enhancing these defenses could be a viable strategy to protect enteric neurons from oxidative damage[41,43]. Strengthening these antioxidant defenses could be a therapeutic approach to protect enteric neurons from oxidative damage.

Autophagy and cellular stress responses

Moreover, autophagy, a process essential for cellular maintenance and stress response, may be altered in diabetes, leading to impaired maintenance and increased vulnerability of enteric neurons[41,43]. This alteration in cellular processes underscores the complexity of diabetic enteric neuropathy's pathophysiology.

Immune responses and ENS damage

The immune response is also a key player in the progression of diabetic enteric neuropathy. Chronic hyperglycemia can trigger autoimmune responses, resulting in inflammation and subsequent damage to the ENS[44,45]. This immune-mediated aspect of neuropathy's pathophysiology is an area of growing research interest, offering potential avenues for therapeutic intervention.

Pro-inflammatory cytokines and GI barrier integrity

Moreover, the integrity of the GI barrier is compromised in chronic diabetes, partly due to the elevated levels of pro-inflammatory cytokines. These cytokines induce stress and apoptosis in neuronal cells, further exacerbating neuropathic conditions[46,47]. The resulting inflammation, along with compromised GI mucosal barrier integrity, increases gut permeability, allowing more harmful substances to directly affect the ENS and aggravate neuropathic symptoms[48-50].

Microvascular complications and ischemic impact on ENS

Diabetes-induced microvascular complications extend to the blood vessels supplying the ENS. Resultant ischemia impairs essential nutrient and oxygen delivery to enteric neurons and glial cells, exacerbating neuronal damage and dysfunction. This ischemic state furthers the degeneration of neural networks in the GIT, compounding neuropathy's impact[36,44,51,52].

Autonomic neuropathy and enteric neuropathy

Diabetic autonomic neuropathy involves significant impairment of the ANS and is a key factor in the development of enteric neuropathy. The ANS, especially the vagus nerve, plays an essential role in the regulation of GI functions. In diabetes, damage to these autonomic nerves compromises their ability to effectively regulate the GIT. This disruption,

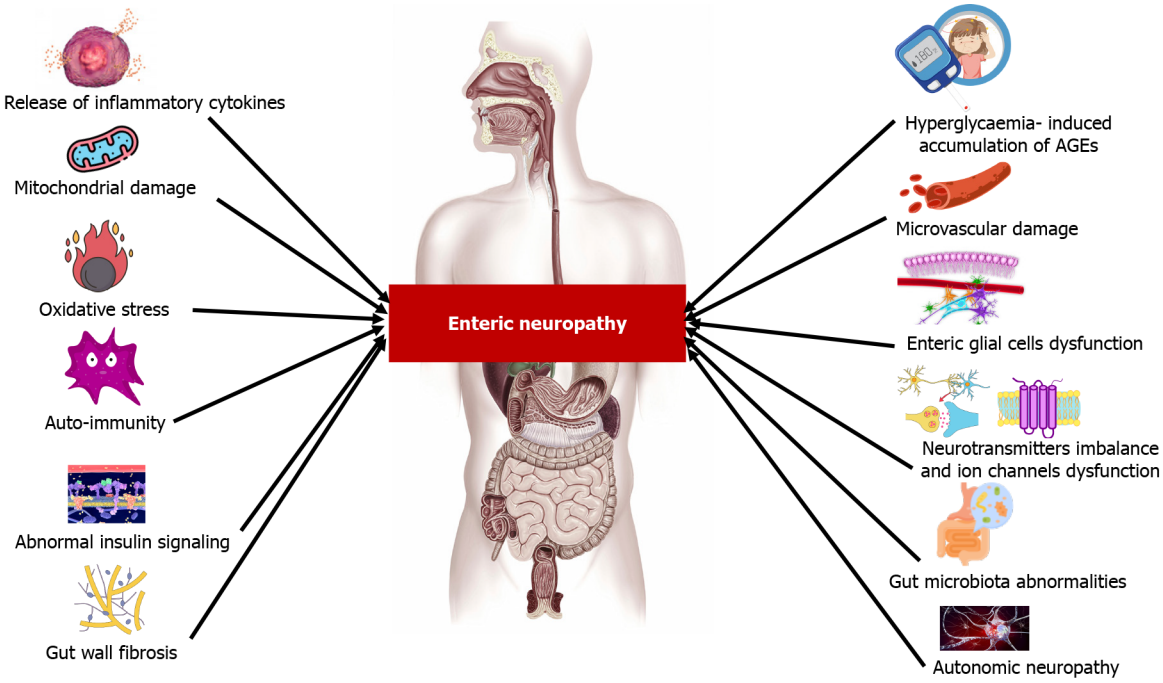

Figure 1 Mechanisms of diabetic enteric neuropathy. AGEs: Advanced glycation end-products.

particularly in the vagus nerve, leads to a breakdown in the coordination between the ANS and ENS. As a result, normal GI motility patterns are altered, manifesting in conditions such as gastroparesis. The altered motility patterns stemming from this neuropathy highlight the interconnectedness and dependency of the ENS on proper ANS functioning for maintaining GI homeostasis[53].

Glial cell dysfunction

In diabetes, enteric glial cell dysfunction emerges as a pivotal factor in the development of enteric neuropathy, leading to a progressive decline in the functionality of the ENS[21]. Chronic hyperglycemia, a hallmark of diabetes, inflicts stress and damage on these cells, triggering pathways such as oxidative stress, inflammation, and impaired cellular signaling [54]. This impairment compromises the glial cells' support for enteric neurons, resulting in a range of detrimental effects on the ENS. These include impaired neurotransmitter handling, disrupted cellular communication, and an increased vulnerability of neurons to damage and apoptosis[55].

Additionally, diabetic-induced dysfunction of enteric glial cells contributes to the breakdown of the mucosal barrier, enhancing gut permeability. This change exacerbates the inflammatory state within the GIT, further affecting neuronal function and potentially disrupting the crucial interaction between the gut microbiota and the ENS[56]. This interaction is essential for maintaining GI motility and overall gut health. The significance of glial cell dysfunction in the progression of diabetic enteric neuropathy underscores their role in GI health and highlights the need for therapeutic strategies targeting the preservation or restoration of glial cell function[57].

Neurotransmitters and ion channel dysfunction

Alterations in neurotransmitter function are also evident in diabetes. Changes in the levels and functions of key neurotransmitters, such as nitric oxide, vasoactive intestinal peptide, and serotonin, which regulate GI motility and secretion, disrupt the necessary balance for coordinated GI function, leading to symptoms like altered bowel habits and dysmotility[58]. Furthermore, diabetes can lead to dysfunctions in ion channels within enteric neurons. These changes, particularly in calcium and potassium signaling, disrupt neuronal excitability and neurotransmitter release in the ENS, contributing to GI motility disorders[59-61].

Connective tissue changes and fibrosis

Furthermore, diabetes can induce changes in the gut wall's connective tissue, leading to fibrosis. This fibrosis disrupts the structure of the ENS and impairs its functionality, contributing to motility disorders[62,63].

Gut microbiota and enteric neuropathy in diabetes

The interaction of the ENS with gut microbiota represents a burgeoning field of research, particularly in the context of diabetic enteric neuropathy. Dysbiosis, or the imbalance in gut microbiome composition, has been identified as a key factor influencing both gut motility and neuronal function. This dysregulation presents novel therapeutic targets, offering significant potential for the management of diabetic enteric neuropathy[64,65].

The relationship between diabetic enteropathy and gut microbiota is intricate and complex. Diabetes-induced alterations in gut motility lead to changes in the composition of the gut microbiota[66]. These alterations have substantial implications for neurotransmission within GIT. This complex interaction is partly moderated by the brain-gut axis, a crucial communication pathway that may involve the vagus nerve. In the diabetic state, where vagal function is often impaired, this communication pathway can be disrupted, exacerbating the symptoms of enteropathy. The gut microbiota exerts its influence on the ENS through the production of neurotransmitter-like molecules, such as Gamma-aminobutyric acid, serotonin, melatonin, histamine, and acetylcholine. These molecules play pivotal roles in regulating gut motility and, by extension, influence the overall function of the GIT[67]. The emerging understanding of this dynamic interaction underscores the importance of gut microbiota in the pathophysiology of diabetic enteropathy. This insight not only advances our comprehension of the disease mechanism but also opens up new avenues for therapeutic intervention, particularly those targeting the microbiota to modulate gut motility and ENS function.

Insulin signaling and enteric neuropathy

In diabetes, especially type 2, altered insulin signaling pathways in enteric neurons can contribute to neuropathic changes, highlighting the potential of restoring insulin sensitivity in the ENS as a therapeutic strategy[44].

Neurotrophic factors and neuronal plasticity

Neurotrophic factors, such as nerve growth factor and glial cell line-derived neurotrophic factor (GDNF), are essential for the health and maintenance of enteric neurons. Diabetes-induced alterations in these factors contribute to the pathology of enteric neuropathy[68-71]. Additionally, the ability of neurons to adapt or undergo neuroplastic changes is also impacted in diabetes, further contributing to ENS dysfunction[72-74].

Epigenetic changes

Epigenetic changes, including DNA methylation and histone acetylation, influence gene expression in diabetic patients. These epigenetic modifications may affect genes crucial for neuronal health and function, thereby playing a significant role in the development and progression of enteric neuropathy[75].

Interaction with systemic metabolic pathways

Metabolic products, hormones, and other signaling molecules in diabetes might have direct or indirect effects on enteric neuronal functions, influencing the overall health of the ENS[76]. The interaction between systemic metabolic dysregulation in diabetes and local gut metabolism is another area of interest.

Gut motility regulatory pathways

Furthermore, the regulatory pathways controlling gut motility, including the functionality of the interstitial cells of Cajal (ICCs), are also affected in diabetes. Disruption in these pathways contributes to the development of enteric neuropathy, as diabetes can impact the function or survival of these cells, leading to disorders in gut motility[61,77,78].

In addition to the mentioned mechanisms and research areas, another important aspect that could be further explored in diabetic enteric neuropathy is the role of extracellular matrix (ECM) remodeling. Diabetes can lead to alterations in the ECM of the GIT, which may affect the structural and functional integrity of the ENS. These ECM changes can impact cell adhesion, tissue architecture, and possibly interfere with nerve signal transmission, contributing to neuropathic complications[27,79].

Another area of interest is the exploration of circadian rhythm disruptions in diabetic patients and their impact on the ENS. Circadian rhythms play a crucial role in regulating various physiological processes, including GI functions. Disruptions in these rhythms, which are common in diabetes due to factors like irregular eating patterns and sleep disturbances, could exacerbate the symptoms of enteric neuropathy[80].

The potential role of exosomes and microRNAs (miRNAs) in diabetic enteric neuropathy also presents a promising research avenue. Exosomes are small vesicles released by cells that can carry miRNAs, proteins, and other molecules, influencing cellular communication and processes. Investigating how diabetes alters exosome production and content, and how these changes affect the ENS, could provide insights into novel mechanisms of disease progression and potential therapeutic targets. miRNAs, in particular, are known to regulate gene expression and could play a role in the pathophysiology of diabetic enteric neuropathy by modulating neuronal survival, inflammation, and cellular stress responses[81].

Additionally, the interaction between vascular health and the ENS is a critical area needing further exploration. Vascular dysregulation, a common occurrence in diabetes, may not only lead to direct ischemic damage to enteric neurons but also induce secondary effects due to impaired nutrient and oxygen delivery. Understanding how vascular changes intertwine with neuropathic processes could open up new strategies for preserving ENS function in diabetic patients.

Finally, exploring the impact of diabetes on the sensory function of the ENS presents another valuable research direction. Sensory neurons in the ENS are crucial for detecting mechanical and chemical changes in the gut. Diabetes may alter the sensitivity or response of these neurons, leading to dysregulated GI reflexes and symptoms. Studies focusing on sensory neuron dysfunction could reveal new aspects of diabetic enteric neuropathy's pathogenesis and potential interventions to restore normal sensory function[82].

Each of these identified mechanisms and pathways offers a potential avenue for future research, and they collectively highlight the complex nature of diabetic enteric neuropathy. Understanding the full spectrum of pathophysiological changes and their intricate interplay remains a critical area of investigation. This comprehensive approach is essential for

developing targeted therapies and improving management strategies for diabetic patients who suffer from GI complications.

IMPACT ON GI FUNCTION

Diabetic enteric neuropathy presents a multifaceted challenge across the entire GIT, with each segment exhibiting distinct yet interrelated dysfunctions due to neuropathic damage[53].

Esophageal dysfunction

In the esophagus, this neuropathy primarily disrupts motility, often leading to gastroesophageal reflux disease and esophageal dysmotility[83]. These motility issues are typically characterized by disrupted peristaltic waves and sphincter dysfunction, frequently linked to prolonged hyperglycemia which intensifies oxidative stress on esophageal neurons[84,85]. Such findings have been elucidated through advanced imaging and manometry techniques, prompting the exploration of novel therapeutic strategies, including targeted neuromodulation, to mitigate these dysfunctions[86,87]. Symptoms commonly experienced by patients include heartburn, regurgitation, and dysphagia, further aggravated by the oxidative stress on esophageal neurons due to hyperglycemia[88].

Gastric complications

In the stomach, diabetic neuropathy frequently culminates in gastroparesis, marked by delayed gastric emptying in the absence of mechanical obstruction[8,89]. This disorder manifests as nausea, vomiting, bloating, and early satiety, severely impacting both nutritional status and glycemic control in diabetic patients. Gastroparesis significantly diminishes the quality of life, leading to poor glycemic control, which is linked with various complications, abdominal discomfort, poor nutrition, and increased hospitalizations. The resulting psychological distress further complicates the patient's overall health[90]. Research has highlighted the crucial role of the ICC in gastric motility disorders in diabetes, with emerging therapies focused on restoring their function[77,78]. The pathophysiology of gastroparesis involves dysfunction in both the gastric myenteric plexus and the ICC, leading to delayed gastric emptying and significant health impacts[8].

Small intestine dysfunction

Diabetic enteric neuropathy causes significant dysfunction in the small intestine, manifesting as a spectrum of symptoms from abdominal discomfort to severe malabsorption. This condition is exacerbated by oxidative stress due to persistent hyperglycemia, leading to damage in enterocytes and neuronal cells[91-93]. Further complicating the scenario is hyperglycemia's impairment of mucosal healing[94] and its impact on insulin growth factors, contributing to accelerated apoptosis[95]. Recent studies have shifted focus from autonomic neuropathy to the loss of nitrergic neurons and ICC, crucial in GI motility[78]. Damage to ICCs by ROS disrupts their function in coordinating gut contractions, altering motility[96]. Additionally, the role of neuronal nitric oxide synthase (nNOS) in intestinal motility is recognized, with hyperglycemia-induced changes in nNOS contributing to small bowel dysmotility[97].

Colonic alterations

Colonic function is similarly impacted, primarily through weakened muscular contractions and oxidative stress induced by persistent hyperglycemia[41,98]. This condition disrupts the normal functioning of ICC and neuronal cells, leading to colonic motility issues like chronic constipation or diarrhea[30,99]. Contributing factors include altered gut microbiota and dysregulation of neurotransmitters and inflammatory mediators, further characterized by abnormalities in neurotransmission and an imbalance between excitatory and inhibitory signals[64,65,76]. Research is focused on developing pharmacological treatments targeting these neurotransmitter systems to improve colonic function in diabetic patients.

Anorectal dysfunction

Lastly, diabetic enteric neuropathy leads to anorectal dysfunction, including impaired sensation and sphincter control, leads to fecal incontinence or severe constipation, severely affecting patient dignity and quality of life[100,101]. Advanced diagnostic techniques such as anorectal manometry have enhanced our understanding of these neuromuscular impairments[102]. Research indicates a potential link between anorectal dysfunction and systemic diabetic complications, emphasizing the need for integrated management approaches[100,103].

Overall, diabetic enteric neuropathy affects the GIT from the esophagus to the anorectum, with each part exhibiting specific dysfunctions and associated symptoms as presented in Figure 2. This complex condition necessitates a comprehensive approach to clinical management, integrating advanced diagnostics, targeted treatments, and ongoing research to improve patient outcomes. The need for continued research into the molecular and cellular underpinnings of this condition is crucial for developing effective interventions.

DIAGNOSTIC METHODS AND CHALLENGES

Diagnosing diabetic enteric neuropathy is a complex and nuanced process that demands a comprehensive approach. It starts with a thorough clinical assessment, where key indicators such as altered bowel habits, GI pain, bloating, and signs

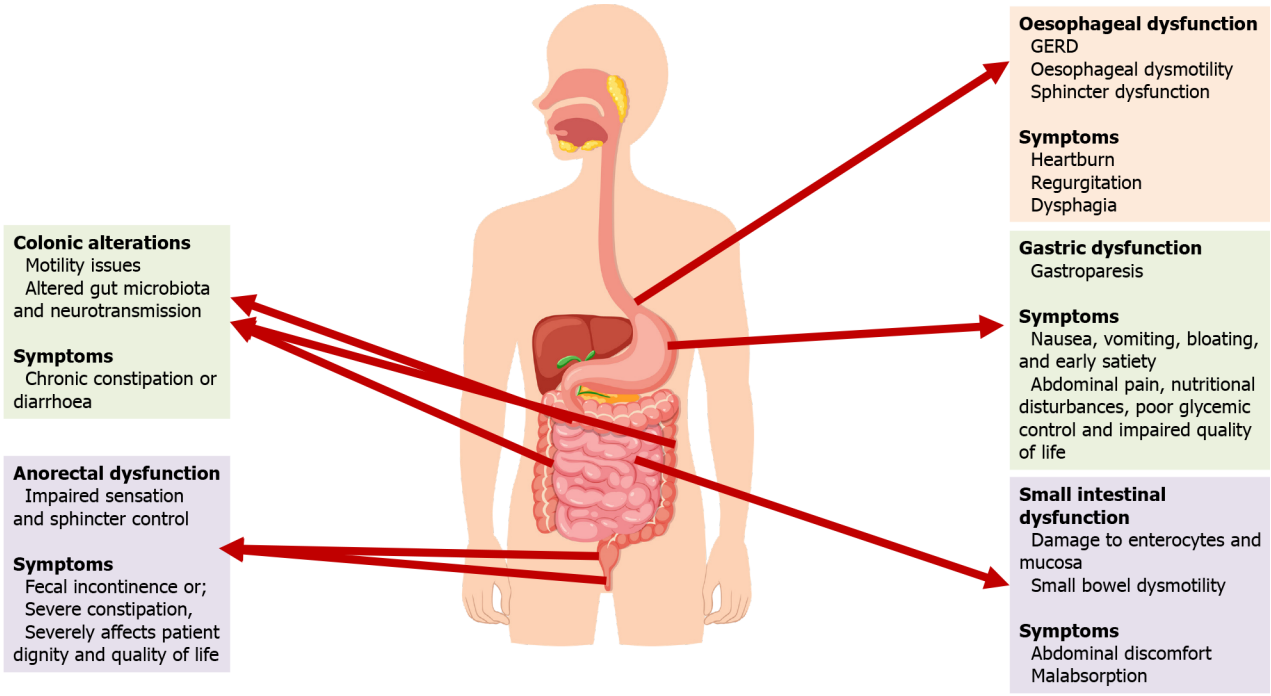

Figure 2 Impact of diabetic enteric neuropathy on gastrointestinal tract. GERD: Gastroesophageal reflux disease.

of gastric emptying disorders like gastroparesis are evaluated. In this stage, a detailed patient history is crucial to differentiate neuropathy from other GI disorders.

Central to the diagnostic process are GI motility studies. These include esophageal manometry and gastric emptying scintigraphy, which provide quantitative data on the motility of different segments of the GIT. Gastric emptying scintigraphy is particularly significant as it's considered the gold standard for diagnosing gastroparesis, a common manifestation of enteric neuropathy[8,104]. Complementing these are endoscopic and radiologic examinations, such as magnetic resonance imaging or computed tomography scans. While these do not directly diagnose neuropathy, they are instrumental in ruling out mechanical obstructions or other structural abnormalities that could present neuropathic symptoms[2,105].

The field of diagnostics is also witnessing the emergence of innovative techniques like capsule endoscopy and smart pills. These technologies, capable of measuring pH, pressure, and temperature, offer a less invasive method to directly visualize and measure GI function[106,107]. Additionally, the identification of specific biomarkers in blood or stool samples, including inflammatory markers and gut peptides, is an area of ongoing research, promising non-invasive diagnostic options[108-110]. Autonomic testing, such as heart rate variability, provides indirect indicators of enteric neuropathy by assessing the integrity of the ANS[111].

However, the diagnostic process is fraught with challenges. Non-specific GI symptoms, the lack of standardized diagnostic criteria, the limited availability of specialized tests, and challenges in interpreting test results all add layers of complexity. Furthermore, the variability in patient presentations, the overlap with other diabetic complications like peripheral neuropathy and autonomic dysfunction, and the potential for psychological factors and functional GI disorders like irritable bowel syndrome to mimic neuropathy symptoms, complicate the diagnosis[111-113].

An interdisciplinary approach enhances the accuracy and comprehensiveness of the diagnosis. Collaborative care models involving gastroenterologists, endocrinologists, primary care physicians, dietitians, and mental health professionals can provide a holistic assessment of the patient's condition[5,35]. The importance of patient history cannot be overstated, as it offers invaluable insights for distinguishing neuropathy from other GI disorders[2,114]. Symptom diaries and quality of life assessments help understand the impact of symptoms on the patient's daily life and psychological well-being[115]. Yet, challenges persist in patient-centered diagnosis. Variability in symptom perception and reporting, cultural and language barriers, and the need for culturally sensitive and linguistically appropriate patient care present additional hurdles[116].

Overall, the diagnosis of diabetic enteric neuropathy requires a concerted, interdisciplinary effort that combines clinical assessment with specialized diagnostic tests. Overcoming the challenges of non-specific symptoms, lack of standardized criteria, and complexity in test interpretation is crucial. Emphasizing patient-centered care and considering individual differences and cultural factors are key to the effective diagnosis and management of this complex condition.

CURRENT MANAGEMENT AND TREATMENT APPROACHES

Diabetic enteric neuropathy presents with a range of GI symptoms. Effective management of these symptoms is crucial

for enhancing patient quality of life and overall disease outcomes.

Pharmacological treatments and dietary management

Pharmacological approaches include prokinetic agents like metoclopramide and domperidone for gastroparesis and other motility disorders[117]. These agents enhance GI motility and facilitate gastric emptying, but their long-term use is limited by potential side effects, such as tardive dyskinesia with metoclopramide[118]. Antiemetics like ondansetron offer relief from nausea and vomiting[119], while antidiarrheal and laxative agents address diarrhea and constipation, respectively[12,120]. However, these treatments mainly provide symptomatic relief.

Clonidine, an alpha-2 adrenergic agonist, has demonstrated significant efficacy in the management of diabetic diarrhea, a debilitating condition often refractory to conventional treatments. This medication exerts its therapeutic effects by reducing GI motility and enhancing fluid absorption in the intestines, mechanisms that are crucial for controlling the symptoms of diabetic diarrhea[121]. Additionally, somatostatin analogs, such as octreotide, have been utilized due to their ability to inhibit the secretion of various GI hormones and slow gastric emptying, thus improving diarrheal symptoms in diabetic patients[122,123]. Selective serotonin 5-hydroxytryptamine type 3 inhibitors also play a critical role in this context by blocking serotonin receptors, which are involved in enhancing gut motility and secretion, thereby reducing the frequency and urgency of diarrhea[124,125]. Collectively, these medications address the complex pathophysiology of diabetes-related enteropathic diarrhea and provide a comprehensive approach to treatment, offering symptomatic relief and improving quality of life for affected individuals.

Dietary management is another cornerstone, with recommendations for small, frequent meals that are low in fat and fiber, particularly beneficial for gastroparesis[126,127]. Adhering to these dietary guidelines is critical, though ensuring adequate nutrition remains a challenge[128].

Glycemic control and emerging therapies

Tight glycemic control is essential in managing diabetic enteric neuropathy. Improved blood glucose levels can alleviate symptoms and prevent further progression of neuropathy[90,129]. However, this strategy requires careful monitoring to avoid hypoglycemia, especially in patients with gastroparesis where absorption is unpredictable[130].

Emerging therapies such as gastric electrical stimulation show promise, especially in gastroparesis cases unresponsive to conventional treatments[131,132]. In severe cases, endoscopic and surgical interventions, like pyloric botulinum toxin injections or gastric per-oral endoscopic myotomy, are considered but are generally reserved for refractory cases due to their invasive nature[133,134].

Alternative approaches and patient-centered care

Alternative and complementary medicines, including acupuncture and herbal supplements, have been explored, though their efficacy is not fully established[135]. These methods should complement, not replace, conventional treatments.

Educating patients about diabetic enteric neuropathy and its impact on GI function is vital. Encouraging self-management practices, such as dietary adjustments and blood glucose monitoring, plays a crucial role in managing symptoms and improving quality of life[136].

Challenges and future directions in treatment

The primary challenge in current treatments is that they offer symptomatic relief without reversing the underlying neuropathic changes. Adherence to treatment protocols can be influenced by lifestyle, economic factors, and individual patient preferences. Emerging therapies, including neuromodulation and personalized medicine, face challenges in efficacy, safety, and accessibility. Ensuring equitable access and integrating these therapies into standard care practices are essential steps for their successful implementation[137].

Implications for clinical practice and healthcare policy

Incorporating new therapies into clinical practice requires continuous medical education and updates in clinical protocols. Regular monitoring and adjustments to treatment plans are vital for effective management. Patient education and engagement, including the use of mobile health applications, are crucial for empowering patients in self-management. Healthcare systems need to adapt and support a multidisciplinary approach, ensuring accessible resources for comprehensive care. Policies should facilitate the integration of various specialties and support necessary infrastructure like shared electronic health records.

RESEARCH GAPS AND FUTURE DIRECTIONS

One of the significant gaps in current research is the incomplete understanding of the mechanistic pathways through which diabetes leads to enteric neuropathy. Although the link between hyperglycemia and neuronal damage is established, the precise molecular and cellular processes remain unclear. Additionally, the field lacks robust biomarkers for the early detection of enteric neuropathy in diabetic patients. The development of such biomarkers could revolutionize early intervention strategies, potentially preventing the progression of GI complications.

Another area that requires further exploration is the long-term efficacy and safety of existing treatments, including pharmacological agents and neuromodulation therapies. Longitudinal studies assessing the risks and benefits over extended periods are scarce, leaving a gap in our understanding of the long-term management of this condition.

Furthermore, the role of the gut microbiota in the context of diabetic enteric neuropathy is not fully explored. Investigating how alterations in gut microbiome composition and function influence the development and progression of neuropathy could unveil new therapeutic targets.

Looking to the future, research should focus on novel therapeutic targets within the pathophysiological pathways of diabetic enteric neuropathy. This includes a deeper investigation into neuroinflammation, oxidative stress, and mitochondrial dysfunction. The development of non-invasive, reliable diagnostic tools is also essential. Advanced imaging techniques, biomarker assays, and smart technology-based monitoring systems could offer new ways to detect and monitor enteric neuropathy more effectively and non-invasively.

Personalized medicine approaches are another promising direction. Tailoring treatment strategies to individual patient profiles, considering genetics, lifestyle, and specific disease characteristics, could lead to more effective management of enteric neuropathy. Additionally, the impact of dietary and lifestyle interventions warrants more comprehensive investigation. Specific dietary components, the role of probiotics, and the influence of physical activity regimens on the management of neuropathy are areas ripe for exploration.

Lastly, the role of psychosocial factors in managing diabetic enteric neuropathy is an area that needs more attention. Investigating how psychological support and behavioral therapies can complement traditional medical treatments could provide a more holistic approach to improving patient outcomes.

CONCLUSION

In conclusion, diabetic enteric neuropathy is a complex and significant complication of diabetes, affecting GI function and patient quality of life. Effective management requires a comprehensive approach, integrating pharmacological treatments, dietary modifications, and glycemic control, supported by patient education. The role of personalized medicine, technological advancements, and mental health care integration are emerging as crucial aspects in treatment strategies. Challenges such as treatment adherence, long-term efficacy of therapies, and access to care need addressing. Future research should focus on novel therapies, improved diagnostics, and understanding the diabetes-gut microbiota relationship. A multidisciplinary approach and updated healthcare policies are essential for optimizing patient care and enhancing outcomes for those with diabetic enteric neuropathy.

FOOTNOTES

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MINIREVIEWS

Histopathological impact of SARS-CoV-2 on the liver: Cellular damage and long-term complications

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Abstract

Coronavirus disease 2019 (COVID-19), caused by the highly pathogenic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily impacts the respiratory tract and can lead to severe outcomes such as acute respiratory distress syndrome, multiple organ failure, and death. Despite extensive studies on the pathogenicity of SARS-CoV-2, its impact on the hepatobiliary system remains unclear. While liver injury is commonly indicated by reduced albumin and elevated bilirubin and transaminase levels, the exact source of this damage is not fully understood. Proposed mechanisms for injury include direct cytotoxicity, collateral damage from inflammation, drug-induced liver injury, and ischemia/hypoxia. However, evidence often relies on blood tests with liver enzyme abnormalities. In this comprehensive review, we focused solely on the different histopathological manifestations of liver injury in COVID-19 patients, drawing from liver biopsies, complete autopsies, and *in vitro* liver analyses. We present evidence of the direct impact of SARS-CoV-2 on the liver, substantiated by *in vitro* observations of viral entry mechanisms and the actual presence of viral particles in liver samples resulting in a variety of cellular changes, including mitochondrial swelling, endoplasmic reticulum dilatation, and hepatocyte apoptosis. Additional-

ly, we describe the diverse liver pathology observed during COVID-19 infection, encompassing necrosis, steatosis, cholestasis, and lobular inflammation. We also discuss the emergence of long-term complications, notably COVID-19-related secondary sclerosing cholangitis. Recognizing the histopathological liver changes occurring during COVID-19 infection is pivotal for improving patient recovery and guiding decision-making.

Key Words: Liver; SARS-CoV-2; COVID-19; Angiotensin-converting enzyme 2; Histopathology; Liver biopsies; Liver autopsy; *In vitro*

Core Tip: Severe acute respiratory syndrome coronavirus 2 infection is linked to significant liver injury, emerging from the facilitated entry of the virus into liver cells, including cholangiocytes and endothelial cells, due to increased receptor expression. This invasion triggers critical cellular alterations such as mitochondrial swelling, endoplasmic reticulum dilation, and hepatocyte apoptosis. Confirmed by biopsy or autopsy, the presence of viral particles in liver tissues correlates with extensive histological damage, characterized by necrosis, steatosis, cholestasis, and inflammation. Such findings highlight the acute hepatic impact of coronavirus disease 2019 (COVID-19) and signal the risk of severe long-term complications, such as COVID-19-associated sclerosing cholangitis, emphasizing the profound and enduring effect of the virus on liver health.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, driven by the pathogenic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, has reshaped the global landscape, causing a catastrophic effect worldwide resulting in over 7 million deaths according to the World Health Organization (https://covid19.who.int/). The primary organ damaged in COVID-19 infection is the lung, but it is now known that SARS-CoV-2 can affect several sites such as the brain, kidney, heart, gastrointestinal tract, and liver. Liver injury is a regular finding in COVID-19 patients and has been reported to be mild, but there are cases of more severe abnormalities[1,2]. Patients usually present with an altered pattern in liver function tests [mild to moderate rise in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels], hypoalbuminemia and hyperbilirubinemia[1-3]. Unfortunately, these patients are hospitalized and undergoing several interventions, including mechanical ventilation and drug administration, thus, the mechanisms behind these liver abnormalities remain unclear as in several cases it is not possible to determine if the observed damage is due to direct SARS-CoV-2 action or is attributable to indirect damage due to systemic disturbances[4].

There are several review articles speculating about possible mechanisms behind the observed abnormalities, including discussions about the hepatotoxic effects of antiviral drugs and steroids, direct cytopathic effect of SARS-CoV-2 infection, systemic immune response, cytokine storm disorder, or a combination of all of them[5-8]. However, due to the complexity of the disease and its systemic involvement, it is difficult to draw a definitive conclusion.

It is known that SARS-CoV-2 infiltrates host cells by connecting its spike glycoprotein (S protein) to angiotensin-converting enzyme 2 (ACE2) receptors. Transmembrane protease, serine 2 (TMPRSS2) plays a crucial role by facilitating the activation of the spike protein, enabling viral entry while circumventing antiviral proteins[9,10]. The high expression of ACE2 in cholangiocytes and other liver cell types, makes the liver a relevant target for SARS-CoV-2 infection[11,12]. Histologically, liver injury after SARS-CoV-2 infection is shown by diverse manifestations including inflammation, necrosis, fibrosis, and steatosis, which are further classified in severity in the literature discussed.

This review comprehensively examines the physiopathology of COVID-19 liver injury, placing a strong emphasis on histopathological evidence. We discuss, based on *in vitro* and *in vivo* evidence, the direct SARS-CoV-2 liver infection and the damage caused by the virus at the cellular and the tissue level. We offer a detailed overview of receptor expression in the different types of cells comprising the liver and its implication in infection and injury, establishing this organ as an important target of SARS-CoV-2 virus infection. In conclusion, our study establishes a robust foundation for future research on understanding the liver's response to COVID-19 infection and the resultant long-term complications.

MECHANISMS OF VIRAL ENTRY AND RECEPTOR EXPRESSION IN LIVER TISSUE

The SARS-CoV-2 virus enters host cells by binding its S protein to the ACE2 receptor[9]. Subsequently, the S protein

undergoes cleavage by furin and cathepsin L[13]. With the assistance of the TMPRSS2, the S protein is activated to facilitate viral entry[10] (Figure 1).

The virus primarily enters cells through endocytosis, with a higher level of transduction in cells expressing ACE2. In this process, phosphatidylinositol 3-phosphate 5-kinase plays a crucial role in endosome formation[14]. The susceptibility of various organs to SARS-CoV-2 entry has been found to correlate with the expression levels of ACE2[11]. However, it has been demonstrated that TMPRSS2 provides SARS-CoV-2 with a replication advantage by enabling viral entry independent of the endosome pathway, thereby evading antiviral proteins such as interferon-induced transmembrane protein. This was corroborated using modified spike variants to infect various human cell lines, including those from intestinal and respiratory epithelium. Interestingly, even among cells expressing ACE2 to varying degrees, those lacking TMPRSS2 exhibited reduced viral entry[15].

The SARS-CoV-2 virus has a highly organized system for infecting host cells, where each component plays a critical role in its virulence. This includes not only the receptors responsible for the initial attachment to host cells, but also various proteins involved in cleaving the S protein, such as furin and cathepsin L. Notably, cathepsin L levels have been observed to increase in the circulation of COVID-19 patients, and this increase has shown a positive correlation with the progression and severity of the disease[13]. *In vitro* evidence further supports the crucial role of cathepsin L in enhancing viral entry[13].

The ACE2 receptor is widely distributed throughout various organs and tissues in the body, including the lungs, heart, kidneys, intestines, and the endothelial lining of blood vessels. Endothelial cells, which line the blood vessels in all organs, exhibit a high expression of ACE2, making them particularly susceptible to infection and damage by the virus [16]. This susceptibility helps explain the widespread organ damage often observed in COVID-19 patients[17]. It occurs due to endothelial dysfunction, leading to extensive microvascular impairment and disruption of vascular homeostasis [18]. This shift towards vasoconstriction results in ischemia, inflammation, a procoagulant state, and edema, aligning with our current understanding of COVID-19's pathogenesis[16]. Indeed, postmortem samples have revealed diffuse endothelial inflammation and the presence of viral inclusions within endothelial cells[16].

Human pluripotent stem cells have been utilized to create organoids representing different lineages for the assessment of ACE2 expression, SARS-CoV-2 tropism, and the response to infection across the entire organism[11].

Using this model, it was observed that endoderm-derived lineages, including pancreatic cells, exhibited ACE2 expression in both alpha and beta cells but not in delta cells. Conversely, in liver cells, ACE2 was detected in the majority of albumin positive (ALB+) hepatocytes. ACE2 expression was also observed in lineages originating from the mesoderm, such as CD31+ endothelial cells, cardiomyocytes, CD206+ macrophages, and microglia. However, ACE2 expression was found to be low in cells derived from the ectoderm, such as cortical neurons[11].

Additional evidence was gathered by utilizing liver bile duct-derived progenitor cells to create human liver ductular organoids, which confirmed the presence of ACE2 and TMPRSS2 in cholangiocytes[19].

This confirmation was further supported by two separate studies that utilized healthy liver tissue and ribonucleic acid sequencing (RNA-seq) analysis. These studies revealed the highest expression of ACE2 in cholangiocytes, exceeding even hepatocyte expression[20,21]. In fact, the ACE2 expression in cholangiocytes was found to be comparable to that observed in alveolar type 2 cells in the lungs[20]. Moreover, several other receptors, previously identified as crucial components, have been shown to be expressed across different cell types in the liver. For instance, TMPRSS2 exhibits widespread expression in cholangiocytes, hepatocytes, periportal liver sinusoidal endothelial cells, erythroid cells, and, to a lesser extent, non-inflammatory macrophages[21].

Similarly, the cleaving enzyme furin is broadly expressed in all cell types throughout the liver, with hepatocytes and cholangiocytes exhibiting the strongest expression, along with endothelial cells[21].

In patients with cirrhosis, we have previously demonstrated a notable increase in hepatic ACE2 and TMPRSS2 expression, alongside increased proinflammatory markers such as interleukin (IL)-6, IL-8, and monocyte chemoattractant protein 1 in the liver. Notably, we observed higher mRNA-level expression of both ACE2 and TMPRSS2 in patients with more advanced disease states, including decompensated cirrhosis and acute on chronic liver failure[22].

Further investigations have demonstrated that, at the protein level, liver expression of both receptors is significantly elevated in patients with non-alcoholic fatty liver disease[23]. Additionally, these patients exhibit higher circulating ACE2 levels compared to those with chronic hepatitis[23]. It is known that patients with metabolic syndrome are very susceptible to developing severe manifestations of COVID-19 infection. Indeed, obese patients with non-alcoholic steatohepatitis have increased hepatic expression of ACE2 and TMPRSS2[24]. Collectively, these findings help partially explain the severe outcomes observed in patients with chronic underlying diseases[1].

IN VITRO EVIDENCE OF SARS-COV-2 INFECTION IN LIVER CELLS

In vitro evidence strongly supports the ability of SARS-CoV-2 to infect various types of liver cells. Understanding the interactions between the virus and these liver cells is essential for uncovering the molecular mechanisms responsible for the hepatic effects of SARS-CoV-2 infection.

Cholangiocytes, the lining epithelium of the bile ducts and the gallbladder, exhibit varying levels of ACE2 expression. Among them, cholangiocytes from the gallbladder display the highest ACE2 expression within the biliary tree, presumably rendering them the most susceptible to viral infection[11,12].

Cholangiocytes play a crucial role in transporting bile acids secreted by hepatocytes into the bile ducts, vital to optimal liver function[25]. Interestingly, it has been observed that the chenodeoxycholic acid (CDCA), a bile acid, can modulate ACE2 expression through the farnesoid X receptor (FXR) signaling pathway[12]. FXR is a direct regulator of ACE2

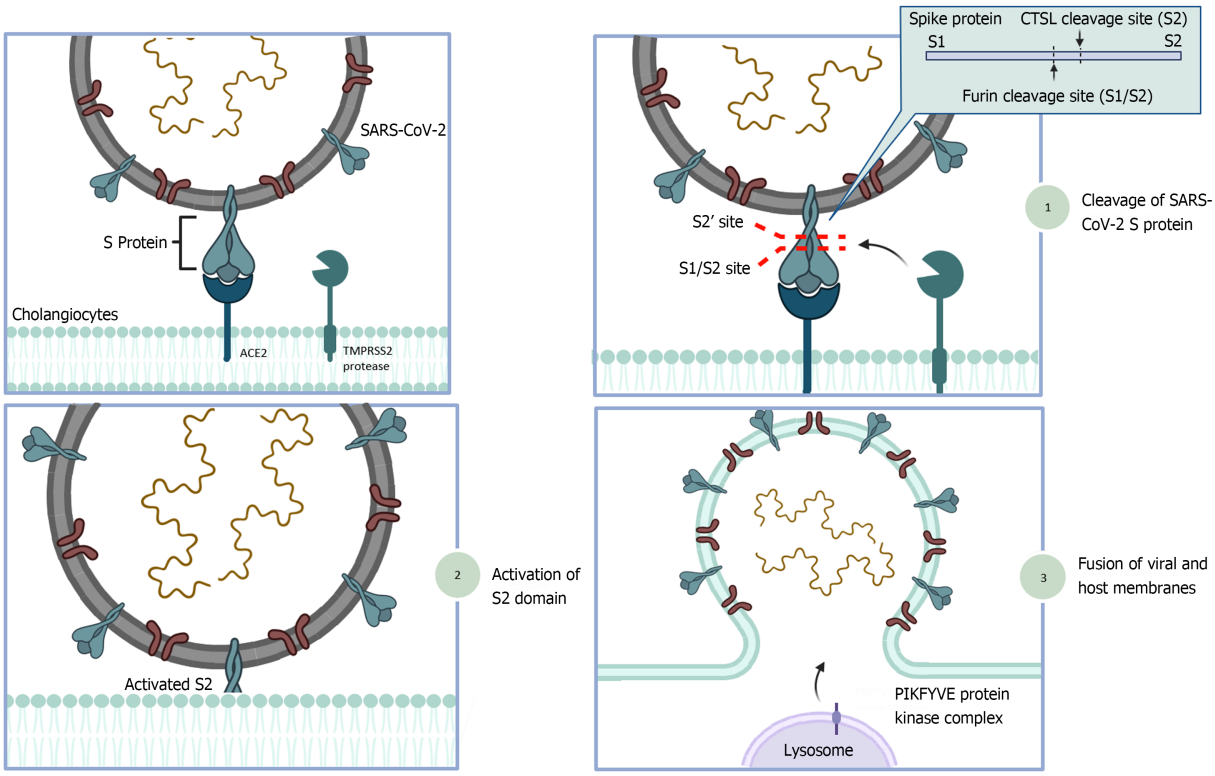

Figure 1 Mechanisms of viral entry and receptor expression in liver tissue. The severe acute respiratory syndrome coronavirus 2 virus enters the host cell using its spike protein (S protein) which binds to the angiotensin I converting enzyme 2 receptor. The S protein gets cleaved by furin and cathepsin L, then with the help of transmembrane serine protease 2 the S protein gets activated to facilitate viral entry. These cells are transduced by the virus, which enters the cell through endocytosis, where lysosomal Phosphatidylinositol 3-phosphate 5-kinase aids in endosome formation and permits fusion of viral and host membranes. ACE2: Angiotensin-converting enzyme 2; CTSL: Cathepsin L; TMPRSS2: Transmembrane serine protease 2; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

transcription in a variety of tissues affected by COVID-19, such as the gastrointestinal system and respiratory systems[12].

Cholangiocytes from the gallbladder exposed to CDCA and subsequently infected with SARS-CoV-2 exhibit a notably high level of viral infection. Susceptibility to this infection can be reduced when FXR signaling is suppressed using compounds such as ursodeoxycholic acid (UDCA) or Z-guggulsterone. UDCA was proven to reduce ACE2 and viral infection *ex vivo* in experiments using human lungs and livers perfused ex situ after exposure at physiologically elevated concentrations of UDCA, though the exact mechanism remains unknown[12].

Ductal hepatic organoid cells expressing ACE2 and TMPRSS2, when inoculated with SARS-CoV-2, exhibited rapid expression of the virus nucleocapsid N and the formation of syncytia after infection[19]. Moreover, they displayed a significant increase in viral load after 24 hours. SARS-CoV-2 also suppressed the expression of certain proteins and genes critical for maintaining barrier integrity and bile acid transport in these cells[19]. Additionally, SARS-CoV-2 expression induced the upregulation of genes associated with cell death and apoptosis. These significant alterations indicate that cholangiocytes are damaged upon infection, leading to the impairment of the liver's bile acid transport mechanisms[19]. Consequently, direct cholangiocyte injury resulting from SARS-CoV-2 infection contributes to liver damage in COVID-19 patients[19]. Indeed, gamma glutamyl transferase (GGT), a biomarker for cholangiocyte injury, has been found to be elevated in hospitalized COVID-19 patients and associated with severe manifestations[26].

In vitro studies have also demonstrated that SARS-CoV-2 can damage hepatocytes. When hepatocyte organoids, derived from human pluripotent stem cells, were exposed to SARS-CoV-2, a significant percentage of viral RNA expression was observed, as confirmed through immunostaining[11]. This infection resulted in the upregulation of chemokines, including C-X-C motif chemokine ligand 1 (CXCL1), CXCL3, and CXCL5, among others. Simultaneously, it led to the downregulation of essential metabolic markers in hepatocytes, such as cytochrome P450 7A1 (CYP7A1), CYP2A6, CYP1A2, and CYP2D6. These changes suggest a metabolic shift towards an immune-like cell state during active SARS-CoV-2 infection[11].

IN VIVO EVIDENCE OF SARS-COV2 INFECTION IN THE LIVER

One of the earliest studies to provide evidence of SARS-CoV-2 hepatic infection was conducted by Wang *et al*[27] They examined liver samples from two deceased COVID-19 patients and demonstrated the presence of viral particles in the cytoplasm of hepatocytes. These particles closely resembled SARS-CoV-2 virions, as they exhibited an envelope with corona-like spikes[27].

Additional cytologic features, such as mitochondrial swelling, endoplasmic reticulum dilatation, shedding of microvilli, and the presence of apoptotic hepatocytes, indicated a cytopathic lesion caused by the SARS-CoV-2 virus[27]. Nevertheless, the absence of viral identification through quantitative polymerase chain reaction (PCR) in the liver biopsies and the limited sample size posed significant limitations in confirming direct viral liver injury by the SARS-CoV-2 virus[27]. Despite that, several other reports have confirmed the presence of viral liver infection[28,29], and isolated case reports provide clear confirmation of direct liver damage caused by the virus, as exemplified by the case reported by Orandi *et al*[30]. The patient developed acute liver failure (ALF) and was urgently listed for liver transplantation with status 1A, meaning a few days to live without a transplant, due to the severe liver damage following COVID-19 infection. No additional risk factors for ALF were identified, and extensive testing to rule out other potential causes was performed [30]. ALF prohibited the use of remdesivir, so casirivimab/imdevimab was administered. The patient showed improvement in coagulopathy and mental status. A liver biopsy was taken ten days after clinical improvement and showed an acute hepatitis pattern of injury, with severe necrosis and cholestasis, residual hepatocytes undergoing ballooning degeneration, and prominent nucleoli. They were able to detect replicating SARS-CoV-2 RNA in hepatocytes using in situ hybridization, a finding confirmed by immunostaining for the SARS-CoV-2 nucleocapsid protein[30].

There have been several other reports of COVID-19-infected patients who, while not directly demonstrating the presence of SARS-CoV-2 in the liver, have contributed significantly to our understanding of the morphological and pathological changes observed following infection. Among these changes, hepatocellular regenerative features such as mitotic figures and antigen Ki67-positive nuclei have been observed[31]. Additionally, there is evidence of vacuolar degeneration and edematous mitochondria in hepatocytes, as well as an enlargement of the endoplasmic reticulum[32]. Sweed *et al*[33] reported the presence of trichrome-positive intrahepatic cytoplasmic globules and ballooning degeneration, which could serve as potential histopathological clues indicative of COVID-19-induced hepatitis.

Cholestatic hepatitis secondary to SARS-CoV-2 has also been reported in patients without pre-existing liver diseases, presenting with markedly elevated total bilirubin levels and exhibiting severe histological findings[34,35]. The main pathological features were observed in the cholangiocytes and included cytoplasmic vacuolization, degenerative changes, and mitosis[34]. Additionally, evidence of viral RNA, as well as spike and nucleocapsid proteins of SARS-CoV-2, has been found in endothelial cells, Kupffer cells, and portal macrophages[29]. Interestingly, in COVID-19 patients where SARS-CoV-2 has been detected by PCR in liver tissue, liver enzymes, including ALT and AST, were significantly higher compared to those with COVID-19 but without SARS-CoV-2 detection in the liver. However, histological evidence of acute hepatitis did not demonstrate higher liver enzymes in comparison with those that did not show lobular necroinflammation[28]. While these reports do not conclusively demonstrate that the liver damage observed in COVID-19 patients is directly caused by a cytopathic injury, they clearly show that the virus is capable of infecting various types of parenchymal and non-parenchymal liver cells, subsequently leading to liver injury.

HISTOPATHOLOGICAL LIVER CHANGES OBSERVED AFTER SARS-COV2 INFECTION

Inflammation, necrosis and fibrosis in liver tissue

Liver injury has been reported to be mild in most patients following COVID-19 infection[36]. However, in patients with moderate to severe liver injury, characterized by a notable elevation of hepatic enzymes, liver involvement plays an important role in the disease course by affecting the production of ALB, acute phase reactants, and coagulation factors[30,37]. Therefore, hepatic dysfunction may contribute to the development of multisystemic manifestations of SARS-CoV-2, such as acute respiratory distress syndrome (ARDS), coagulopathy, and multiorgan failure[4].

COVID-19 is characterized by an overactivation of the immune system[38], and the liver plays a crucial role as it houses the largest reservoir of macrophage in the body[39,40]. The liver's parenchymal and non-parenchymal cells are well-equipped to sense and initiate immune responses, facilitated by its extensive blood supply[40]. This makes the liver highly effective in recognizing pathogens and mounting immune responses. Due to this immune response, multiple pathological changes occur following COVID-19 infection, including inflammation, necrosis, fibrosis, and combinations thereof (Figure 2).

After COVID-19 infection, the inflammatory process in the liver manifests in various forms. In some reports, it appears to be an acute liver injury, which can range from mild to moderate lobular necroinflammation[28]. There have also been isolated cases with significant liver injury, leading to ALF[30,37]. However, it is more common to observe cases characterized by portal or lobular inflammation, which accounts for approximately 50% of all reported cases[28,32,41-44] (Table 1).

Some of the lobular inflammation is characterized by CD4 Lymphocyte infiltrates, with severity ranging from mild (48%) to moderate (2%)[45]. In a case of fatal ALF associated with SARS-CoV2 infection, the predominant inflammatory infiltrate in the portal area consisted mainly of CD8 cytotoxic T cells. T cells accounted for 60% of the observed infiltrate in the liver of this patient[37].

In patients with COVID-19 and liver involvement, it is common to observe lobular inflammation characterized by neutrophilic infiltration[41,44]. Additionally, increased Kupffer cells are often present, and occasionally eosinophils have been reported[28,31,44]. In a series of 26 liver samples from COVID-19-related autopsies, three of them showed common histopathological features related to the inflammatory process and immune cell activation that led to hepatocellular regenerative changes, with the presence of mitotic figures and Ki67-positive cells[31].

Hepatobiliary damage can be observed in patients with severe presentations of COVID-19[46]. More severe histopathological liver findings in patients with COVID-19 include evidence of liver necrosis, which ranges from moderate to severe [32-43]. Necrosis predominantly affects centrilobular areas, and occasionally midzonal areas with confluent necrosis have

Table 1 Liver injury in patients with coronavirus disease 2019 infection, *n* (%)

Ref.	Condition	Present
Lagana *et al*[28]	Lobular necroinflammation	20/40 (50)
Sonzogni *et al*[45]	Inflammation and fibrosis	24/48 (50)
Chu *et al*[32]	Inflammation and necrosis	24/24 (100)
Schmit *et al*[43]	Centrilobular necrosis	11/13 (85)
	Lobular inflammation	8/13 (62)
Duarte-Neto *et al*[51]	Centrilobular/midzonal necrosis	49/75 (65)
Sweed *et al*[33]	Inflammation and necrosis	1/1 (100)
Vishwajeet *et al*[44]	Lobular inflammation	13/20 (65)
	Kupffer cell hypertrophy	17/20 (85)
Yurdaisik *et al*[48]	Extensive necrosis	2/7 (29)
	Patchy necrosis	4/7 (57)
Canillas *et al*[52]	Fibrosis	8/14 (57)
Ramos-Rincon *et al*[47]	Necrosis	5/39 (13)
Santana *et al*[49]	Necrosis	26/27 (96)
	Lobular inflammation	2/27 (7)
Pesti *et al*[29]	Fibrosis	78/150 (52)
	Necrosis	103/145 (71)
	Chronic inflammation	63/146 (43)

Inflammation cell types varied between neutrophils, monocytes, and lymphocytes.

been reported[30,32,43,47]. Necrosis is a common finding, reported in as many as 86% of cases[43,48]. Within hepatic parenchyma, multiple foci of necroinflammatory activity have been observed[33], sometimes with extensive hepatocyte necrosis or patchy necrosis[33,48-50]. In some cases, necrosis was a common alteration and thought to be due to shock[49, 51]. Inflammation and necrosis are common histopathological liver findings in patients who died from severe COVID-19 complications (Table 1). However, most of this information arises from post-mortem liver biopsies conducted in critically ill patients, in whom cardio-respiratory dysfunction characteristic of severe COVID-19 cases could also account for some of the ischemia-related liver alterations.

The inflammatory infiltrate surrounding the necrotic areas consists of mononuclear cell infiltration, including lymphocytes, plasmacytic infiltrate with histiocytes; eosinophils and neutrophils have been also observed (Figure 2)[47, 48].

Liver fibrosis has also been documented in patients with COVID-19 infection. It is a common phenomenon that affects different areas of the liver, but predominantly, portal or periportal fibrosis has been reported[29,31,33,44,45,52]. It is not clear whether fibrosis is the result of the severe inflammatory process of COVID-19 that affects the liver, at least during the acute phase of infection. However, most of the cases documenting fibrosis report it as mild in severity, suggesting it is not a consequence of COVID-19, but rather linked with preexisting medical conditions and comorbidities frequently found in clinically significant COVID-19 cases (Figure 2)[29,53].

What has been even more controversial, is the debate surrounding whether a pre-existing chronic liver disease is exacerbated by the acute phase of COVID-19 or not[1,3,54].While some reports provide evidence of aggravation, others assert the absence of severe acute alterations, such as extended necrosis, hemorrhage, and inflammation[29]. Overall liver injury is prominent in SARS-CoV-2 infection. Clinically, it is important to closely monitor liver chemistries during treatment and recovery, particularly when the patient has additional risk factors for hepatic dysfunction, such as the use of antibiotics and vasopressors, or the presence of ischemic or hypoxic injury following circulatory or respiratory failure.

Steatosis

Liver steatosis has been shown to be prevalent in patients with infection by the SARS-CoV-2 virus, ranging between 54% to 75% according to some case series[28,32,45]. Reports from various authors have characterized steatosis as ranging from mild (< 10%) to severe (> 10%), with distinctions made between microvesicular and macrovesicular steatosis (Table 2)[32, 45].

Macrovesicular steatosis often presents as fat droplets with panlobular distribution affecting liver zones 1, 2, and 3[28]. Steatosis tends to develop early during COVID-19 infection. For instance, mild steatosis was detected in a 15-year-old girl who underwent a liver biopsy on hospital day 15 after displaying clinical signs of liver disease[30]. However, while liver

Table 2 Liver steatosis in patients with coronavirus disease 2019 infection, *n* (%)

Ref.	Histological findings	Present
Lagana *et al*[28]	Macrovesicular steatosis	30/40 (75)
Sonzogni *et al*[45]	Steatosis	26/48 (54)
Chu *et al*[32]	Microvesicular steatosis	20/24 (83)
	Macrovesicular steatosis	5/24 (21)
Vishwajeet *et al*[44]	Macrovesicular steatosis	18/20 (90)
Duarte-Neto *et al*[51]	Steatohepatitis	3/75 (4)
	Steatosis	42/75 (56)
Schmit *et al*[43]	Steatosis	9/13 (69)
Sweed *et al*[33]	Macrovesicular steatosis	1/1 (100)
Santana *et al*[49]	Steatosis	17/27 (63)
Yurdaisik *et al*[48]	Macrovesicular steatosis	4/7 (57)
Canillas *et al*[52]	Steatohepatitis	10/14 (71)
	Steatosis	1/14 (7)
Ramos-Rincon *et al*[47]	Steatosis	12/39 (31)
Pesti *et al*[29]	Steatosis	93/147 (63)

Some authors refer to the severity of steatosis as mild < 10% or severe > 10%, and others as macrovesicular or microvesicular steatosis.

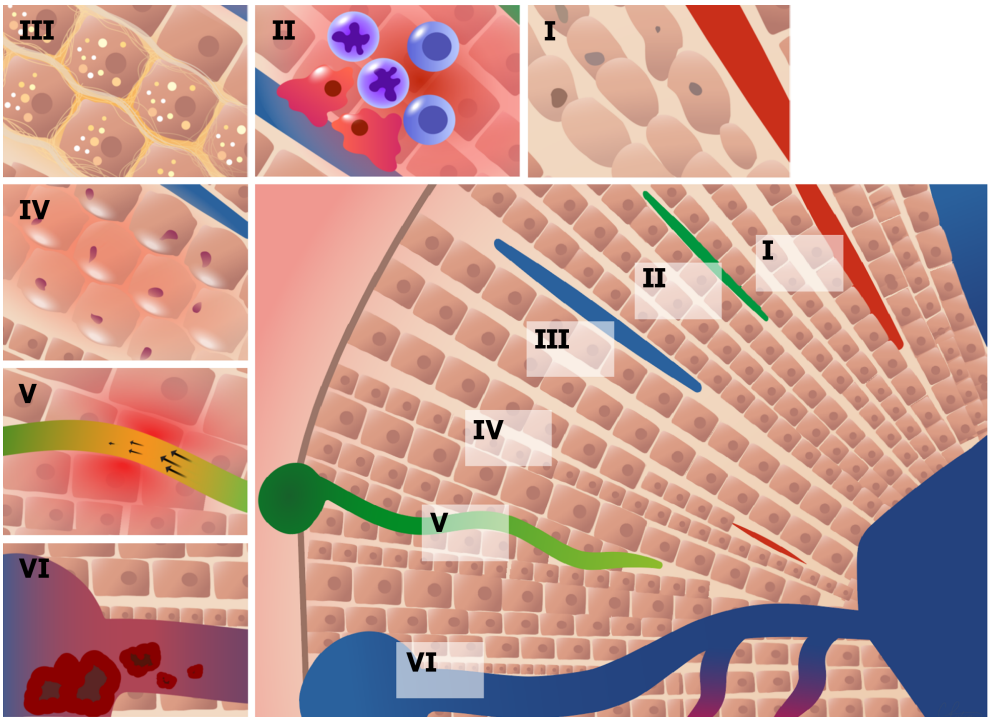

Figure 2 Direct coronavirus disease 2019 liver injury is observed through various histopathological changes. After analyzing several cohorts of liver biopsies, the most common findings associated with severe acute respiratory syndrome coronavirus 2 hepatic infection were reported and described. I: Centrilobular areas of confluent necrosis. II: The inflammatory infiltrate surrounding necrosis showed lymphoplasmacytic infiltrate with histiocytes, few eosinophils, and neutrophils. III: Periportal fibrosis and presence of both micro and macrovesicular steatosis. IV: Ballooning degeneration shown by swelling and rounding up of hepatocytes. V: Canalicular cholestasis with discrete ductular reaction, predominantly in zone 3. VI: Chronic venous congestion, endotheliitis, portal vein thrombosis and platelet-fibrin thrombi in hepatic sinusoids.

steatosis is common, steatohepatitis occurs at a lower rate[44]. For example, Duarte-Neto *et al*[51] reported 3 cases of steatohepatitis among 75 COVID-19 patients, while 42 patients exhibited only steatosis.

While the exact mechanisms behind hepatic steatosis remain elusive, a contentious debate persists regarding its causality. On one hand, compelling evidence suggests that elevated levels of serum IL-6, IL-10, and tumor necrosis factor-α along with subsequent inflammatory signaling, might indeed contribute to its development[55]. On the other hand, there is a prevailing belief that steatosis in COVID-19 affected livers may not be intrinsically tied to the severity of SARS-CoV-2 infection; instead, it could be construed as a secondary consequence associated with comorbidities or treatments administered during or prior to the infection[29]. What is clear is that liver steatosis is a common pathological feature in COVID-19 patients being found in 30%-90% of patients with a confirmed SARS-CoV-2 infection, as reported by multiple studies. The assessment of liver steatosis in these studies was made through histopathological findings from autopsies following COVID-19-related deaths. The studied populations were from different countries around the world and included predominantly middle-aged and elderly individuals, some of whom had at least one risk factor for developing liver steatosis. Despite liver steatosis being a common finding, the results of these studies indicate a prevalence that surpasses the reported rates in the general population worldwide (Table 2)[28,29,32,43,44,51,52,56].

Typical risk factors for hepatic steatosis are chronic alcohol use, higher body mass index, male gender, older age, longer waist circumference, and higher levels of cholesterol[57]. While unaware of most patients' status on hepatic steatosis previous to their COVID-19 infection, it can be observed in young patients without risk factors and could be a predictive factor for a faster progression of liver disease.

Autoimmune hepatitis

SARS-CoV-2 infection can trigger autoimmune responses in genetically predisposed individuals. It is widely acknowledged that COVID-19 is associated with increased serum pro-inflammatory cytokines. This cytokine storm is directly linked to disease severity and is a major factor contributing to COVID-19-related deaths. Due to the molecular resemblance between human proteins and viral components, this immune system hyperstimulation can potentially lead to the production of autoantibodies and the development of autoimmune liver diseases[58,59].

Multiple autoantibodies including antinuclear antibodies (ANA), anticardiolipin antibodies, and anti-β2-glycoprotein I antibodies are frequently present in patients with SARS-CoV-2 infection, particularly in those with COVID-19-associated pneumonia, potentially indicating a role of immune dysregulation in disease severity. Patients who tested positive for autoantibodies had a worse prognosis, with higher mortality and respiratory rates compared to those without autoantibodies[60]. ANA reactivity in COVID-19 patients has been reported in several cohorts, with frequencies ranging between 25% and 50%, and has consistently been associated with increased disease severity[60,61].

There is also evidence of a possible association between the development of autoimmune hepatitis (AIH), following SARS-CoV-2 infection. While the mechanisms are not well understood, molecular mimicry is hypothesized to play a role [62]. It has been previously reported that viral infections and certain drugs may serve as potential stimuli for the development of AIH, suggesting that these stimuli might share epitopes resembling self-antigens that disrupt self-tolerance. Additionally, it has been demonstrated that peripheral CD4+ and CD8+ T cells show reduction and hyperactivation in patients with severe SARS-CoV-2 infection[63]. In addition, a defective subpopulation of CD4+ CD25+ regulatory T cells is a well-described mechanism involved in the impaired regulation of self-antigens observed in AIH, which can be an additional factor that predisposes patients to the development of this disease following COVID-19[62]. However, it remains uncertain whether SARS-CoV-2 infection induces an impaired immune response that results in de novo AIH, or if this response unmasks a possible pre-existing latent autoimmune disease[59].

Osborn *et al*[64], described a possible association between the development of a type 2 AIH, diagnosed by an elevated anti-liver-kidney-microsomal antibody titer of 1:1280, following severe hepatic damage proceeded by a SARS-CoV-2 infection. In this case, a 3-year-old patient experienced ALF, characterized by extensive hepatic necrosis, lobar collapse, and substantial inflammatory infiltrate following a mild COVID-19 infection. Isolated severe liver dysfunction related to SARS-CoV-2 is rare and has been measly reported, however this pediatric case had an excellent response to high-dose steroids followed by maintenance immunosuppressive therapy with azathioprine. One year after, a follow-up biopsy revealed complete liver recovery with only mild residual periportal and portal inflammation and ductular reaction[64]. In this case, there was a slight genetic predisposition conferred by a family history of Hashimoto's thyroiditis and type 1 diabetes mellitus in first-degree relatives. While it is not possible to confirm whether SARS-CoV-2 infection caused AIH in this case, the temporal association between the infection and the development of fulminant hepatic failure accentuates the importance of evaluating underlying causes of liver injury in patients with isolated severe hepatic dysfunction following SARS-CoV-2 infection[64].

Although AIH involves a complex interplay of genetic, immunologic, and environmental factors, SARS-CoV-2 infection and vaccination have been associated with the development of several autoimmune diseases in adults, such as AIH, myocarditis, immunological thrombocytopenic purpura, immune-mediated nephropathy, and type 1 diabetes[65-67].

With the global distribution of COVID-19 vaccines, documented case reports of COVID-19 vaccine-associated AIH-like syndromes have been published, with an estimated risk as low as 1 in 14 million. In contrast, the estimated incidence of idiopathic AIH ranges from 0.67 to 2 cases per 100000 people per year[68]. A systematic review involving 39 cases of COVID-19 vaccine-associated AIH-like syndromes reported a marked female predominance (76.9%), while most cases occurred in patients over 50 years old (61.5%). Interestingly, in this study, 64.7% of the patients had a history of autoimmune disease, liver disease, or were taking AIH-inducing drugs[69]. Most of the patients in this study population developed symptoms after receiving the first dose of the vaccine, with a median time to symptom onset of two weeks. All patients in this cohort underwent liver biopsy, which revealed interface hepatitis, centrilobular necrosis, and lymphocyte or plasma cell infiltration as the main findings. The overall prognosis was favorable after initiating steroid-based

treatment, and only four deaths were observed, two of which were related to complications of liver disease[69].

The precise mechanism underlying the development of AIH following COVID-19 vaccination remains incompletely understood[69]; however, it is hypothesized that molecular mimicry, where similarities between vaccine peptides and human self-peptides result in the production of homologous self-antigens, leads to autoimmune-mediated tissue damage. Recent research has demonstrated that 21 out of 50 tissue antigens had moderate to strong reactions with the SARS-CoV-2 antibodies, suggesting that cross-reaction between SARS-CoV-2 proteins and a various tissue antigens could be responsible for the development of different vaccine-related autoimmune diseases[70]. Other theories propose that the formation of immune complexes may affect the balance between effector and regulatory T-lymphocytes, while certain molecular adjuvants added to most vaccines might trigger cell activation, leading to an exaggerated immune response [71].

Various types of vaccines can induce autoimmunity through different mechanisms. The incorporation of lipid nanoparticles and adenovirus vectors in authorized vaccines could potentially induce an amplified immune response. Moreover, mRNA vaccines can bind to pattern recognition receptors triggering multiple pro-inflammatory cascades, and T-cell and B-cell immune responses. Additionally, viral vector vaccines may activate immune responses by the involvement of toll-like receptor 9, leading to type I interferon secretion[67,72,73].

Clinicians should remain vigilant regarding the potential onset of AIH following SARS-CoV-2 infection or COVID-19 vaccination. Clinical manifestations such as jaundice, choluria, pruritus, or prolonged fatigue and anorexia, coupled with abnormal liver function test results, should prompt suspicion of this complication, particularly if there is temporal alignment with exposure to risk factors[69].

BILIARY TRACT INJURY AND SCLEROSING CHOLANGITIS AS A LONG-TERM SEQUELA OF COVID-19

Hepatocyte injury and a pattern of hepatocellular damage are observed in most specimens. Nevertheless, the elevated expression of ACE2 in cholangiocytes raises the possibility that they could potentially act as a reservoir within the liver or serve as an entry point for the virus[19,74-76]. Several reports have found histological abnormalities in the intrahepatic biliary tract. In some cases, only mild lobular cholestasis with intact interlobular bile ducts, or canalicular cholestasis has been observed[30,32,37,44,47]. Some other cases have noted cholestasis accompanied by discrete bile duct proliferation [43], or a more critical bile duct injury, including profound cholestasis, ductular reaction, and bile infarcts[77]. Severe cholestatic hepatitis with intense zone 3 hepato-canalicular cholestasis and prominent bile duct damage has also been observed[34]. Cytokeratin 7 (CK7), a marker of bile ducts, has been commonly used to detect intralobular canalicular cholestasis[29].

Sclerosing cholangitis

Recently, cases of secondary sclerosing cholangitis (SSC) have been observed in individuals who developed cholestatic liver disease as a result of cholangiocyte injury following acute COVID-19 infection. While the reports are not so common, there are some of them describing progressive cholestatic disease following severe COVID-19, which upon confirmation with biopsy or imaging techniques, have been determined to be COVID-19-SSC[78-82].

Post-COVID-19-SSC in critically ill patients rarely develops in patients treated in a critical care unit[78] from recent studies have found a significant increase in the incidence of SSC in critically ill COVID-19 patients, more than 46 times higher compared with data from before the pandemic[79].

In a study involving 1082 hospitalized patients with COVID-19 pneumonia who required invasive mechanical ventilation, it was determined that approximately one in every 43 of these invasively ventilated COVID-19 patients developed SSC, with an incidence rate of 2.3 per 100 patients (95%CI: 1.5-3.4)[79].

Some mechanisms related to hyperinflammation, cytokine release, and ischemia of the biliary ducts have been proposed as potential causes of COVID-19-SSC. However, a direct mechanism of damage mediated by SARS-CoV-2 towards cholangiocytes has not been identified.

Most COVID-19-SSC cases documented in the literature are from cohorts of critically ill patients who were diagnosed using magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiography, or histopathological findings assessed by liver biopsy or autopsy.

Among these cohorts, one includes 334 patients admitted to the intensive care unit (ICU), where six patients began experiencing alterations in the intrahepatic biliary tract. Notably, these patients had no prior history of biliary tract issues, and these changes manifested during their hospitalization. The patients spent an average of 35.5 days in the ICU and all of them developed ARDS, necessitating invasive mechanical ventilation. After discharge, they were monitored for a median duration of 282 days (ranging from 89 to 452 days). Interestingly, these patients did not return to normal levels in their liver laboratory parameters, and three of them even developed portal hypertension, one of them experiencing decompensation. These complications strongly suggest the presence of COVID-19-related SSC in these patients[81].

Some unique histopathological findings were reported in a small series of three cases, which involved intrahepatic microangiopathy with superimposed injury to cholangiocytes. It was believed that these findings could represent a confluence of SSC and direct hepatic injury from SARS-CoV-2[83]. The patients were three young adults. Each patient had a prolonged hospitalization because of acute hypoxemic respiratory failure requiring mechanical ventilation while also having additional COVID-19 complications. On admission, liver chemistries ranged from normal to mildly elevated, however, on repeat parameters each patient had severe but brief aminotransferase elevations which were attributed to ischemic hepatitis by clinicians. Further on their hospitalization they developed marked cholestasis with associated jaundice that persisted even after cardiopulmonary and renal recovery. Laboratory studies, serologies and liver imaging

ruled out other liver pathologies. Nonetheless, imaging of patient 1 showed intrahepatic beading with multiple short segmental strictures and intervening dilatation, patient 2 intra and extrahepatic dilatation, and patient 3 had no signs of bile duct dilatation. Percutaneous liver biopsies exhibited at least moderate portal and periportal fibrosis and extensive degenerative cholangiocyte injury, with prominent cholangiocyte vacuolization, regenerative changes, apoptosis, and necrosis of the cholangiocyte epithelial layer of terminal bile ducts and marginal ductules. Only patient 3 demonstrated metaplastic expression of CK7 in periportal hepatocytes[83].

A separate study also reported three cases presenting with severe COVID-19 and shortly after developed persistent cholestasis and chronic liver disease. They all required ICU admission, mechanical ventilation, vasopressor support, and broad-spectrum antibiotics due to secondary infections. All 3 patients had a history of chronic kidney disease type 2 diabetes mellitus and systemic arterial hypertension. In case 1, SARS-CoV-2 infection was confirmed on admission by reverse transcription PCR. During a 33-day stay in the ICU the patient experienced gastrointestinal bleeding, acute renal failure, and metabolic acidosis, necessitating hemodialysis. Liver tests showed cholestatic patterns, with persistently elevated alkaline phosphatase (ALP) levels, despite normal imaging results initially. After discharge, he developed jaundice, pruritus, and hypercholesterolemia. Imaging revealed bile duct dilatation and sludge. Endoscopic procedures were performed, showing bile duct obstruction and stenosis. Despite treatment, liver chemistry remained altered. Various liver conditions were considered but ruled out *via* specific tests, and hepatic biopsy was performed, which showed signs of cholestasis, inflammation, and fibrosis. In case 2, the patient experienced severe respiratory failure requiring mechanical ventilation and prone positioning. Complications included bacteremia and ventilator-associated pneumonia, leading to multiorgan dysfunction and necessitating hemodialysis, red blood cell transfusions, and vasopressor support. Liver tests showed a cholestatic pattern, with persistently elevated ALP and GGT levels despite initial negative imaging findings. After discharge, the patient developed jaundice, with further liver tests indicating cholestasis. Despite negative viral hepatitis and autoimmune disease panels, imaging revealed stenosis consistent with SSC. Endoscopic retrograde cholangiopancreatography (ERCP) identified bile duct filling defects, but liver function did not improve. In case 3, the patient initially presented with normal liver chemistry but elevated inflammatory markers. Within 72 hours of admission, she required ICU admission and mechanical ventilation due to severe hypoxemia. During her 20-day ICU stay, she underwent hemodialysis, received high positive end-expiratory pressure, norepinephrine, and antibiotics for ventilator-associated pneumonia. Liver chemistry progressively showed cholestasis, with significantly elevated bilirubin, GGT, and ALP levels. Imaging revealed intra and extrahepatic biliary dilation, and other potential causes were ruled out. Magnetic resonance cholangiography demonstrated irregular bile duct morphology without obstruction, indicating a severe cholestatic liver injury[84]. All three cases were subsequently treated with UDCA with no clinical improvement on liver chemistries.

Unfortunately, there is no effective clinical treatment for COVID-19-SSC, and liver transplantation remains the only option for selected patients[78,82]. The 1-year transplant-free survival rate of COVID-19-associated SSC has been shown to be 40%[79]. Clinicians have chosen to treat post-COVID cholangiopathy with UDCA and obeticholic acid, which halt hepatic damage by reducing the accumulation of bile acids that are not excreted through the digestive system. Both drugs have even been combined to enhance treatment potency and efficacy following unsuccessful monotherapy with UDCA. In severe cases with an unfavorable prognosis, even after drug treatment fails, clinicians have resorted to invasive procedures such as ERCP and sphincterotomy. The aim is to prevent biliary tract obstruction caused by sedimentation formed due to alterations produced by the virus in the biliary ducts[85].

All this evidence suggests that cholestatic liver disease and SSC may be long-term sequelae of COVID-19 acute illness as a longstanding manifestation of critical illness.

VASCULAR THROMBOSIS AND ENDOTHELIAL INFLAMMATION

Some of the proposed pathophysiological mechanisms of liver injury associated with COVID-19 include endothelial damage which leads to vascular changes due to coagulopathy and endotheliitis[29,86]. Coagulopathy has been described to be exacerbated by the severe inflammatory response syndrome associated with SARS-CoV2 infection[86,87]. There have been several reports providing histological evidence of vascular alterations in hepatic parenchyma. These include abnormal vessels in the portal or periportal areas[45,46]. Herniated portal veins in periportal tissue ranging from focal, to diffuse have been also reported[45]. Zone 3 sinusoidal ectasia with significant red cell congestion and portal tract vein luminal dilation have been common findings in some reports, observed in up to 84% and 72% of the cases respectively [31]. Other findings include sinusoidal diffuse platelet-fibrin microthrombi (PMT), sinusoidal erythrocyte aggregation (SEA), portal vein thrombosis, centro-acinar ischemic-type hepatic necrosis[31,51,56]. PMT was found to be associated with increased liver injury but not SEA[56]. In patients that undergo shock, liver histological evidence in some reports shows hepatic centrilobular congestion in 50%-100% of the patients, and centrilobular/midzonal necrosis causing hepatocytic loss[49,51]. CD31, CD34 and claudin-5 have been used as markers to assess the integrity or damage of endothelial cells in some of these cases (Table 3)[29].

Different series of postmortem liver biopsies from patients affected by severe COVID-19 have reported liver sinusoidal microthrombosis and partial portal thrombosis in at least 50% of the patients. Data for these series are mostly obtained from autopsies of patients whose cause of death was completely related to severe COVID-19. Therefore, the population studied in these series presents the classical risk factors for COVID-19 clinical progression and mortality (older age, comorbid conditions). Although the mechanism of liver vascular thrombosis is likely multifactorial, the reported findings are rare to observe and could hardly be triggered by other comorbidities of the patients[56]. Endotheliopathy is a key component of the prothrombotic imbalance in patients with COVID-19, which is related to a worse outcome in this

Table 3 Vascular thrombosis and endothelial inflammation in patients with coronavirus disease 2019 infection, *n* (%)

Ref.	Histological findings	Present
Pesti *et al*[29]	Endothelial cell damage	119/119 (100)
	Sinus dilatation	119/119 (100)
	Fibrin	119/119 (100)
Duarte-Neto *et al*[51]	Centrilobular congestion	75/75 (100)
	Sinusoidal thrombosis	5/75 (7)
Chu *et al*[32]	Portal inflammation	23/24 (96)
Schmit *et al*[43]	Portal inflammation	12/13 (92)
Santana *et al*[49]	Centrilobular congestion	23/27 (85)
	Portal inflammation	14/27 (52)
Fassan *et al*[31]	Sinusoidal ectasia	21/25 (84)
	Sinusoidal microthrombi	5/25 (20)
	Portal vein thrombosis	3/25 (12)
Sonzogni *et al*[45]	Portal inflammation	32/48 (66)
Kondo *et al*[56]	Sinusoidal thrombosis	23/43 (53)
	SEA	19/43 (44)
	PMT	14/43 (32)
Lagana *et al*[28]	Portal inflammation	20/40 (50)
Vishwajeet *et al*[44]	Portal inflammation	10/20 (50)

PMT: Platelet microthrombi; SEA: Sinusoidal erythrocyte aggregation.

disease and has been reported to persist following COVID-19. Some markers of endothelial cell activation, such as soluble thrombomodulin levels and the von Willebrand Factor antigen, have been shown to correlate with mortality[88].

While these findings align with the possibility of vascular-related injury in the hepatic parenchyma[45], and considering that SARS-CoV-2 has been detected in blood clots and endothelial cells, it remains uncertain whether these phenomena stem from direct endothelial damage caused by the virus or result from the immunological and inflammatory response triggered by the virus.

CONCLUSION

In conclusion, the comprehensive exploration of liver involvement in COVID-19 presented in this article underscores the virus´s capacity to impact hepatic tissue directly and indirectly[27]. The study of viral entry mechanisms and *in vitro* observations allow for an improved understanding of direct liver injury and a superior analysis of tissular involvement in pathogenesis[9]. The evidence surrounding hepatic parenchyma histopathological changes such as necrosis, steatosis, cholestasis, and lobular inflammation, endothelial dysfunction-induced endotheliitis and procoagulant factors support the claim that SARS-CoV-2 infection produces liver injury through a variety of mechanisms even when other factors such as COVID-19 and vasoactive medication, invasive ventilation, and infection-induced cytokine storm, also produce significant liver injury[29,86]. This study provides evidence that will support future insight when producing new therapeutic targets to reduce morbidity and mortality due to systemic complications following COVID-19 infection.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Heparin is an effective treatment for preventing liver failure after hepatectomy

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Abstract

BACKGROUND

Posthepatectomy liver failure (PHLF) is one of the most important causes of death following liver resection. Heparin, an established anticoagulant, can protect liver function through a number of mechanisms, and thus, prevent liver failure.

AIM

To look at the safety and efficacy of heparin in preventing hepatic dysfunction after hepatectomy.

METHODS

The data was extracted from Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC-III) v1. 4 pinpointed patients who had undergone hepatectomy for liver cancer, subdividing them into two cohorts: Those who were injected with heparin and those who were not. The statistical evaluations used were unpaired *t*-tests, Mann-Whitney *U* tests, chi-square tests, and Fisher's exact tests to assess the effect of heparin administration on PHLF, duration of intensive care unit (ICU) stay, need for mechanical ventilation, use of continuous renal replacement therapy (CRRT), incidence of hypoxemia, development of acute kidney injury, and ICU mortality. Logistic regression was utilized to analyze the factors related to PHLF, with propensity score matching (PSM) aiming to balance the preoperative

disparities between the two groups.

RESULTS

In this study, 1388 patients who underwent liver cancer hepatectomy were analyzed. PSM yielded 213 matched pairs from the heparin-treated and control groups. Initial univariate analyses indicated that heparin potentially reduces the risk of PHLF in both matched and unmatched samples. Further analysis in the matched cohorts confirmed a significant association, with heparin reducing the risk of PHLF (odds ratio: 0.518; 95% confidence interval: 0.295-0.910; P = 0.022). Additionally, heparin treatment correlated with improved short-term post-operative outcomes such as reduced ICU stay durations, diminished requirements for respiratory support and CRRT, and lower incidences of hypoxemia and ICU mortality.

CONCLUSION

Liver failure is an important hazard following hepatic surgery. During ICU care heparin administration has been proved to decrease the occurrence of hepatectomy induced liver failure. This indicates that heparin may provide a hopeful option for controlling PHLF.

Key Words: Liver resection; Posthepatectomy liver failure; Prophylactic treatment; Heparin; Prognosis of hepatectomy

Core Tip: This study emphasizes that heparin, which is commonly identified with its anticoagulant characteristics, also offers benefits in prevention of posthepatectomy liver failure (PHLF). Application of the Multiparameter Intelligent Monitoring in Intensive Care III database shows that the administration of heparin in the postoperative intensive care unit (ICU) setting is linked to a decreased occurrence of PHLF, shortened ICU stays, and lesser need for mechanical ventilation and renal support. These outcomes underscore heparin's potential as a valuable therapeutic option to enhance short-term postoperative results for patients undergoing liver surgery.

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INTRODUCTION

Posthepatectomy liver failure (PHLF) stands as one of the most critical complications after liver surgery, marked by significant rates of morbidity and mortality[1,2]. Studies recently published indicate that the occurrence of PHLF fluctuates between 4.9% and 9.0%[3]. The International Study Group of Liver Surgery defines PHLF with a grading system: Grade A involves an elevation in international normalized ratio (INR) or total bilirubin (TBIL) without altering the clinical pathway; Grade B includes clinical deviations that are managed non-invasively; and Grade C encompasses deviations requiring invasive interventions[4]. An alternative diagnostic measure, the 50-50 criterion, is applied on the fifth postoperative day, characterizing PHLF by serum total bilirubin levels exceeding 50 μmol/L and a prothrombin time (PT) index below 50%[4]. The onset of PHLF indicates a decline in the liver's ability to synthesize, excrete, and detoxify, evidenced by heightened levels of INR and bilirubin shortly after surgery[5]. The regeneration of the liver remnant is crucial for a patient's prognosis following hepatectomy. Factors such as hepatic hemodynamic disturbances, immune-inflammatory responses, and metabolic dysfunctions can exacerbate hepatocyte death, thereby impairing the function of the liver remnant and precipitating liver failure[6]. In the context of liver resection, predominant risk factors encompass pre-existing liver conditions, the extent of resection, and the specifics of the intraoperative procedures. Mitigating the risk of PHLF hinges on thorough preoperative assessment and preparation, choosing the optimal surgical techniques, and implementing rigorous postoperative surveillance and management[7]. Despite these measures, comprehensive strategies to address PHLF remain incomplete, necessitating further investigations to bridge these gaps and enhance the understanding of contributory factors to PHLF.

Coagulation abnormalities are widely acknowledged as strong indicators predicting adverse outcomes in liver diseases. Heparin, a prevalent anticoagulant, not only shields endothelial cells and prevents the thrombosis of hepatic vessels but also mitigates hepatic hemodynamic abnormalities[8]. It further serves as a hepatoprotective agent by modulating cellular metabolism and the inflammatory response, which in turn reduces hepatocyte damage. Dr. Silva's recent in vivo research highlighted that heparin significantly reduces hepatic cell apoptosis during hemorrhagic shock and reperfusion injuries[9]. Additionally, another investigation illustrated that heparin influences lipoprotein processing within the liver[10]. Despite these findings, the use of heparin as a prophylactic treatment in liver surgery is scarcely documented. The clinical consensus on the early administration of heparin post-liver surgery is still under debate. Consequently, this retrospective study was designed to assess heparin's efficacy in preventing PHLF.

MATERIALS AND METHODS

Data source

Data for this study were sourced from version 1.4 of the Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC-III) database. MIMIC-III, which is freely accessible, contains records for over 50000 critical care patients who were treated at Beth Israel Deaconess Medical Center between 2001 and 2012. Prior to accessing the database, completion of the "Protecting Human Research Participants" course offered by the National Institutes of Health was mandatory (record ID: 11186516). Both the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center's Institutional Review Boards approved the use and creation of this database. The need for informed consent was waived due to the de-identification of all data.

Study population

To be included in the study, patients were required to meet several criteria: They needed to be between 18 and 79 years old, undergoing their initial admission to the intensive care unit (ICU), with a postoperative stay of more than two days following a hepatectomy. We established exclusion criteria to refine the study population further: patients diagnosed with additional cancer types, those undergoing treatment with warfarin or other anticoagulants, individuals with pre-existing liver failure or dysfunction in other organs, a history of embolic or thrombotic events, or other significant hematological disorders, and any cases where more than 10% of the essential data were missing.

Data collected

For the study, comprehensive baseline characteristics and pre-surgical laboratory values were meticulously recorded. These included demographic details such as gender, age, height, and weight, along with clinical data encompassing the presence of malignant tumors, the use of laparoscopic techniques, smoking status, ethnic background, and medical history of conditions like hypertension and portal vein tumor thrombosis (PVTT). Preoperative liver conditions noted were cirrhosis and portal hypertension, the latter defined by a hepatic venous pressure gradient exceeding 6 mmHg[11]. Additionally, patient histories of chronic obstructive pulmonary disease, chronic kidney disease, and essential hematological indices such as red blood cell (RBC), plasma, and laboratory diagnostics including TBIL, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase, albumin (ALB), serum creatinine (Cr), blood urea nitrogen, glomerular filtration rate, white blood cell, platelets (PLT), INR, PT, and activated partial thromboplastin time (APTT) were also systematically collected.

Groups and outcomes

Study participants were divided into two cohorts: The heparin group consisted of patients who were administered heparin either subcutaneously or *via* continuous infusion in preventive or therapeutic doses (either 0.1 U/mL or 0.2 U/mL or higher) for a duration of over five consecutive days; the control group included patients who did not receive anticoagulant therapy or received it for fewer than five days[12]. The principal measure of the study was the rate of PHLF. Liver failure was identified by a TBIL level of 5 mg/dL or higher, or a PT of less than 40%, indicative of a worsening underlying liver condition. Secondary outcomes measured were the duration of ICU stay, the need for respiratory support, continuous renal replacement therapy (CRRT), occurrences of hypoxemia, incidents of acute kidney injury, and deaths in the ICU.

Propensity score matching

Due to notable differences in baseline characteristics between the two groups, propensity score matching (PSM) was utilized to mitigate the influence of confounding variables. The propensity score was developed considering all the variables listed in Table 1. Then, the caliper 0.05 was used where patients of both cohorts were matched one to one through nearest neighbor matching.

Statistical analysis

The representation of continuous variables in the study was adjusted to their distribution, which were either presented as means plus or minus standard deviations (SD) or as medians with interquartile ranges (IQR). Categorical variables were shown by means of their counts and corresponding percentages. Analysis of covariates and interactions across these variables was performed using various statistical tests such as unpaired Student's *t* test, Mann-Whitney test, Two-way ANOVA for group comparisons, chi-square and Fisher's exact tests for nominal data, chosen based on appropriateness to data type. Logistic regression analyses were performed before and after introduction of the PSM to look deeper into the association between different factors and PHLF. At first, all the variables underwent a univariate logistic regression to identify the variables mainly associated with PHLF, where the variables with *P* value less than 0.1 were evaluated using multivariable with a backward stepwise selection strategy. The investigation extended to examining the influence of heparin on other adverse clinical outcomes employing a bivariate logistic regression framework. Detailed subgroup analyses were also performed to evaluate the differential effects of heparin on PHLF across various stratified groups. Statistical significance for all tests was determined at a *P* value of less than 0.05, using a two-tailed hypothesis test. These analyses were carried out utilizing SPSS software, version 25.0 (IBM SPSS, Chicago, IL, United States), and R software, version 4.2.1 (Institute for Statistics and Mathematics, Vienna, Austria; http://www.r-project.org/).

Table 1 Baseline of patients between two groups

	Before matching			After matching		
	Heparin-free group (*n* = 421)	Heparin group (*n* = 967)	*P* value	Heparin-free group (*n* = 213)	Heparin group (*n* = 213)	*P* value
Gender (male/female)	243/178	507/409	0.069	133/80	122/91	0.277
Age (yr)	56.70 ± 14.88	58.10 ± 14.46	0.100	56.00 ± 14.90	57.58 ± 15.58	0.274
Height (cm)	169.20 ± 8.82	168.30 ± 8.57	0.080	170.00 ± 9.09	169.50 ± 9.10	0.551
Weight (kg)	68.10 ± 14.55	66.30 ± 13.28	0.820	69.00 ± 14.36	68.81 ± 14.03	0.870
Malignant tumor (Yes/No)	119 (28.3%)	421 (43.5%)	**0.000**	55 (25.8%)	74 (34.7%)	0.045
Laparoscopic (Yes/No)	379 (90.0%)	802 (82.9%)	**0.001**	206 (96.7%)	198 (93%)	0.080
Smoking (Yes/No)	50 (11.9%)	100 (10.3%)	0.397	38 (17.8%)	39 (18.3%)	0.900
Ethnicity (white/not white)	296 (70.3%)	625 (64.6%)	**0.040**	146 (68.5%)	161 (75.6%)	0.105
Hypertension (Yes/No)	190 (45.1%)	231 (54.9%)	0.787	94 (44.1%)	97 (45.5%)	0.770
PVTT (Yes/No)	21 (5.0%)	37 (3.8%)	0.320	12 (5.6%)	14 (6.6%)	0.686
Diabetes (Yes/No)	5 (1.2%)	61 (6.3%)	**0.000**	1 (0.5%)	2 (0.9%)	0.562
Cirrhosis (Yes/No)	81 (19.2%)	137 (14.2%)	**0.017**	56 (26.3%)	50 (23.5%)	0.501
Portal hypertension (Yes/No)	61 (14.5%)	75 (7.8%)	**0.000**	40 (18.8%)	25 (11.7%)	**0.043**
COPD (Yes/No)	25 (5.9%)	45 (4.7%)	0.315	14 (6.6%)	10 (4.7%)	0.401
CKD (Yes/No)	39 (9.3%)	40 (4.1%)	**0.000**	23 (10.8%)	19 (8.9%)	0.516
Transfusion (Yes/No)	83 (19.7%)	92 (9.5%)	**0.000**	48 (22.5%)	44 (20.7%)	0.638
Laboratory tests						
TBIL (mg/mL)	1.1 [0.5, 3.9]	0.9 [0.5, 1.8]	**0.002**	1.3 [0.5, 4.7]	1.1 [0.6, 3.8]	0.808
AST (U/L)	65 [33, 158]	116 [53, 277]	**0.000**	68.0 [35.0, 186.5]	89.0 [44.0, 240.0]	0.704
ALT (U/L)	54 [27, 158]	101 [43, 237]	**0.000**	55.0 [28.0, 168.5]	76.0 [30.0, 210.5]	0.847
LDH (U/L)	263.0 [192.0, 405.0]	272.0 [198.8, 403.5]	0.882	274.0 [199.5, 437.5]	288.0 [201.0, 440.5]	0.487
ALB (g/dL)	3.4 [2.8, 3.8]	3.3 [2.9, 3.7]	0.724	3.4 [2.8, 3.8]	3.2 [2.8, 3.7]	0.639
Cr (mg/dL)	0.9 [0.7, 1.3]	1 [1.0, 1.0]	**0.000**	0.9 [0.7, 1.4]	1.0 [0.7, 1.4]	0.901
BUN (mg/dL)	16 [11, 28]	14 [11, 20]	**0.000**	18 [12, 31]	16 [11, 26]	0.629
GFR (mg/dL)	16 [11, 28]	14 [11, 20]	**0.000**	18 [12, 31]	16 [11, 26]	0.629
WBC (K/μL)	7.3 [5.0, 10.0]	10.0 [7.0, 14.0]	**0.000**	6.9 [4.7, 9.7]	8.1 [5.0, 12.3]	0.241
PLT (K/μL)	177 [113, 261]	205 [145, 266]	**0.001**	160.0 [96.0, 235.5]	187.0 [117.5, 245.0]	0.054
INR	1.2 [1.1, 1.6]	1.2 [1.1, 1.4]	**0.000**	1.2 [1.1, 1.6]	1.3 [1.1, 1.6]	0.408
PT (s)	13.6 [12.1, 18.1]	13.4 [12.2, 15.3]	**0.000**	13.5 [11.9, 17.8]	14.2 [12.4, 17.3]	0.436
APTT (s)	32 [28.1, 38.7]	29.9 [27.2, 33.9]	**0.004**	31.6 [28.2, 37.3]	31.0 [27.6, 37.0]	0.202

Variables are shown as "mean (SD)" or "median [IQR]". Comparisons were made by unpaired student's test, chi-square test or Mann-Whitney test according to their distribution before propensity score matching (PSM), while paired student's test, paired chi-square test or Mann-Whitney test are then used after PSM. The bold indicates statistical significance. PVTT: Portal vein tumor thrombus; PSM: Propensity score matching; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; RBC: Red blood cell; TBIL: Total bilirubin; AST: Aspartate transaminase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; ALB: Albumin; Cr: Serum creatinine; BUN: Blood urea nitrogen; GFR: Glomerular filtration rate; WBC: White blood cell; INR: International normalized ratio; PLT: Platelets; PT: Prothrombin time; APTT: Activated partial thromboplastin time.

RESULTS

A review of 1388 patients who underwent liver resection identified the same number for inclusion in the final study cohort. Of these, 967 were treated with heparin while the remaining 421 constituted the heparin-free group, as depicted in Figure 1A. Baseline characteristics and laboratory findings are detailed in Table 1. Prior to PSM, significant imbalances in several factors were noted between the groups. For example, the heparin group showed a higher incidence of malignant tumors and a reduced use of laparoscopic procedures. Additionally, notable differences were observed across most laboratory parameters. These disparities suggest that those in the heparin group were typically more severely ill. To address these imbalances, PSM was employed, resulting in 213 matched pairs. Post-PSM analysis showed that most variables were well-balanced between the two groups, with portal hypertension being the primary exception.

The association between the use of heparin and the subsequent clinical outcomes is systematically detailed in Table 2. In the broader patient sample, 142 individuals experienced liver failure following surgery. Notably, the incidence of PHLF was less prevalent among patients who did not receive heparin, with figures reported at 15.7% compared to 7.9% in the non-heparin group, resulting in an odds ratio (OR) of 2.180 and a 95% confidence interval (CI) ranging from 1.533 to 3.099, with a significant *P* value of less than 0.001. Following the application of PSM, the trend persisted, though with a narrower margin (21.1% *vs* 13.1%, OR: 0.530; 95%CI: 0.303-0.928; $P = 0.026$). For secondary outcomes, unadjusted logistic regression analysis of the entire cohort demonstrated that patients not treated with heparin experienced longer durations in the ICU [hazard ratio (HR): 1.501; 95%CI: 1.104-2.040; $P = 0.01$]. Additionally, this group required more extensive respiratory support (HR: 2.479; 95%CI: 1.745, 3.523; $P < 0.001$) and were more likely to undergo CRRT (HR: 5.044; 95%CI: 2.160, 11.782; $P < 0.001$). They also faced higher risks of developing hypoxemia (HR: 1.260; 95%CI: 1.955-3.032; $P = 0.003$) and increased chances of ICU mortality (HR: 2.354; 95%CI: 1.543-3.593; $P < 0.001$). Post-operative blood tests aimed at evaluating liver function and the coagulation system revealed no significant variations in total bilirubin, ALT, and AST levels as shown in Figure 2A-F. However, the INR values significantly improved in the heparin group, both before and after PSM (Figure 2G and H, $P < 0.001$). The results related to other coagulation indicators such as PT and PLT initially showed poorer outcomes in patients treated with heparin pre-PSM, but these markers improved post-PSM, as depicted in Figure 2I-L, likely indicating the effectiveness of the PSM in balancing these groups.

In the univariate analysis conducted post-PSM, 13 variables emerged as potential risk factors for PHLF, each with an unadjusted *P* value below 0.1. These variables were subsequently incorporated into a multivariate model, from which five factors were identified as significantly correlated with PHLF. These include treatment with heparin, which demonstrated a protective effect (OR: 0.518; 95%CI: 0.295-0.910, $P = 0.022$), diagnosis of PVTT (OR: 3.825; 95%CI: 1.486-9.844; $P = 0.005$), blood transfusion (OR: 3.316; 95%CI: 1.851-5.940; $P < 0.001$), total bilirubin (TBIL) (OR: 1.050; 95%CI: 1.011-1.089; $P = 0.010$), and ALB levels (OR: 0.473; 95%CI: 0.296, 0.755; $P = 0.002$) as detailed in Table 3. The receiver operating characteristic curves for this refined model are displayed in Figure 1B, highlighting its promising predictive capacity for PHLF. Conversely, the regression analysis conducted on patients before PSM identified 17 variables with an unadjusted *P* value below 0.1, as detailed in Supplementary Table 1. Following the multivariate selection process, only four factors were retained in the final model, including PVTT, transfusion, PLT, and ALB levels. Notably, in this pre-PSM analysis, heparin did not emerge as a significant prognostic factor for PHLF.

In the detailed subgroup analysis conducted, regardless of the patients' cirrhosis status, the type of surgical approach (laparoscopic or not), their ethnicity, or whether they had portal hypertension, those who were administered heparin showed consistently lower rates of PHLF across all categories compared to their counterparts who did not receive heparin treatment. This was statistically significant, as indicated in Figure 1C, where all *P* values were below 0.05. However, a deeper examination of the data stratified by tumor presence revealed a more nuanced relationship. Specifically, the protective effects of heparin were predominantly observed in patients undergoing liver surgeries for benign diseases, with these patients showing a significantly reduced risk of developing PHLF (OR: 0.19; 95%C: 0.38-0.76; $P = 0.006$).

DISCUSSION

Coagulation disturbances, commonly observed following liver surgery, are often linked to liver failure and a negative prognosis due to microvascular thrombosis[13]. Therefore, moderating the excessively activated coagulation cascade post-hepatectomy could serve as an effective strategy to mitigate the risk of PHLF. This retrospective study, utilizing clinical data from a publicly accessible database, illustrates that short-term heparin administration post-liver surgery or during ICU stays can decrease the incidence of PHLF and enhance overall clinical outcomes, including organ functionality. Moreover, our analysis, which incorporates both multivariable analysis and PSM, substantiates heparin's independent association with reduced rates of PHLF[14].

Heparin, a heterogeneous mixture of heparan sulfate glycosaminoglycans isolated from porcine intestines, exerts a potent anticoagulant effect through selective interactions with numerous proteins. Among these proteins is the serine protease inhibitor antithrombin-III (AT III), which influences thrombin, factors Xa, IXa, XIa, XIIa, and tissue plasminogen activator. Extensive clinical research has confirmed the efficacy and safety of heparin for treating patients at high risk of coagulation disorders. Notably, a retrospective analysis by Peng *et al*[15] demonstrated that un-fractioned heparin could enhance outcomes for patients with sepsis-induced coagulopathy. However, the benefits of heparin therapy following surgery are still under debate, with some studies indicating reduced hospital mortality[16], while others report no impact on short-term surgical outcomes[17]. A primary limitation of these studies is the lack of a predefined target population for heparin use and the absence of a universally recognized clinical biomarker for its application. Moreover, the selection of anticoagulation or hemostasis strategies after liver surgery remains complicated due to the heterogeneity of patient

Table 2 Association between heparin use and clinical outcomes

	Heparin-free group, *n* (%)	Heparin group, *n* (%)	OR (95%CI)	*P* value
Before PSM	*n* = 421	*n* = 967		
PHLF	66 (15.7)	76 (7.9)	2.180 (1.533, 3.099)	< 0.001
ICU stay	79 (18.8)	129 (13.3)	1.501 (1.104, 2.040)	0.010
Respiratory support	70 (16.6)	72 (7.4)	2.479 (1.745, 3.523)	0.000
CRRT	17 (4)	8 (0.8)	5.044 (2.160, 11.782)	< 0.001
Hypoxemia	39 (9.3)	48 (5.0)	1.955 (1.260, 3.032)	0.003
AKI	40 (9.5)	66 (6.8)	1.433 (0.951, 2.161)	0.086
ICU death	43 (10.2)	43 (4.4)	2.354 (1.543, 3.593)	< 0.001
After PSM	*n* = 213	*n* = 213		
PHFL	45 (21.1)	28 (13.1)	0.530 (0.303, 0.928)	0.026
ICU stay	49 (23.0)	51 (23.9)	1.722 (0.933, 3.177)	0.082
Respiratory support	43 (20.2)	30 (14.1)	0.502 (0.262, 0.960)	0.037
CRRT	5 (2.3)	4 (1.9)	1.059 (0.249, 4.496)	0.939
Hypoxemia	23 (10.8)	23 (10.8)	1.181 (0.598, 2.334)	0.631
AKI	22 (10.3)	21 (9.9)	1.017 (0.525, 1.971)	0.960
ICU death	27 (12.7)	24 (11.3)	0.956 (0.469, 1.949)	0.901

Bivariate logistic regression analysis with patients before and post propensity score matching was all applied to investigate variables potentially associated with all secondary clinical outcomes. PSM: Propensity score matching; CRRT: Continuous renal replacement therapy; PHFL: Post-hepatectomy liver failure; AKI: Acute kidney injury.

conditions and the complexity of surgical techniques[18]. Our findings suggest that heparin therapy serves as a valuable organ protection strategy in major surgeries, reducing dysfunction in both respiratory and urinary systems, and even decreasing ICU mortality rates. Initially, our multivariable model before PSM showed no statistically significant association between heparin treatment and PHLF, likely due to confounding factors. This aligns with findings from other randomized clinical trials suggesting that less critically ill patients might not benefit from anticoagulant therapy[19]. Following PSM, two matched cohorts were established, featuring patients with lower severity and reduced PHLF rates.

The evidence gathered supports the premise that initiating anticoagulation with heparin immediately following hepatic surgery can significantly prevent the onset of liver failure, likely attributed to the elevated risk of microthrombosis following extensive liver resections. Extensive surgical and occlusion times have been associated with increased instances of liver failure and mortality. These conditions facilitate hypothermia or ischemia-reperfusion injury, which stimulates Kupffer cells to produce oxygen-free radicals, initiating inflammatory responses that ultimately lead to endothelial damage and impairments in coagulation mechanisms[20]. These findings underscore the necessity for assertive anticoagulation therapy following hepatic operations. However, the use of heparin in the early postoperative period is hampered by concerns over potential severe hemorrhagic events, a risk exacerbated by the partially understood mechanisms of thrombosis[21]. Recent clinical studies have disclosed an unexpected prevalence of bleeding complications with conventional heparin used as prophylaxis against postoperative thrombosis, particularly highlighting that patients predisposed to heparin allergies or heparin-induced thrombocytopenia are at an increased risk of experiencing significant hemorrhagic events[22]. On the contrary, prior meta-analyses have shown that heparin does not elevate the risk of major bleeding events in patients with sepsis[23,24]. Clinical decisions regarding the application of heparin are therefore frequently influenced by the surgeon's evaluation of blood loss during the operation. An additional concern remains the paucity of definitive evidence regarding the efficacy of alternatives such as heparin derivatives, heparinoids, or other anticoagulants compared to standard heparin. Research utilizing animal models has indicated that low molecular weight heparins are less prone to cause hemorrhagic complications[25].

Several significant limitations are inherent to this study and merit discussion. Given the retrospective nature of this analysis, there is a potential for both selection and ascertainment biases. Table 1 illustrates marked discrepancies across numerous variables between the groups, with those receiving heparin typically exhibiting more severe medical conditions. In response, we applied both multivariate regression analysis and PSM to mitigate these confounding influences effectively. Furthermore, the database from which this study draws its data lacks essential peri-operative variables, including intra-operative blood loss records, and fails to analyze methodologies related to ICU treatments or interventions. Another critical gap is the absence of data on tumor stage and the impact of preoperative treatments such as radiotherapy or chemotherapy, which significantly influence the residual liver volume: An essential factor in determining the likelihood of PHLF. This gap highlights a significant limitation of the MINIC database, which is

Table 3 Univariate and multivariate analyses of factors associated with liver failure in matched groups

Factors	B	SE	Wald	OR (95%CI)	*P* value
Univariate					
Heparin	-0.571	0.263	4.703	0.565 [0.337, 0.947]	**0.030**
Gender	-0.231	0.267	0.749	0.794 [0.470, 1.340]	0.387
Age	-0.009	0.008	1.099	0.991 [0.975, 1.008]	0.294
Height	0.021	0.014	2.055	1.021 [0.992, 1.050]	0.152
Weight	0.026	0.008	9.392	1.026 [1.009, 1.043]	**0.002**
Malignant tumor	-0.169	0.287	0.347	0.845 [0.482, 1.481]	0.556
Laparoscopic	-0.802	0.468	2.929	0.449 [0.179, 1.123]	**0.087**
Smoking	0.032	0.252	0.016	1.032 [0.630, 1.691]	0.900
Ethnicity	-0.361	0.274	1.732	0.697 [0.407, 1.193]	0.188
Hypertension	0.085	0.258	0.108	1.088 [0.656, 1.804]	0.743
PVTT	1.207	0.426	8.003	3.343 [1.451, 7.703]	**0.005**
Diabetes	0.891	1.232	0.523	2.437 [0.218, 27.243]	0.469
Cirrhosis	0.635	0.276	5.319	1.888 [1.100, 3.239]	**0.021**
Portal hypertension	0.854	0.310	7.579	2.348 [1.279, 4.312]	**0.006**
COPD	0.389	0.631	0.380	0.678 [0.197, 2.334]	0.537
CKD	0.465	0.388	1.440	1.592 [0.745, 3.404]	0.230
Transfusion	1.565	0.275	32.311	4.783 [2.788, 8.205]	**0.000**
Laboratory tests					
TBIL	0.068	0.017	15.985	1.070 [1.035, 1.107]	**0.000**
AST	0.000	0.000	2.462	1.000 [1.000, 1.001]	0.117
ALT	0.000	0.000	0.308	1.000 [1.000, 1.001]	0.579
LDH	0.000	0.000	3.279	1.000 [1.000, 1.000]	**0.070**
ALB	-1.020	0.218	21.989	0.360 [0.235, 0.552]	**0.000**
Cr	0.054	0.105	0.264	1.056 [0.859, 1.298]	0.608
BUN	-0.005	0.008	0.457	0.995 [0.979, 1.010]	0.499
GFR	-0.005	0.008	0.457	0.995 [0.979, 1.010]	0.499
WBC	0.025	0.016	2.278	1.025 [0.993, 1.058]	0.131
PLT	-0.006	0.002	13.876	0.994 [0.991, 0.997]	**0.000**
INR	0.529	0.158	11.266	1.697 [1.246, 2.312]	**0.001**
PT	0.049	0.014	11.643	1.050 [1.021, 1.081]	**0.001**
APTT	0.010	0.007	1.797	1.010 [0.996, 1.024]	0.180
Multivariate					
Heparin	-0.657	0.287	5.236	0.518 [0.295, 0.910]	0.022
PVTT	1.342	0.482	7.734	3.825 [1.486, 9.844]	0.005
Transfusion	1.199	0.297	16.248	3.316 [1.851, 5.940]	< 0.000
TBIL	0.048	0.019	6.558	1.050 [1.011, 1.089]	0.010
ALB	-0.749	0.239	9.815	0.473 [0.296, 0.755]	0.002

The initial screening *via* univariable logistic regression analysis; all variables with $P < 0.1$ are considered as potential risk factors, and then allowed in the multivariable analysis with a backward stepwise selection process. Factors with $P < 0.05$ (the bold) in the final multivariate model means significance. PVTT: Portal vein tumor thrombus; PSM: Propensity score matching; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; RBC:

Red blood cell; TBIL: Total bilirubin; AST: Aspartate transaminase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; ALB: Albumin; Cr: Serum creatinine; BUN: Blood urea nitrogen; GFR: Glomerular filtration rate; WBC: White blood cell; INR: International normalized ratio; PLT: Platelets; PT: Prothrombin time; APTT: Activated partial thromboplastin time.

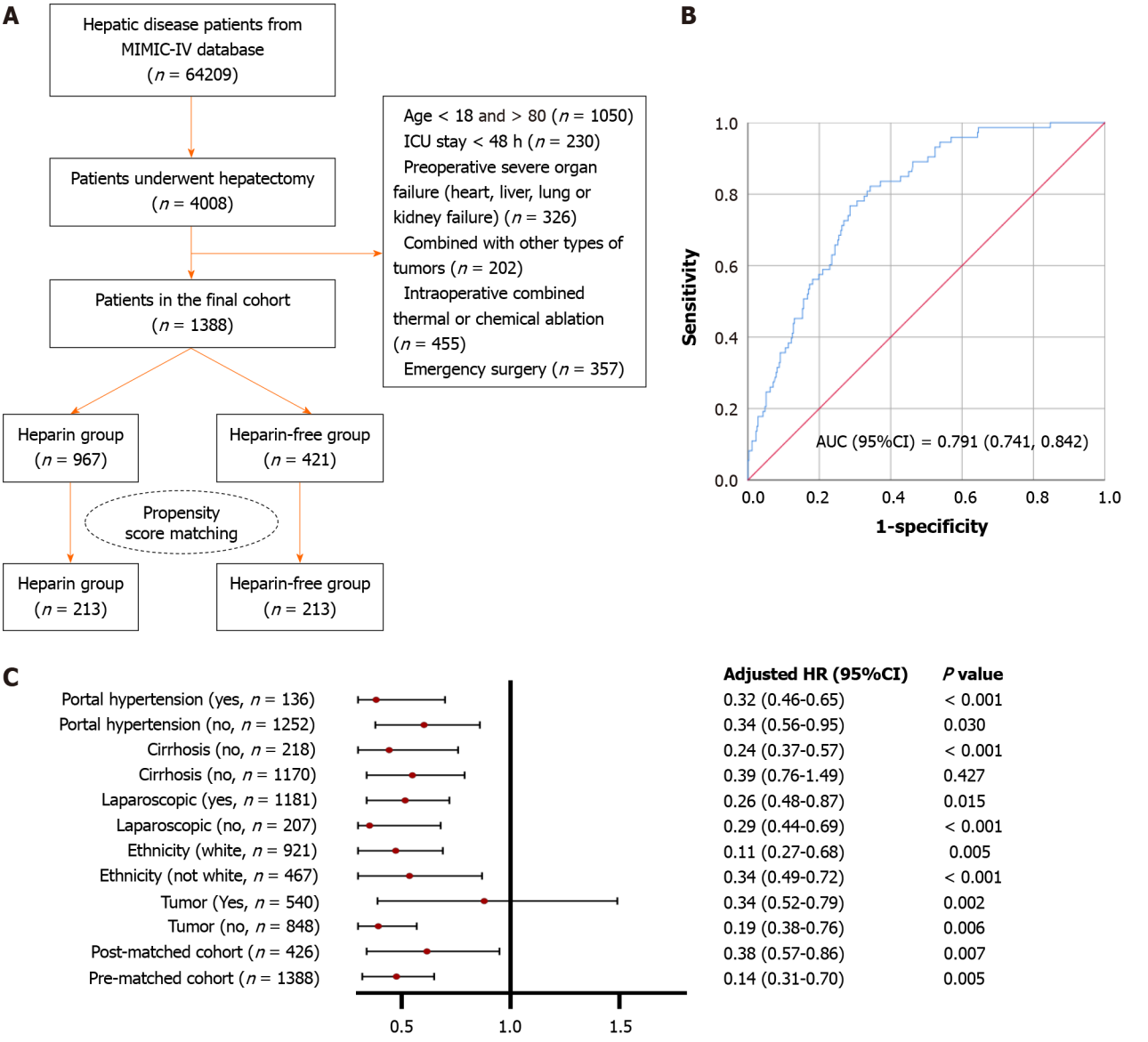
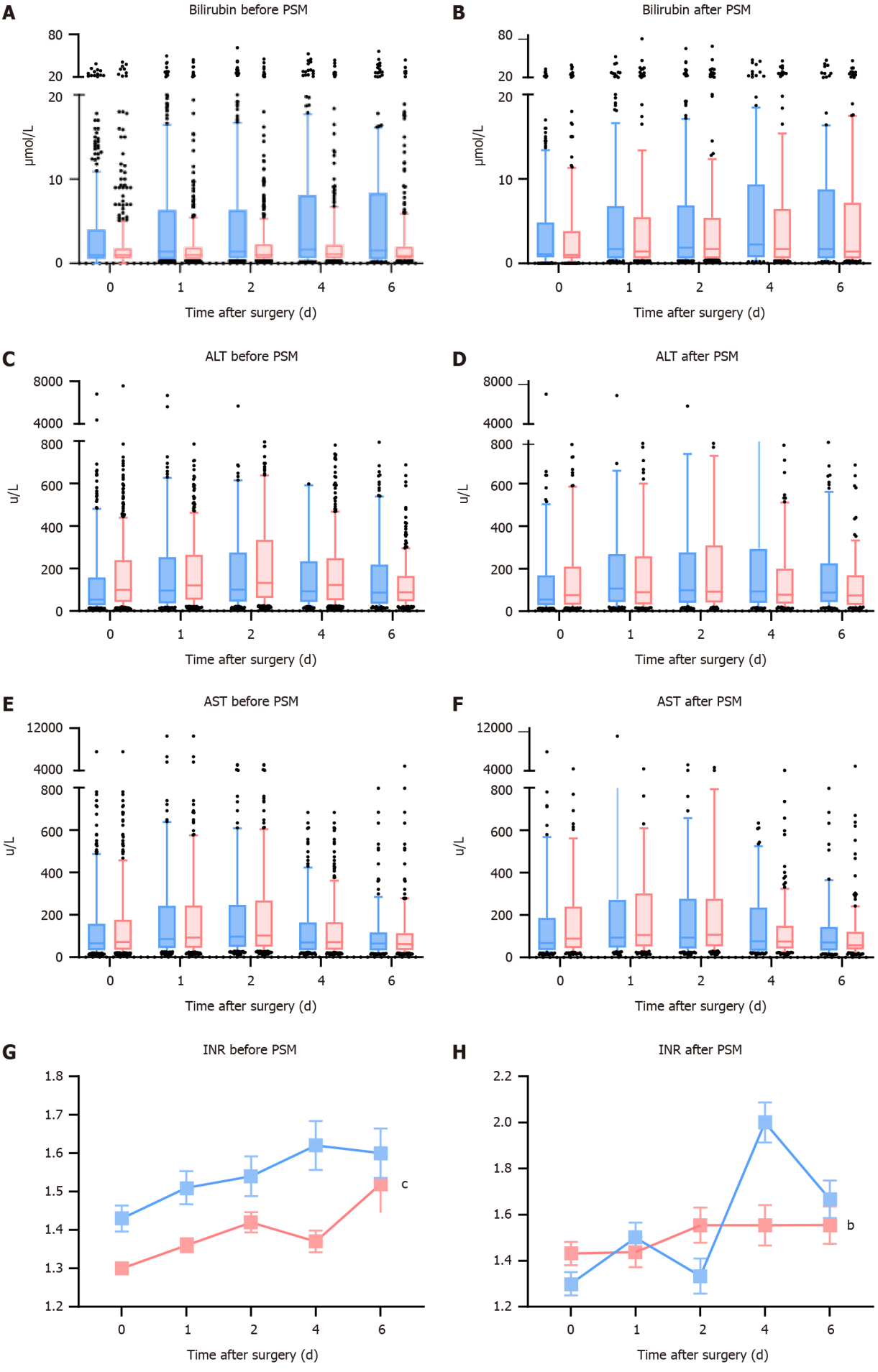


Figure 1 Study pipeline, prediction model performance, and effect of heparin on post-hepatectomy liver failure. A: Study pipeline showing the selection of hepatic disease patients from the Multiparameter Intelligent Monitoring in Intensive Care III database, criteria for inclusion and exclusion, and the final cohort of patients who underwent hepatectomy. Propensity score matching was used to balance the heparin and heparin-free groups; B: Receiver operating characteristic curve showing the performance of the prediction model; C: Forest plot illustrating the effect of heparin on various clinical outcomes in the post-hepatectomy liver failure cohort. MIMIC: Multiparameter Intelligent Monitoring in Intensive Care; ICU: Intensive care unit; HR: Hazard ratio; 95%CI: 95% confidence interval; AUC: Area under the curve.

primarily geared towards gathering data from patients within ICU settings. As such, interpretations of our findings should be approached with caution due to these dataset constraints.

CONCLUSION

In summarizing the findings from the MIMIC-3 database analysis, it was determined that administration of heparin not only diminishes the rate of post-hepatectomy liver failure but may also contribute to improved clinical outcomes overall. Interestingly, heparin application was associated with enhanced INR values within the treatment group and did not elevate bleeding risks. To substantiate these observations and elucidate the underlying mechanisms, future prospective clinical trials are warranted.


A
Bilirubin before PSM
μmol/L
Time after surgery (d)
B
Bilirubin after PSM
μmol/L
Time after surgery (d)
C
ALT before PSM
u/L
Time after surgery (d)
D
ALT after PSM
u/L
Time after surgery (d)
E
AST before PSM
u/L
Time after surgery (d)
F
AST after PSM
u/L
Time after surgery (d)
G
INR before PSM
c
Time after surgery (d)
H
INR after PSM
b
Time after surgery (d)

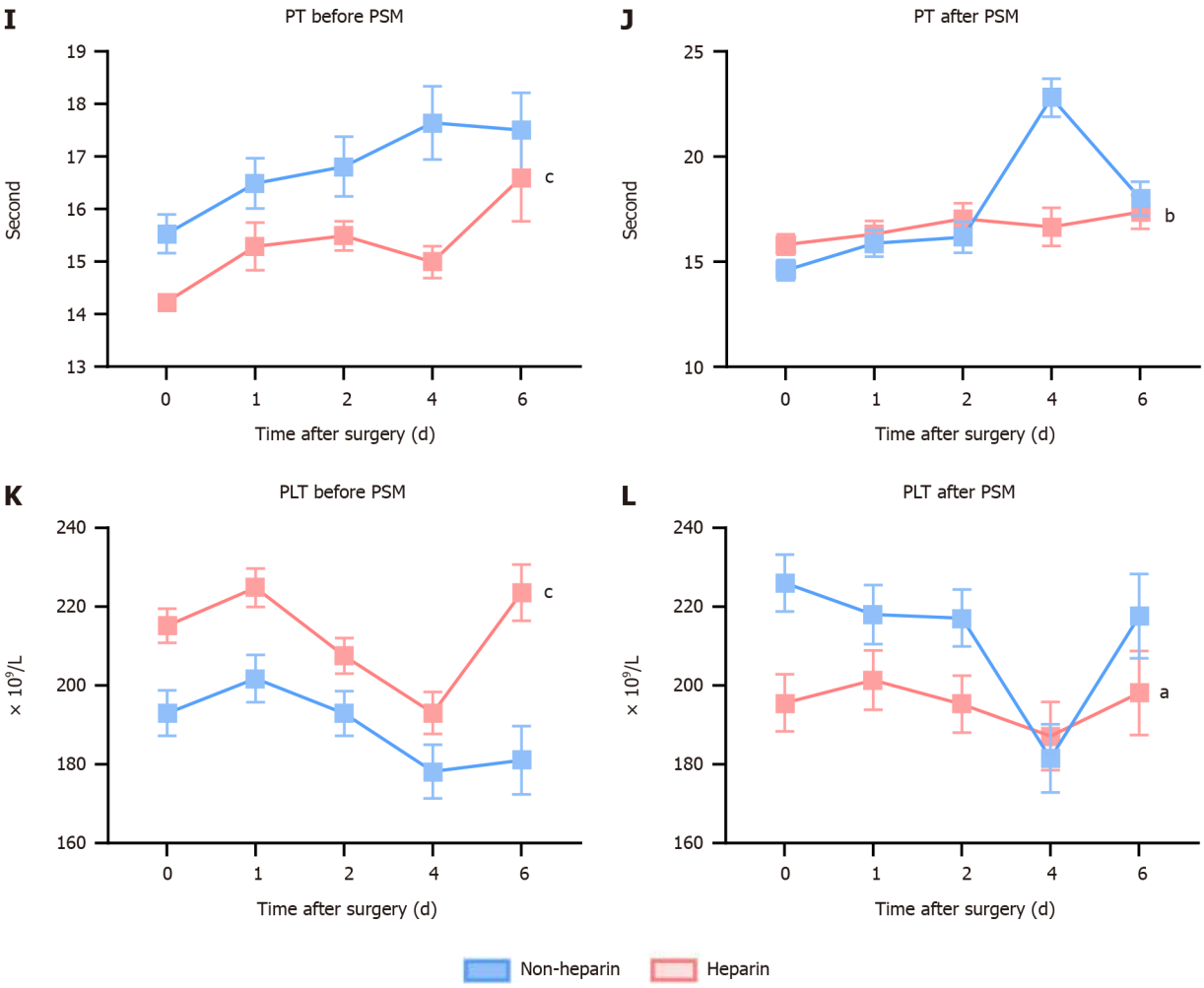


Figure 2 Baseline and postoperative liver function and coagulation results before and after propensity score matching. A: Baseline total bilirubin levels in the heparin and non-heparin groups before propensity score matching (PSM); B: Baseline total bilirubin levels in the heparin and non-heparin groups after PSM; C: Baseline alanine transaminase (ALT) levels in the heparin and non-heparin groups before PSM; D: Baseline ALT levels in the heparin and non-heparin groups after PSM; E: Baseline aspartate transaminase (AST) levels in the heparin and non-heparin groups before PSM; F: Baseline AST levels in the heparin and non-heparin groups after PSM; G: Baseline international normalized ratio (INR) values in the heparin and non-heparin groups before PSM; H: Baseline INR values in the heparin and non-heparin groups after PSM; I: Baseline platelets (PLT) levels in the heparin and non-heparin groups before PSM; J: Baseline PLT levels in the heparin and non-heparin groups after PSM; K: Baseline prothrombin time (PT) levels in the heparin and non-heparin groups before PSM; L: Baseline PT levels in the heparin and non-heparin groups after PSM. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$. PSM: Propensity score matching; AST: Aspartate transaminase; ALT: Alanine transaminase; INR: International normalized ratio; PLT: Platelets; PT: Prothrombin time.

FOOTNOTES

Author contributions: Xu ZY and Peng M contributed equally to the study; Li YR contributed to conception and design of the research; Zou QF and Jiang D contributed to acquisition of data; Xu ZY and Peng M contributed to analysis and interpretation of data; Fan MM contributed to statistical analysis; Xu ZY contributed to drafting the manuscript; Li YR and Peng M contributed to revision of manuscript for important intellectual content. Li YR and Jiang D should be considered as co-corresponding authors because of their significant contributions throughout the research; Li YR was responsible for the overall research direction, experimental design, and manuscript preparation, ensuring the study's scientific integrity and quality; Jiang D contributed crucially to the acquisition of data and provided essential support during the analysis phase; both authors played critical roles that made them integral to the successful completion of this study.

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Institutional review board statement: Data for this study were sourced from version 1.4 of the Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC-III) database. MIMIC-III, which is freely accessible, contains records for over 50,000 critical care patients who were treated at Beth Israel Deaconess Medical Center between 2001 and 2012. Prior to accessing the database, completion of the "Protecting Human Research Participants" course offered by the National Institutes of Health was mandatory (record ID: 11186516). Both the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center's Institutional Review Boards approved the use and creation of this database.

Informed consent statement: Data for this study were sourced from version 1.4 of the Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC-III) database. The need for informed consent was waived due to the de-identification of all data.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

Data sharing statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Observational Study

Qualitative exploration of home life experiences and care needs among elderly patients with temporary intestinal stomas

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Abstract

BACKGROUND

This study employed a phenomenological research approach within qualitative research to explore the challenges encountered by elderly individuals with temporary colostomies in managing their daily lives and care needs. Protecting the anus surgery combined with temporary colostomy has emerged as a prevalent treatment modality for low rectal cancer. However, the ileostomy is susceptible to peri-stoma skin complications, as well as fluid, electrolyte, and nutritional imbalances, posing challenges to effective management. The successful self-management of patients is intricately linked to their adjustment to temporary colostomy; nonetheless, there remains a dearth of research examining the factors influencing self-care among temporary colostomy patients and the obstacles they confront.

AIM

To investigate the lived experiences, perceptions, and care requirements of temporary colostomy patients within their home environment, with the ultimate goal of formulating a standardized management protocol.

METHODS

Over the period of June to August 2023, a purposive sampling technique was utilized to select 12 patients with temporary intestinal stomas from a tertiary hospital in Shanghai, China. Employing a phenomenological research approach, a

semi-structured interview guide was developed, and qualitative interviews were conducted using in-depth interview techniques. The acquired data underwent coding, analysis, organization, and summarization following Colaizzi's seven-step method.

RESULTS

The findings of this study revealed that the experiences and needs of patients with temporary intestinal stomas can be delineated into four principal themes: Firstly, Temporary colostomy patients bear various burdens and concerns about the uncertainty of disease progression; secondly, patients exhibit limited self-care capabilities and face information deficits, resulting in heightened reliance on healthcare professionals; thirdly, patients demonstrate the potential for internal motivation through proactive self-adjustment; and finally, patients express a significant need for emotional and social support.

CONCLUSION

Home-living patients with temporary intestinal stomas confront multifaceted challenges encompassing burdens, inadequate self-care abilities, informational deficits, and emotional needs. Identifying factors influencing patients' self-care at home and proposing strategies to mitigate barriers can serve as a foundational framework for developing and implementing nursing interventions tailored to the needs of patients with temporary intestinal stomas.

Key Words: Elderly; Temporary intestinal stomas; Life experiences; Intestinal ostomy complications; Qualitative study

Core Tip: This study delves into the obstacles encountered by elderly individuals with temporary colostomies, with a particular focus on the complications affecting the skin around the stoma and the challenges associated with maintaining proper fluid, electrolyte, and nutritional balance. While effective self-management is crucial, there is a noticeable gap in research examining the factors that influence self-care and coping mechanisms. The findings highlight the significant burdens, insufficient self-care abilities, informational deficits, and emotional needs experienced by these patients at home. Identifying the key determinants of self-care and proposing effective coping strategies can significantly contribute to the development of personalized nursing care plans. Moreover, the study emphasizes the importance of providing enhanced informational support, utilizing social resources, and improving the quality of post-discharge assistance to adequately address the diverse needs of individuals with temporary colostomies.

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INTRODUCTION

Colorectal cancer stands as a prevalent malignancy within the digestive system, ranking third globally in incidence and second in mortality, as reported by the 2020 Global Cancer Report, with respective proportions of 10.0% and 9.4%[1]. Notably, for cases of low rectal cancer[2], sphincter-preserving surgery combined with temporary intestinal stomas has emerged as a common therapeutic approach. This method aims to divert fecal flow and mitigate the occurrence of anastomotic leakage post-surgery[3]. With escalating treatment demands, there has been a notable increase in the number of patients necessitating temporary stomas. Although the closure of temporary intestinal stomas is generally successful, the median duration for stoma reversal is 148 d (equivalent to 5 months)[4], with 24% of patients eventually transitioning to permanent intestinal stomas due to varied reasons[5]. Research underscores the intimate correlation between the success of stoma reversal in temporary intestinal stomas and patients' self-management[3]. Hence, effective self-management among patients with temporary intestinal stomas is pivotal. With advancements in fast-track recovery surgical techniques, the hospitalization duration for stoma patients has significantly shortened, leaving only 29.1% of patients fully self-sufficient before discharge[6]. As stoma care transitions from hospitals to homes, compounded by the prevalence of ileostomies in temporary intestinal stomas, which yield copious excrement rich in digestive enzymes, challenges such as peristomal skin issues, water-electrolyte imbalances, and nutritional deficiencies are prone to manifest [7]. Especially for older adults, challenges in memory decline and visual changes may increase the complexity of caregiving. Presently, research on rectal cancer patients predominantly focuses on the status quo of permanent intestinal stomas, interventions to enhance patient health outcomes, and the application of relevant theories in permanent stoma patients. Identifying factors influencing self-care among patients with temporary intestinal stomas and devising strategies to surmount self-care barriers can furnish practical evidence to augment the self-management capabilities of temporary stoma patients in China, thereby facilitating the formulation and implementation of stoma care protocols. Consequently,

this study adopts a qualitative research approach to conduct in-depth interviews with 12 patients harboring temporary intestinal stomas, aiming to discern how these specific cohorts navigate life adjustments and articulate their needs. This endeavor will furnish empirical insights and direction for clinical nursing personnel in crafting appropriate care plans and devising corresponding intervention strategies.

MATERIALS AND METHODS

Study subjects

A purposive sampling method was utilized to select patients with temporary intestinal stomas who attended follow-up consultations at the colorectal surgery outpatient department and wound ostomy outpatient department of a tertiary hospital in Shanghai, China, between June and August 2023. Inclusion criteria comprised: (1) Age ≥ 60 years old; (2) Pathological diagnosis of rectal cancer with temporary stoma surgery performed; and (3) Willingness to participate in the study. Exclusion criteria included: (1) Cognitive impairment or language communication barriers; and (2) Presence of other tumor types, tumor recurrence, or metastasis. Sample size determination was guided by information saturation. Ultimately, 12 patients were selected for interviews, labeled in sequence from "N1" to "N12". Among them, there were 10 males and 2 females, aged 60 to 77 years old, with stoma creation performed 2 to 10 months prior. The general characteristics of the interviewees are presented in Table 1.

Development of interview outline

The initial interview outline was drafted by reviewing relevant literature in alignment with the research objectives. Subsequently, the outline underwent revisions following consultations with an ostomy therapist and a clinical nursing expert specializing in colorectal surgery. Furthermore, pre-interviews were conducted with two postoperative patients having temporary intestinal stomas to enhance the refinement of the interview outline. Consequently, the final interview outline was formulated to facilitate semi-structured interviews with participants, aiming to delve into their perceptions and self-management experiences regarding temporary intestinal stomas during the home care phase. The interview outline encompassed the following topics:

Could you describe any physical and psychological changes you encountered following stoma surgery?

What challenges have arisen post-stoma surgery, and how did you manage them?

Who currently takes primary responsibility for stoma care? Are you capable of independently performing stoma bag cleaning and replacement?

What are the primary issues you currently face in stoma care?

What are your considerations regarding future life and work?

What forms of support and assistance do you feel are most crucial?

Data collection methods

Data were gathered utilizing a semi-structured interview methodology. Prior to the interviews, communication was initiated with the patients to coordinate the timing and location of the interviews. The interviews were conducted face-to-face in a quiet, private office setting. Researchers introduced themselves prior to the interviews and elucidated the interview's purpose to the patients. Upon obtaining consent from the patients, the interviews were audio recorded and documented on paper, with assurances of confidentiality. Establishing a comfortable atmosphere throughout the interview process was deemed crucial. The interview content adhered to the interview outline. Seven skills, including questioning, probing, listening, paraphrasing, and responding, were utilized during the interviews, with careful attention paid to non-verbal cues such as tone, facial expressions, and body language[8]. Patients were encouraged to express their thoughts and experiences openly. Each interview session was limited to a maximum duration of 30 min. At the conclusion of the interviews, no novel themes emerged, signifying data saturation.

Data analysis methods

Within 24 h following the conclusion of the interviews, audio recordings were transcribed into written text, and the interview data were refined with reference to the transcripts. During the data analysis process, the real names of the interviewees were concealed and replaced with identifiers. The analysis employed the Colaizzi 7-step method[9], which involved a meticulous review of the original data to extract phrases or sentences relevant to the themes. The specific analysis steps comprised: (1) Immersion in the material to obtain a comprehensive understanding; (2) Identification of meaningful statements or descriptive sentences; (3) Organization of meaningful statements into coherent units; (4) Categorization and summarization of coherent units to identify common themes; (5) Detailed description of each theme, summarizing its characteristics and essence; (6) Derivation of a basic structure from the detailed descriptions, elucidating the core content; and (7) Verification of the accuracy and completeness of the basic structure through feedback. Upon completion of the data analysis, the research findings were presented to the interviewees for validation to ensure the accuracy of the information.

Ethical considerations

Prior to enrollment in the study, careful consideration was given to obtaining written informed consent from all research participants. Participants were informed of their right to refuse participation or withdraw from the interview at any time. Additionally, confidentiality of all participant data was strictly maintained throughout the study.

Table 1 Socio-demographic data of respondents

ID	Sex	Age (yr)	Educational background	Marital status	Stoma duration	Complications	Primary caregiver
N1	Male	64	Junior high	Married	5 months	Incontinence dermatitis	Spouse
N2	Male	60	University	Divorced	2 months	Incontinence dermatitis	Sister
N3	Male	64	Junior high	Divorced	8 months	None	Children
N4	Male	60	Undergraduate	Married	9 months	Eczema	Spouse
N5	Male	68	Undergraduate	Married	10 months	None	Spouse
N6	Male	61	High school	Divorced	3 months	None	Living alone
N7	Female	75	Undergraduate	Married	2 months	None	Spouse
N8	Male	77	High school	Married	4 months	Stoma edema, prolapse	Spouse
N9	Female	70	High school	Married	2 months	None	Children
N10	Male	70	Undergraduate	Married	3 months	Incontinence dermatitis	Children
N11	Male	64	Undergraduate	Married	2 months	Incontinence dermatitis	Spouse
N12	Male	63	Junior high	Married	10 months	Parastomal hernia	Spouse

RESULTS

Theme 1: Existential burdens and fear of disease progression

Patients with temporary intestinal stomas undergo a multifaceted experience characterized by various burdens and an apprehension regarding the uncertain trajectory of their illness.

Disruption of daily life due to specific symptoms of anal and ileostomy: Patients encountered significant disruptions in their customary routines attributable to the distinct symptoms associated with anal and ileostomy. Postoperatively, patients reported experiencing a spectrum of symptoms including wound pain, infections, chemotherapy-related side effects, and stoma-related complications.

I have no control over my bowel movements, and the wound aches whenever the weather turns cloudy (N3).

The chemotherapy drugs leave me feeling fatigued all day long, rendering me bedridden. Despite sleeping throughout the day, I still lack energy and cannot engage in any activities (N11).

I often observe my stoma, sometimes it feels enlarged or swollen, and now it seems slightly prolapsed. I wonder if this indicates a problem (N8).

Additionally, challenges such as incontinence dermatitis around the stoma, exacerbated by inadequate care or climatic conditions, significantly distressed patients.

The scorching weather exacerbates dermatitis despite frequent changes of the stoma bag (N4).

Many patients struggled with timing stoma bag changes, particularly at night, impacting their sleep quality.

I sleep poorly at night and have to change the bag immediately if there's an issue. Otherwise, I feel psychological pressure, fearing the bed will become soiled. The anxiety prevents me from falling back asleep, and I must get up multiple times during the night, only catching up on sleep in the morning (N4).

I can only sleep on one side at night, otherwise, the feces won't pass through (N11).

Furthermore, some patients faced limitations in basic physical activities post-stoma surgery, such as squatting, bending, or exerting force, significantly altering their daily routines.

I'm apprehensive about lifting anything heavy for fear of causing stoma prolapse. I often refrain from lifting and wait for assistance from family members (N12).

Negative emotional responses accompanying physical and mental health challenges: The presence of intestinal stomas alters both the body's physical structure and its excretory pathways, resulting in challenges in returning to normal social activities post-surgery. Additionally, patients grapple with issues such as pain, fatigue, disruptions in sleep quality, and disturbances in self-perception. These factors contribute to the emergence of prevalent negative emotions, including anxiety, depression, and feelings of loneliness[10].

The discomfort is unbearable. I'm frustrated with this stoma. I feel unlucky to have this disease (N1).

The family doctor dismissed it as just a stomachache and prescribed some medicine. If it had been diagnosed earlier, things might have been better. I hold resentment toward that family doctor (N3).

Confronted with the repercussions of inadequate stoma care, patients experience fear and a sense of helplessness.

Initially, it leaked every day, and I cried every day at home. I couldn't sit or sleep. I was particularly anxious, fearing that the condition wouldn't improve. My family members also voiced their dissatisfaction. They felt it would have been better without surgery, but following the procedure, the situation deteriorated, with leaks everywhere, necessitating frequent changes of the bed sheets (N8).

Furthermore, beyond the direct burden of the illness, family members also endure the impact of the patient's negative emotional state.

When I feel unwell, my mood sours, leading to friction with my family (N1).

I visit the hospital twice a week. At home, it's always my wife assisting me. I have to empty it 7 or 8 times a day, always anxious about leaks. My entire family is worn out from dealing with my illness (N4).

Constraints on social interaction: Post stoma surgery, patients lose the ability to defecate autonomously, and the leakage and unpleasant odor from the stoma frequently result in feelings of reduced self-esteem and shame.

I'm hesitant to socialize. After meals, the discharge quickly emerges from the stoma. Changing it in public is inconvenient, and there's an odor. Only when I no longer have the Peripherally Inserted Central Venous Catheters (PICC) line and stoma can I lead a normal life (N6).

Treatment-related factors prompt some patients to avoid or fear exposure, thus limiting their social interactions.

We don't socialize much now; we simply converse more with fellow patients. I'm reluctant to inform relatives and friends. If they find out, they'll inquire, which exacerbates my discomfort (N5).

I try to minimize social engagements now. I fear standing for extended periods, fearing stoma prolapse. Mentally, I resist. I prefer solitude when unwell, seeking only rest (N10).

Regular stoma bag changes and challenges in managing diet outdoors further curtail patients' outdoor activities, particularly long-distance travel.

This stoma bag poses challenges. I'm hesitant to travel. Although others encourage me, I remain apprehensive. I fear it'll be cumbersome, inconveniencing others, or tarnishing my image (N12).

Fear of cancer recurrence: Patients exhibit sensitivity to subtle changes and discomfort in their bodies, experiencing fear and concern regarding the potential recurrence of cancer or the repercussions of inadequate stoma care during the reversion period. This perception of unpredictability leads to uncertainty about the disease[11].

I am concerned about the possibility of cancer recurrence and metastasis, which weighs heavily on my psyche. I fear that any bodily discomfort may signify metastasis, creating a psychological burden. As cancer survivors, we understand that any misstep could lead to its spread and recurrence elsewhere, compounding the difficulties (N5).

Initially, I managed my emotions well, but as time passed without reversion, my anxiety grew. The prospect of being unable to revert worries me greatly. If there is no improvement, I fear being tethered to a stoma bag for the remainder of my life. What kind of life quality would that entail (N12)?

Theme 2: Patients' limited self-care abilities and insufficient information leading to excessive dependence

Patients lack disease-related knowledge, resist learning new information, and overreliance on healthcare professionals: Managing an ileostomy poses significant challenges, particularly for elderly individuals who may experience fatigue and a sense of helplessness due to factors such as advanced age, diminished memory, and inadequate coping abilities[12].

The elderly gentleman struggles to change the stoma properly; it often leaks. He hasn't bothered to learn. Besides, he's only wearing it temporarily for three months; he'll revert next month. Learning seems pointless (N7).

Some patients living alone encounter difficulties in self-care due to factors like the stoma's low position and challenges in performing personal tasks.

I can't manage to change the stoma bag on my own. The stoma sits low and is hard to see. Aligning it correctly is a challenge. I rely on a mirror to assist. If not done properly, it leaks, creating a mess on the bed (N6).

Insufficient self-care skills prompt patients to hesitate in performing tasks independently, resulting in a heavy reliance on healthcare professionals for assistance.

I attempted to change it myself, but it leaked. It's too bothersome. I lack understanding of this. If I make a mistake, I don't want to handle it. I've lost interest in learning. Whenever issues arise, I simply turn to you guys (N1).

The most inconvenient aspect is dealing with the stoma bag. I'm unsure how to handle it. I visit the stoma clinic for changes, which provides a sense of security. Although the nurse provided guidance, I still harbor apprehensions. If I cut it too small, I fear it may block the stoma; if too large, it might lead to leakage. I've experienced leaks before, resulting in skin irritation. It took two weeks of care here before it healed (N9).

Patients exhibit insufficient comprehension of the disease, and the reliability and scientific rigor of information sourced from the Internet remain ambiguous: The majority of rectal cancer patients are elderly individuals who encounter difficulty in distinguishing trustworthy information from the myriad of intricate online resources.

In today's world, accessing such content on your phone is effortless. Even if you're not affected by this disease, you're bound to come across it. Once big data identifies my interest in this content, it continuously pushes similar content to me. I typically acquire knowledge from platforms like TikTok, Kuaishou, and Toutiao. Initially, I had no fear whatsoever. When I received my initial diagnosis, I was completely unaware of its implications. My mindset was, 'Just undergo the surgery. What's the worst that could happen?' Inevitably, humans will succumb to mortality. However, as I listened to the doctors and perused various online opinions, the psychological burden began to mount. I gradually recognized the severity of this disease (N7).

Theme 3: Temporary intestinal stoma patients elicit intrinsic motivation through active self-adjustment

Patients foster positive expectations, and express gratitude for received support: Temporary stoma surgery imbues patients with optimistic expectations regarding their disease recovery, mitigating pessimism and excessive rumination. Therefore, they feel fortunate and content, expressing appreciation to healthcare professionals for their invaluable

guidance on treatment.

I focus on positive aspects. It's already like this. There's no point in worrying excessively. We'll manage as it unfolds. Besides, many people live with lifelong stomas. With advancements in medicine, preserving the anus is already commendable. It's quite a burden to wear this for life (N5).

The doctor mentioned that I'm eighty percent through. My cancer cells haven't spread, and it was detected early. If it had been discovered late, it would have been in the advanced stage. I'm thankful to the doctors here (N9).

My family notices my good progress, so they're not overly saddened. I'm able to cook now, and I can even go out for a walk. It's just inconvenient to be exposed to cold water (N4).

Patients proactively seek avenues to comprehend disease-related information.

Should I cleanse the stoma with tap water or boiled water? What does my intestine look like after intestinal stoma surgery? Is it normal to occasionally experience sticky discharge from the anus after having a stoma (N2)?

Intense desire for reversion: The distinctive characteristics of temporary intestinal stomas, coupled with the traditional value of preserving bodily integrity, lead all patients to eagerly anticipate resuming normal life after stoma reversion.

The doctor mentioned that if my physical condition improves, I might revert earlier. I am eagerly looking forward to reverting on the same day (N8).

I simply wish to revert as swiftly as possible. Once reverted, I will no longer have the PICC line and stoma, allowing me to live just like any other person (N4).

Theme 4: Strong emotional and social support needs among temporary intestinal stoma patients

Importance of family support: Patients express a strong need for care and understanding from their families, as they find solace and a sense of belonging through this support network. Family support emerges as a crucial lifeline for most patients following their diagnosis.

I'm quite content with life; my family takes excellent care of me (N1).

My family doesn't burden me; they rise early every morning. Normally, I handle the grocery shopping, but since falling ill, they've taken over. They also manage the laundry. Whenever I experience leaks, it's my daughter who assists with changing. They even handle purchasing my medications. I feel incredibly fortunate (N5).

I'm rather satisfied with life. Although my children are grown, they still make time to visit whenever they can (N9).

Patients encounter insufficient preparation for the transition period, seeking professional guidance from healthcare providers: As advancements in rapid recovery medicine progress, patients are often discharged from hospitals earlier, frequently lacking comprehensive understanding of the various stages of their illness. Consequently, they find themselves unprepared for the transition period. Patients earnestly seek professional advice from healthcare providers to address queries arising during their care.

I'm unsure about what to anticipate post-reversion. I hope to engage with doctors and nurses at that juncture to understand the necessary precautions (N7).

When seeking assistance, I'm uncertain whom to approach. During stoma reversal, I hope for increased communication with patients regarding issues like stoma-related pain. I'm unsure whether to consult the doctor or the stoma nurse. I feel lost and have to navigate through it alone (N10).

Patients grappling with anxiety during their illness urgently require support and reassurance from healthcare providers.

Initially, preserving the anus seemed unfeasible, but after chemotherapy, the lesions diminished, presenting an opportunity for treatment, hence the surgery (relief). I was deeply distressed, but it was the nurses who instilled confidence in me. They consistently reassured me, alleviating my worries. Only then did I experience some relief. Now, they affirm that I've made significant progress, and with no more leaks, my emotions have stabilized (N9).

Patients' expectations of adequate stoma care resources from relevant departments to meet healthcare needs: Inadequate social support fails to meet the healthcare needs of patients. Combined with limited avenues for information retrieval and relatively insufficient coping abilities, not all patients can access stoma nurses in the community after discharge. Patients who are unable to obtain stoma care attempt to resolve issues independently, leading to severe complications around the stoma site.

My home is far away, and it's inconvenient to travel back and forth. So, I made an appointment with a stoma nurse online for home service to help me change the stoma bag. However, the situation worsened with each change. Eventually, my skin became inflamed, and I had to consistently return to the hospital for changes. Each trip takes a long time. It would be beneficial if home services were available, even if they were more costly (N5).

Patients often have to commute long distances for stoma maintenance.

The nurse is outstanding. I have no complaints. I live in Qingpu and still travel this far for changes. The round trip costs over a hundred yuan. I was referred by others. I had used home services before, but I experienced leaks every other day, and my skin became sore. However, everything is fine now (N7).

Patients look forward to more comprehensive medical services to receive timely care and treatment to prevent worsening of their condition.

It would be ideal if the stoma clinic were also open in the afternoon (N5).

The hospital is overcrowded, and there is a shortage of beds. My stoma reversion surgery has been postponed. I'm worried about developing a hernia next to my stoma. Now, the surgery has been delayed again. If my condition worsens and I can't revert, what should I do (N12)?

DISCUSSION

Psychological burden on temporary intestinal stoma patients: need for dynamic assessment and personalized care strategies

Temporary intestinal stoma patients bear a significant psychological burden, necessitating dynamic assessment and the application of tailored care strategies. The effluent from ileostomies contains high levels of digestive enzymes, which can provoke strong irritation of the peristomal skin, leading to inflammation. Moreover, patients often endure heightened symptom burden and diminished self-esteem during postoperative chemotherapy, characterized by fatigue, weakness, nausea, vomiting, pain, discomfort, and physical changes[13-15]. Consequently, they frequently lack the capacity for self-management.

In light of this, healthcare providers must conduct ongoing assessments to accurately discern the evolving needs of patients at different stages. Establishing a cohesive and structured care environment for patients, encompassing stoma management, post-stoma reversion care, and informational support, is paramount[16]. This can be achieved through the development of customized discharge plans, chemotherapy schedules, and continuous follow-up strategies tailored specifically to temporary intestinal stoma patients[17]. Proactive communication with patients about potential adverse reactions at various stages and the corresponding management strategies is vital to ensure patients receive comprehensive care from admission to discharge. This comprehensive approach aims to enhance the health outcomes of temporary intestinal stoma patients and facilitate their smooth reversion process.

Enhancing the positive impact of temporary colostomy and improving patient health education

This study revealed that patients undergoing temporary colostomy demonstrate a significant inclination towards stoma reversal. Influenced by traditional Chinese cultural beliefs, temporary colostomy surgery contributes to achieving a degree of bodily integrity for patients, thereby notably alleviating the psychological burden on both patients and their families in comparison to permanent colostomy. Consequently, healthcare practitioners should closely observe the positive implications emerging from patients and their caregivers during the adaptation period, promptly recognizing the advantageous transformations occurring and encouraging active expression of emotions to bolster positivity. Nonetheless, throughout this process, it remains crucial to provide patients with comprehensive insight into potential physical alterations following stoma reversal surgery, including manifestations such as diarrhea, increased bowel movements, and fecal incontinence. This proactive approach aims to prevent patients from forming inaccurate assessments regarding potential complications associated with bodily functions.

Strengthening information support, mobilizing social resources, and enhancing the quality of subsequent assistance and services

Patients' perspectives on temporary intestinal stomas are often significantly influenced by misinformation. However, due to limited abilities to seek and discern valid information among the elderly, they may easily succumb to feelings of fear, despair, and pessimism. To tackle this challenge, organizing educational workshops[11] can prove beneficial. These workshops can introduce a range of topics including rectal cancer treatment and prognosis, stoma bag replacement techniques, daily stoma care, dietary recommendations, identification of abnormal changes around the stoma and peristomal skin, and management of both early and late stoma complications[16,18]. Additionally, guidance on identifying and coping with Low Anterior Resection Syndrome post-stoma reversion, postoperative pelvic floor muscle rehabilitation exercises, and other strategies can aid in patients' post-reversion recovery.

Furthermore, it is imperative to refine the format, timing, and content of health education, utilizing diverse methods such as stoma model tools, educational handbooks, video demonstrations, *etc.*, to ensure patients acquire essential stoma care skills. This approach empowers patients and their caregivers to scientifically understand and address temporary stoma-related challenges, thereby facilitating adaptation to their lives. For patients encountering difficulties in accessing and utilizing disease care-related resources, establishing an informative website is recommended. This platform can feature engaging graphics and text concerning stoma care knowledge, provide trustworthy information on stoma nurses capable of offering home services as recommended by local community nursing teams, and create a referral page for stoma nurses within specific geographic areas. Additionally, it can showcase contact information for stoma nurse resources that patients can leverage when transitioning to the community, thereby enhancing patients' access to medical services.

Moreover, for elderly patients who may not be comfortable using the internet, offering assistance hotlines to inform them of available support for non-emergency situations can prove invaluable. These hotlines can serve as a vital resource in aiding patients in overcoming stoma care barriers and reducing the incidence of stoma-related complications.

Strengths and limitations

Strengths: This study employs qualitative research methods, highlighting the unique perspective of temporary colostomy patients, exploring their experiences and coping strategies during home care. Through face-to-face communication, it delves into the challenges, difficulties, and needs encountered by temporary colostomy patients in self-care, adding new dimensions and depth to the field of study.

Limitations: However, this study has some potential limitations. Firstly, insufficient sample size may limit a comprehensive understanding of the research phenomenon, leading to an inability to cover all the diversity and complexity. Secondly, the proportion of male patients in the sample is significantly higher than that of female patients, which may result in the research outcomes being more inclined to reflect the experiences of male patients, while neglecting the

unique needs and experiences of female patients, potentially causing gender bias and impacting the applicability and generalizability of the research. Future studies should consider increasing the sample size and the number of interviews with female patients. Given the recruitment of patients with varying durations post-surgery, potential recall bias may be present. Thus, healthcare providers should delve deeper into the evolving nature of patient needs over time to inform enhancements in nurse training. Future investigations could delve into unmet patient needs, as well as explore the interplay between emotional adaptation and disease self-management, with the aim of mitigating barriers encountered during the transitional phase following temporary intestinal stomas.

CONCLUSION

Temporary intestinal stoma patients encounter a range of challenges in their daily lives, encompassing burdens, limited self-care capabilities, and informational deficits. Moreover, they express a pronounced need for emotional and social assistance, resulting in a spectrum of requirements for home-based care. To enrich their well-being, healthcare practitioners should prioritize coping strategies, actively evaluate patient concerns across different phases, establish a cohesive and structured care milieu, aid in discharge readiness, and devise post-discharge plans to facilitate stoma adjustment. Additionally, leveraging social networks and refining subsequent aid and services can address the multifaceted needs and coping mechanisms of patients.

FOOTNOTES

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SYSTEMATIC REVIEWS

Approach to loss of response to advanced therapies in inflammatory bowel disease

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Abstract

BACKGROUND

Remarkable progress over the last decade has equipped clinicians with many options in the treatment of inflammatory bowel disease. Clinicians now have the unique opportunity to provide individualized treatment that can achieve and sustain remission in many patients. However, issues of primary non-response (PNR) and secondary loss of response (SLOR) to non-tumour necrosis factor inhibitor (TNFi) therapies remains a common problem. Specific issues include the choice of optimization of therapy, identifying when dose optimization will recapture response, establishing optimal dose for escalation and when to switch therapy.

AIM

To explores the issues of PNR and SLOR to non-TNFi therapies.

METHODS

This review explores the current evidence and literature to elucidate management options in cases of PNR/SLOR. It will also explore potential predictors for response following SLOR/PNR to therapies including the role of therapeutic drug monitoring (TDM).

RESULTS

In the setting of PNR and loss of response to alpha-beta7-integrin inhibitors and interleukin (IL)-12 and IL-23 inhibitors dose optimization is a reasonable option to capture response. For Janus kinase inhibitors dose optimization can be utilized to recapture response with loss of response.

CONCLUSION

The role of TDM in the setting of advanced non-TNFi therapies to identify

patients who require dose optimization and as a predictor for clinical remission is not yet established and this remains an area that should be addressed in the future.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Crohn; Biologics; Interleukin-12 and interleukin-23 inhibitors; Alpha-beta7-integrin inhibitors; Janus kinase inhibitors; Sphingosine-1-phosphate receptor modulators

Core Tip: In the setting of primary non-response (PNR) and loss of response (LOR) to alpha-beta7-integrin inhibitors and interleukin (IL)-12 and IL-23 inhibitors dose optimization is a reasonable option to capture response. For Janus kinase inhibitors dose optimization can be utilized to recapture response with LOR is less successful in the setting of PNR. The role of therapeutic drug monitoring in the setting of non-tumour necrosis factor inhibitor therapies to identify patients who require dose optimization and as a predictor for clinical remission is not yet established and this remains an area that should be addressed in the future research.

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INTRODUCTION

It has been over two decades since tumor necrosis factor antagonists revolutionized the management of inflammatory bowel disease (IBD) and allowed for the achievement of sustained disease remission with relatively few side effects from treatment including in people who were previously refractory to medical therapy[1]. Many advanced therapies have subsequently been approved for use in IBD with varying mechanisms of action, including alpha-beta7-integrin inhibitors, interleukin (IL)-12 and IL-23 inhibitors, Sphingosine-1-phosphate (S1P) receptor modulators and Janus kinase (JAK) inhibitors[2]. With the shift in the treatment paradigm favoring earlier utilization of advanced therapies, there is added complexity in determining the best methods for optimizing, switching, and escalating medical therapy to achieve the best outcomes. With the growing therapeutic armamentarium, it is important that the choice of therapy is individualized and both patient and disease related factors are considered to improve the likelihood of achieving disease remission while being tolerable for the patient. Yet, there is complexity in identifying the most appropriate individualized treatment for patients, with no single factor being able to identify which agent is most suitable. Similarly, identifying patients who are not responding to a treatment early, and deciding the best course of action can also be challenging. Determining why a particular therapy was not effective can be useful in deciding the best approach to a patient with an inadequate response to treatment and what further measures should be taken. Treatment non-response can be classified into two broad categories-primary non-response (PNR) which refers to a lack of clinical response during initial treatment or secondary non-response which refers to an initial response to therapy follow by a loss of response (LOR) over time[1]. This review will focus on the management options before class switching for clinicians faced with PNR and secondary LOR of non-tumour necrosis factor inhibitor (TNFi) based advanced therapy.

MATERIALS AND METHODS

This review aims to explore the efficacy of dose intensification and in-class switching in cases of PNR and LOR with non-TNFi advanced therapy. A literature search was performed in PubMed and Ovid Medline up to November 2023 for original articles and reviews under the subject headings "inflammatory bowel disease," "Crohn's disease," "CD," "ulcerative colitis," "JAK Inhibitors," "Tofacitinib," "Upadacitinib," "Ustekinumab," "anti- IL- 12/23p40," "alpha-beta7-integrin inhibitors," "Vedolizumab," "Sphingosine-1-phosphate," "ozanimod," "dose escalation," "dose intensification," "re-induction," "drug levels," "TDM," and their synonyms .In addition, the reference lists from the selected articles were reviewed to identify additional studies of potential interest. Only studies conducted in adults were included.

RESULTS

What is treatment failure?

There is no clear consensus on the definition of PNR but in general PNR refers to a failure to display improvement in clinical signs or symptoms during the induction phase[3-5] with significant variability in time to clinical response noted

between therapeutics[6,7]. The time of expected response varies with different therapies, but it is usually considered PNR if there is a lack of response to induction treatment or within 14 weeks of commencing therapy[6,7]. Our understanding of the mechanism of PNR comes from experiences with anti-tumour necrosis factors (TNFs). The two major recognised mechanisms of PNR to anti-TNFs are pharmacokinetic (due to rapid drug clearance resulting in low trough levels) and pharmacodynamic (mechanistic) failure[8], which refers to failure due to inflammation mediated by alternative pathways to the mechanism targeted by the allocated therapy[9]. Secondary non-response or LOR describes the clinical phenomenon whereby patients who initially respond to advanced therapy then subsequently lose response[10]. As with PNR, our understanding of the mechanisms leading to LOR are primarily derived from experiences with anti-TNFs. The main causes of LOR with anti-TNFs are suboptimal drug concentrations due to low trough level drug concentrations and/or anti-drug antibodies or mechanistic failure due to disease transitioning to another pathway of inflammation[11,12].

Predictors for failure of advanced therapies in IBD

Predictive factors for PNR and LOR appear to be similar with different agents and seem to relate to the underlying inflammatory burden. For vedolizumab the GEMINI trials demonstrated that less severe disease activity at baseline was associated with higher likelihood of remission in IBD[13,14] which has since been reflected in real word studies[15-23]. Furthermore, an association of elevated inflammatory markers with lower rates of clinical response and remission has also been described[13-15,24-26]. A post-hoc analysis of the GEMINI trials reported higher rates of rates of induction and maintenance of clinical remission among TNF antagonist naïve patients[27,28] which has been confirmed by real world trials[17,21,23,26,29-32]. Patients who achieve early response to vedolizumab also appear to be more likely to have a long-term response[15,16,30,33,34]. Similar to vedolizumab, a higher rate of clinical response and remission is expected with ustekinumab in both Crohn's and ulcerative colitis (UC) among patients with less severe disease activity at baseline[35-44] with an elevated C-reactive protein (CRP) associated with lower rates of clinical remission[45,46]. With ustekinumab therapy, failure of both TNF and vedolizumab was associated with lower rates of clinical remission[38,47,48]. As with other advanced therapy, patients lower baseline disease activity were more likely to achieve remission with tofacitinib[49-51] whereas higher CRP levels[50,52] and prior TNF[50,53] or biologic therapy[51,54] was associated with lower rates of clinical response. Interestingly, younger patients were less likely to demonstrate clinical response or remission[50,52] with tofacitinib. For ozanimod, a similar rate of clinical remission of UC is seen among patients with prior biologic use with a slower rate of onset[55,56] whereas lower rates of clinical remission are seen with etrasimod among patients with prior biologic or JAK-inhibitor exposure[57].

Approach to PNR to therapies?

The approach to patients with suspicion for PNR or LOR requires detailed assessment to determine if worsening symptoms are caused by increased IBD activity and then to determine the possible causes of PNR or LOR[10,58]. Disease activity is assessed through assessing clinical symptoms aided by evaluation with a combination of objective measures such as laboratory testing, endoscopy, and cross-sectional imaging[10,58]. It is essential at this stage that alternative causes for presumed PNR and LOR are excluded such as co-infection[59], poor adherence[60], improper drug storage [61], irritable bowel disease, bacterial overgrowth and bile acid malabsorption[58]. There is a consensus in guidelines for reactive therapeutic drug monitoring (TDM) in patients who fail to respond to anti-TNF therapy[11,62] however the role of TDM with other advanced therapies is less clearly defined. Thereafter the clinician is faced by three main methods of recapturing response-treatment escalation, addition of immunomodulator therapy, switching to a different therapy with a similar mechanism (in class switch) or switching to a therapy with a different mechanism (out of class switch).

Vedolizumab-management options for PNR/LOR

Vedolizumab is a full human IgG1 monoclonal antibody which targets α4β7 integrin, modulating lymphocyte trafficking in the gut[63]. Vedolizumab is administered intravenously (at a dose of 300 mg) with induction does at week 0 and 2 and maintenance doses thereafter at an interval of 4, 6 or 8 weekly[13,14]. The seminal GEMINI trials established the role of vedolizumab in IBD with clinical response rates of 47.1% and 25.7% in the treatment of UC and Crohn's disease (CD) respectively[13,14]. Despite the recognised efficacy of vedolizumab, eventual LOR to treatment is common, with rates reported to be 47.9 per 100 person-years in Crohn's and 39.8 per 100 person-years in UC[64]. Where mechanistic failure is thought to be unlikely clinicians will most often dose escalate from 300 mg every 8 weeks to every 4 week and less commonly every 6 weeks to attempt to induce or recapture remission[65]. Yet it is unclear if vedolizumab levels can be utilised to identify patients who will not respond to dose escalation and hence require therapy class-switching (Table 1).

Dose escalation: Observational data suggest that dose escalation of vedolizumab is effective in overcoming PNR and secondary LOR. The GEMINI long-term safety trials confirmed that vedolizumab 300mg dose escalation to 4 weekly restored clinical remission following LOR in UC and Crohn's[66,67] in a clinical trial setting. A retrospective study of 192 IBD patients among whom 58 patients were dose escalated (largely to 4 weekly vedolizumab) for secondary LOR or subclinical disease reported a clinical response rate of 62%[68]. Another observational study of 23 IBD patients who underwent dose optimisation of vedolizumab for primary or secondary LOR showed that increased vedolizumab dosing frequency resulted in a treatment response in more than half of IBD[69]. Similar findings establishing the efficacy of vedolizumab dose intensification were described in further recent retrospective and prospective studies[23,68-76]. This has been confirmed in a systematic review by Peyrin-Biroulet *et al*[64] which reports that dose intensification of vedolizumab following secondary LOR restores clinical response in more than half of IBD patients on maintenance vedolizumab therapy.

Table 1 Dose optimisation approaches for advanced therapies in inflammatory bowel disease

Ref.	Number	Disease	PNR and/or SLOR	Study design	Intervention	Follow-up	Outcome	Result
Trials: Vedolizumab dose escalation								
Loftus *et al* [66]	32	UC	LOR	Single-arm open label-multicentre	4 weekly 300 mg	28 weeks	Clinical response/clinical remission	53.1% (19% with response prior to escalation)/25.0% (6% in remission prior)
Vermeire *et al* [67]	57	Crohn's	LOR	Single-arm open label-multicentre	4 weekly 300 mg	28 weeks	Clinical Response/Clinical Remission	54.4% (39% with response prior to escalation)/22.8% (4% in remission prior)
Vaughn *et al* [68]	58	Crohn's or UC	LOR	Retrospective cohort study-multicentre	4-7 weekly 300 mg	15 weeks	Clinical Response	62.0%
Gouynou *et al*[69]	23	Crohn's or UC	PNR/LOR	Retrospective cohort study-single centre	NS-increased frequency	9 months	Clinical response	52.2%
Outtier *et al* [70]	59	Crohn's or UC	LOR	Prospective observational study-multicentre	4 weekly 300 mg	8 weeks	Clinical response	54.2%
Kolehmainen *et al*[71]	36	Crohn's or UC	PNR/LOR	Retrospective cohort study-single centre	NS-increased frequency	12 months	Clinical response	33.3%
Perry *et al*[23]	24	UC	PNR/Partial Responder	Retrospective cohort study-single centre	4 weekly 300 mg	51 weeks	Clinical response/corticosteroid free remission	41.7%/41.7%
Christensen *et al*[72]	43	Crohn's or UC	NS	Prospective cohort study-single centre	4 or 6 weekly 300 mg	26 weeks	Clinical response/clinical remission	58.1%/55.8%
Dreesen *et al* [74]	16	Crohn's or UC	NS	Retrospective cohort study-single centre	4 weekly 300 mg	14 weeks (UC), 22 weeks (Crohn's)	Clinical response	56.3%
Kopylov *et al* [73]	48	Crohn's or UC	NS	Retrospective cohort study-multicentre	4 weekly 300 mg	52 weeks	Clinical response	62.5%
Williet *et al* [75]	15	Crohn's or UC	PNR	Prospective cohort study-single centre	4 weekly 300 mg	36 weeks	Clinical response	53.8%
Attauabi *et al* [76]	37	Crohn's or UC	LOR	Retrospective cohort study-2 centre	4-7 weekly 300 mg	< 70 weeks	Clinical remission	62.2%
Jairath *et al* [77]	55	UC	PNR	Open label multicentre RCT	4 weekly 300mg or 600 mg	30 weeks	Clinical response/clinical remission	30.9/9.1%
Trials: Ustekinumab frequency								
Dalal *et al*[41]	75	Crohn's	LOR	Retrospective cohort study-single centre	4 or 6 weekly 90 mg	12 months	Corticosteroid free clinical remission	54.7%
Derikx *et al* [48]	47	Crohn's	NS	Retrospective cohort study-single centre	4 or 6 weekly 90 mg	8.9 months	Corticosteroid free remission	29.6%
Bundschuh *et al*[98]	27	Crohn's	LOR	Retrospective cohort study	4 or 6 weekly 90 mg	NS	Clinical response	54.5%
Haider *et al* [100]	15	Crohn's	PNR	Retrospective cohort study-single centre	4 weekly 90 mg	78 weeks	Clinical response/clinical remission	46.6%/33.3%

Fumery *et al* [101]	100	Crohn's	Partial Response/LOR	Retrospective cohort study-single centre	4 weekly 90 mg	2.4 months	Clinical response/clinical remission	61%/31%
Ollech *et al* [102]	51	Crohn's	NS	Retrospective cohort study-single centre	4 weekly 90 mg	5.9 months	Clinical remission	27.5%
Dalal *et al*[96]	157 (Crohn's: 117, UC: 40)	Crohn's or UC	Partial Response/LOR	Retrospective cohort study-single centre	4 or 6 weekly 90 mg	12 months	Steroid free clinical remission	Crohn's 57.3%/UC 52.5%
Rowbotham *et al*[107]	24	UC	NS	Randomised-withdrawal maintenance study	8 weekly 90 mg	16 weeks	Clinical remission	58.3%
Trials: Ustekinumab reinduction								
Sedano *et al* [109]	15	Crohn's	Partial Response/LOR	Retrospective cohort study-single centre	IV reinduction	14.9 weeks	Clinical response/clinical remission	66.7%/53.3%
Heron *et al* [110]	65	Crohn's	Partial Response/LOR	Retrospective cohort study - multicentre	IV reinduction	14 weeks	Clinical Remission with either biochemical and endoscopic response or remission	31.0%
Bermejo *et al* [111]	43	Crohn's	LOR	Retrospective cohort study-multicentre	IV re-induction	16 weeks	Clinical response/clinical remission	52.8%/43.3%
Ten Bokkel *et al*[112]	29	Crohn's	LOR	Prospective cohort study-multicentre	IV re-induction	52 weeks	Clinical remission	44.8%
Trials: Ustekinumab increased frequency and/or reinduction								
Cohen *et al* [99]	68	Crohn's	PNR/Partial Response	Retrospective cohort study-single centre	IV induction + 4 or 6 weekly 90 mg	3-6 months	Clinical response/clinical remission	79.4%/30.9%
Yao *et al*[114]	128	Crohn's	Partial Response/LOR	Retrospective cohort study-single centre	4 weekly 90 mg +/- IV Re-induction	3 months	Clinical remission	62.9% Shortening/69.6% re-induction
Hudson *et al* [113]	18	Crohn's	SLOR	Retrospective case series-single centre	IV re-induction +/- 4 or 6 weekly 90 mg	4-8 weeks	Clinical remission or response	83.3%
Ramaswamy *et al*[106]	31	Crohn's	Partial response/LOR	Retrospective cohort study-single centre	4 weekly 90 mg +/- IV re-induction	12 weeks	Clinical response	64.5%
Chaparro *et al*[40]	60	Crohn's	PNR/LOR	Retrospective cohort study-multicentre	4 weekly 90 mg /IV re-induction	NS	Clinical remission	78.3%
Ma *et al*[115]	24	Crohn's	LOR	Retrospective cohort study-multicentre	4 or 6 weekly 90 mg +/- IV reinduction	NS	Clinical response	54.2%
Young *et al* [97]	21	Crohn's	PNR/LOR/partial response	Retrospective cohort study-single centre	4 or 6 weekly 90 mg +/- IV induction	177 days	Clinical response	52.4%
Johnson *et al* [103]	229	Crohn's	PNR/LOR	Retrospective cohort study-multicentre	4 or 6 weekly 90 mg + IV reinduction/IV reinduction	NS	Clinical response	45.9%
Olmedo *et al* [104]	91	Crohn's	PNR/LOR	Retrospective cohort study-multicentre	4 or 6 weekly 90 mg + IV reinduction	16 weeks	Steroid free clinical response/Steroid free clinical remission	62.6%/25.3%
Kopylov *et al* [105]	142	Crohn's	NS	Retrospective cohort study-multicentre	4 or 6 weekly 90 mg +/- IV induction	16 weeks	Clinical response/clinical remission	51.4%/38.7%
Trials: Tofacitinib dose escalation								
Ma *et al*[51]	71	UC	LOR	Prospective	10 mg BD	NS	Clinical response	54.9%

				cohort study-multicentre				
Honap *et al* [52]	19	UC	LOR	Retrospective cohort study-multicentre	10 mg BD	NS	Clinical response	47.4%
Sandborn *et al*[150]	57	UC	LOR	Prospective cohort study-multicentre	10 mg BD	12 months	Clinical response/clinical remission	64.9%/49.1%
Trials: Upadacitinib dose escalation								
Sandborn *et al*[151]	60	Crohn's	NS (inadequate response)	Phase II placebo controlled RCT	12 mg BD/24 mg BD IR	52 weeks	Clinical remissions	15% 12 mg BD/24 mg BD 39%
Panaccione *et al*[153]	190	UC	LOR/inadequate response	Prospective cohort study	30 mg ER daily	48 weeks	Clinical remission	27.9%

PNR: Primary non-response; LOR: Loss of response; BD: Twice a day; UC: Ulcerative colitis; ER: Extended release; IR: Immediate release; SLOR: Secondary loss of response.

However, a recent randomized control trial (RCT) including 278 UC patients reported that among patients with early nonresponse to vedolizumab (at week 6) and high drug clearance, vedolizumab dose escalation ranging from 300 mg to 600 mg every 4 to 6 weeks did not lead to higher rates of clinical remission and response. In fact, Jairath *et al* reported that approximately 10% of patients with early non-response achieved clinical remission at week 30 irrespective of the dose received[77]. The findings of this RCT may explain the heterogeneity of data regarding the correlation of vedolizumab trough levels with remission and support the fact that time on therapy with careful monitoring may be sufficient to ensure adequate response is eventually achieved rather than switching therapies.

Role of TDM: In 2017, post-hoc analysis of the GEMINI trial reported that higher vedolizumab serum concentrations were associated with higher remission rates after induction therapy in patients with moderately to severely active UC or CD[32]. These finding were confirmed in a prospective trial of 51 IBD patients which showed that vedolizumab trough levels were higher at weeks 6 and 22 in patients with combined clinical and endoscopic remission[78]. The correlation between vedolizumab levels and response has subsequently been described in further studies including an association with endoscopic response and histological healing[74,79-81]. Furthermore, observational studies describe the role of early vedolizumab trough level as a predictor for clinical[78,82-84] and histological remission[85] and the need for dose intensification within 6 months[75]. Interestingly a multicentre retrospective study of 58 patients with IBD with secondary LOR to vedolizumab reports reported an odds ratio of 3.7 for clinical response to dose escalation with vedolizumab concentration < 7.4 μg/mL compared to a vedolizumab concentration ≥ 7.4 μg/mL[68] and a small retrospective study of 23 patients showed that early changes in the pharmacokinetic profile of vedolizumab may predict recapture of response after dose optimization[69]. A prospective study of 47 primary non-responders to vedolizumab with IBD who were dose-escalated reported that all patients with vedolizumab trough levels < 19.0 mg/mL at week 6 required dose escalation and achieved clinical response 4 weeks later[75]. Furthermore, Singh *et al*[86] undertook a meta-analysis in UC patients which reported vedolizumab trough concentration ≥ 18.5-20.8 μg/mL at week 6, and ≥ 9.0-12.6 μg/mL during maintenance may be associated with clinical remission at week 14 and clinical/endoscopic/biochemical response or remission with maintenance therapy respectively. A systematic review by Cao *et al*[87] suggested a blood concentration of vedolizumab surpassing 25.0 μg/mL indicated mucosal healing in UC patients under maintenance therapy but was unable to provide a clear predictive cut-off value of blood concentration on mucosal healing or endoscopic remission under induction therapy in IBD reporting a range between 8.0 and 28.9 μg/mL.

Given these findings, it would appear TDM may have a role in monitoring response to treatment in vedolizumab and in determining mechanistic failure. However, more recent observational data has not found an association with trough vedolizumab levels and clinical remission[88,89]. A prospective study of 159 patients with IBD did not find a correlation between trough vedolizumab concentration and clinical remission among patients on maintenance therapy[89]. Furthermore, the utility of vedolizumab trough levels to guide dose escalation was explored by a multicentre retrospective study which found no difference in vedolizumab trough levels prior to optimisation among those reaching clinical remission compared with those with active disease after dose escalation[81]. Similar findings were reported in a prospective study that found baseline trough levels of vedolizumab were not predictive of clinical and biological response at weeks 4 and 8 to dose escalation[70].

Predictors of failure to respond to dose escalation: With this apparent equipoise, the role of vedolizumab drug monitoring to guide management and identify patients with mechanistic failure in IBD is unclear. Currently, there is also insufficient data to establish predictive factors for response to dose intensification. A prospective study of maintenance vedolizumab in UC reported that clinical improvement was similar magnitude following an increase in dosing frequency among TNF antagonist-naïve and TNF antagonist-failure subgroups, although the absolute rates of response were higher in the former group[66]. While a retrospective study of vedolizumab maintenance in IBD found that concurrent steroid use was associated with lower rates of clinical remission following dose escalation[68].

Further RCTs are required to clearly delineate the optimal frequency and dose for optimisation of vedolizumab therapy. With regards to TDM, further research is required to establish if TDM could aid in management of patients on vedolizumab and identify potential predictors for response to dose escalation. Currently, it appears that a strategy of persisting with therapy and possible dose escalation in patients with early nonresponse to therapy or following secondary LOR to treatment can overcome LOR to therapy.

Ustekinumab-management options for PNR/LOR

Ustekinumab is a humanised monoclonal antibody targeting the p40 subunit of IL-12 and IL-23[90]. The landmark UNITI trials established the utility of Ustekinumab in Crohn's disease and UC[90,91]. LOR also occurs with ustekinumab therapy[92,93] and is estimated to occur in 21% per person-year on standard dosing and 25% per person- year for dose interval shortened therapy[94]. Approximately 20% of patients will require dose-interval shortening during the maintenance therapy[95]. The optimal management of primary nonresponse and secondary LOR to standard ustekinumab dosing remains unclear[96]. Potential approaches include empiric dose intensification through reduction of dose interval, re-induction to recapture clinical response in both CD and UC or use of TDM as outlined below[41] (Table 1).

Dose-escalation: Treatment intensification with 4 weekly or 6 weekly ustekinumab to capture response in Crohn's disease is an established management strategy for LOR to therapy[41,48,97-106]. A multicentre study of 100 patients with active CD showed clinical remission at a median follow-up of 2.4 months in approximately 30% of patients following treatment intensification with ustekinumab 90 mg every 4 weeks for LOR or incomplete response[101]. Similar findings were also described in a recent retrospective study of 110 patients with CD which reported that shortening ustekinumab 90 mg dose interval to 4 weekly among 55 patients with PNR or LOR achieved clinical remission in 28% and endoscopic remission in 36% of patients at a median follow-up of 5.9 months[102]. Furthermore, Dalal *et al* reported in a retrospective study of 123 patients with Crohn's disease that dose intensification to both 4 weekly and 6 weekly is clinically effective with 50% of patients in both groups achieving corticosteroid-free clinical remission within 12 months[41]. The efficacy of treatment intensification of ustekinumab was further demonstrated in a recent large retrospective multicentre study including 1113 CD patients treated with ustekinumab which reported among 77 patients who experienced loss of remission and underwent dose optimisation 57% achieved clinical response and among 152 patients who were dose-optimized because of primary nonresponse or incomplete response to ustekinumab approximately 40% achieved clinical response[103].

While there is less evidence for dose intensification in UC, it still appears robust with a single retrospective cohort study including 123 patients with CD and 40 patients with UC which described corticosteroid free clinical remission rates > 50% among all CD and UC patients at 12 months after ustekinumab dose intensification and ≥ 40% at 24 months[96]. Rowbotham *et al*[107] report 58% rate of clinical remission at week 16 in UC patients with increase in frequency of ustekinumab to 8 weekly from 12 weekly.

Re-induction: Re-induction following LOR to ustekinumab in Crohn's is another strategy that can be used and is supported by several observational studies[105,108-113]. A retrospective study of 65 patients with Crohn's reported that clinical remission was achieved at week 14 in approximately 30% of patients even among those already on escalated maintenance dosing of ustekinumabevery 4 weeks[110]. A recent retrospective observational study of 128 patients with Crohn's which compared dose optimisation of ustekinumab by shortening interval or through intravenous reinduction reported greater increases in ustekinumab trough level and higher rates of clinical and endoscopic remission at 3 months with intravenous reinduction compared with shortening of drug intervals[114]. Similar findings were described in a retrospective observational study which reported that among patients with severe CD optimization of ustekinumab with 2 initial intravenous inductions was more effective than standard with clinical response and clinical remission rates of 92% and 88% respectively[115]. The findings suggest that even a temporary increase in the dose of ustekinumab therapy may be sufficient to recapture response to ustekinumab treatment so should be considered for patients losing response to therapy.

While more data is needed to delineate efficacy of dose optimisation of ustekinumab with reinduction as opposed to interval shortening and the role of dose optimisation, the findings of meta-analyses by Meserve *et al*[116] and Yang *et al* [94] provide strong evidence for a benefit to recapture clinical response with dose escalation in Crohn's disease following LOR or inadequate response.

Switch from subcutaneous to intravenous therapy or risankizumab: Switching from subcutaneous to intravenous ustekinumab or to therapies with a similar mechanism is an evolving area of practice with potential to overcome LOR to ustekinumab[117]. Argüelles-Arias *et al*[117] describe a clinical remission rate of approximately 43% with the use of intravenous ustekinumab maintenance following LOR to subcutaneous dosing. This is not unexpected given the established role of re-induction of ustekinumab[105,108-112] however further data is needed to support this switch from subcutaneous to intravenous ustekinumab. A switch from ustekinumab to risankizumab which isa selective inhibitor of the p40 subunit of IL-23 has shown potential in inducing early response in cases of treatment failure with ustekinumab as reported in recent case report[118].

Role of TDM: Despite some contrary findings regarding the association between trough levels and Crohn's disease response (clinical or biochemical)[119-123], there is robust evidence to suggest that ustekinumab trough levels correlate with clinical, biomarker and/or endoscopic response in Crohn's[124-139]. This was confirmed in meta-analysis which showed higher median ustekinumab trough concentrations occur in individuals who achieve clinical remission compared with those who do not achieve remission[140].

In UC, a single prospective study by Adedokun *et al*[129] evaluates ustekinumab levels in UC describing dose-proportional serum concentrations of ustekinumab and association of serum concentrations with clinical and histologic response as well as normalization of inflammation markers.

However, despite these findings the role of TDM to guide ustekinumab therapy is limited. The significant variations between studies in reported ustekinumab levels to achieve response in conjunction with the heterogeneity in methods of reporting ustekinumab levels do not currently permit a clear cutoff value for defining a response to therapy[140]. Furthermore, there is only sparse data evaluating ustekinumab levels following dose escalation[110,123,133,141] and endoscopic remission was associated with an increase in ustekinumab levels in only one of these observational studies [133]. Interestingly, Hanžel *et al*[133] reported that patients with ustekinumab concentrations < 3.5 mg/L following dose optimisation were unlikely to achieve endoscopic or biochemical remission. There is currently a lack of data regarding optimal drug levels and drug level response to dose escalation with ustekinumab and further clinical studies are required in order to guide treatment.

Predictors for failure to respond to dose escalation: Given the current lack of sufficient data to utilise ustekinumab levels to guide therapy, factors including patient and disease characteristics may potentially be used to identify patients at risk of mechanistic failure. Dalal *et al*[41] reported that perianal disease, pre-intensification Harvey-Bradshaw Index, current opioid use, and current corticosteroid use were associated with ustekinumab failure after dose intensification in Crohn's disease. Heron *et al*[110] did not identify any predictors of clinical response or remission to ustekinumab reinduction and Cohen *et al*[99] described response to initial ustekinumab induction therapy as the only independent predictor of response to ustekinumab dose escalation. Therefore, while factor such as perianal disease and disease severity should be considered when considering dose-escalation of ustekinumab for LOR, there is insufficient evidence for these predictors to identify patients unlikely to respond to dose optimisation. Further research is required to establish predictors of response to ustekinumab dose escalation or reinduction as well as identifying a drug level that can reliably delineate patients with clinical remission. As a result, dose escalation or reinduction in patients with early nonresponse to ustekinumab therapy or following secondary LOR is a viable management option.

JAK-inhibitors-management options for PNR/LOR

In recent times the JAK inhibitors have emerged as efficacious therapy in IBD[142-144]. Tofacitinib is an oral, small molecule JAK inhibitor which inhibits all JAKs but preferentially inhibits JAK1 and JAK3[145] and upadacitinib is an oral selective reversible inhibitor of JAK1[146]. The landmark OCTAVE and U-ACHIEVE/U-ACCOMPLISH trials established the efficacy of tofacitinib and upadacitinib respectively in induction and maintenance of remission in UC[142,143] and Loftus *et al*[144] established the efficacy of upadacitinib in induction and maintenance therapy in Crohn's disease. Yet despite their efficacy, a significant portion of patients experience primary or secondary LOR with JAK Inhibitor therapy. There is a reported PNR rate of approximately 20% and LOR rate of 39% per person year in UC patients treated with tofacitinib[142,147]. With upadacitinib treatment there is a PNR rate of approximately 50% in Crohn's and 65%-75% in UC[143,144] (Table 1).

Dose escalation of tofacitinib: Higher numerical rates of remission (total mayo score ≤ 2) in UC have been noted at 40.6% with 10 mg twice daily dosing of tofacitinib compared to 34.3% with 5 mg twice daily tofacitinib during maintenance therapy[142]. Furthermore, dose-escalation of tofacitinib from 5 mg twice daily to 10 mg twice daily whilst on maintenance therapy can be effective in recapturing response to tofacitinib in patients with UC[51-53,148,149]. In fact, the OCTAVE long-term extension study reported that dose escalation to 10 mg bowel disease (BD) following treatment failure with 5 mg BD tofacitinib recaptured clinical response in approximately 65% of patients and clinical remission in approximately 50% at 12 months of escalated therapy[148]. Similarly in a retrospective study of patients with UC, Honap *et al*[52] and Ma *et al*[51] described recapture of response with dose-escalation of tofacitinib to 10mg BD in approximately half of patients who had lost response. However, in a post hoc analysis which evaluated tofacitinib treatment persistence in this same group described discontinuation among the dose escalation group of approximately 49% with a median time to discontinuation of 4.4 years[53]. In the setting of PNR, extended induction therapy from 8 weeks to 16 weeks of tofacitinib 10 mg BD is able to capture clinical response in 52.2% of patients at week 16[150].

Dose escalation of upadacitinib: The U-ACHIEVE and U-ENDURE trials both reported higher rates of remission with 30 mg upadacitinib compared to 15 mg upadacitinib[143,144]. Furthermore, early data from the phase 2 CELEST study in Crohn's disease reported that patients with inadequate response obtained clinical remission and endoscopic response with upadacitinib dose escalation[151]. Reassuringly, the long-term extension study of CELESTE described clinical remission at 30 months in 55% of patients dose escalated from 15 mg to 30 mg maintenance[152]. Panacionne *et al* also noted the efficacy of dosing escalation of upadacitinib to 30 mg daily for LOR or inadequate response with clinical remission following escalation in 30% of UC patients at 48 weeks[153]. Extended induction therapy for PNR from 8 weeks to 16 weeks of upadacitinib 45 mg daily is able to capture clinical response in 46.6% of patients at week 16[154].

Switch between JAK inhibitors: Furthermore, the addition of upadacitinib as a treatment option for UC permits within drug class switching following treatment failure of tofacitinib with PNR or LOR. Two small case series have reported clinical remission with upadacitinib in UC patients with PNR or LOR to tofacitinib[155,156]. Furthermore a prospective study of 26 patients with IBD reported that upadacitinib was effective in inducing clinical and biochemical remission following primary or secondary nonresponse to tofacitinib[157]. There are currently no published studies assessing the efficacy of switching from upadacitinib to tofacitinib following PNR or LOR.

Role of TDM: Given the recent integration of the JAK Inhibitors in IBD therapeutic armamentarium the role of drug monitoring with JAK-Inhibitors is unclear[158]. Early pharmacokinetic studies of tofacitinib in UC reported that while plasma tofacitinib concentrations increased proportionately with dose there was no difference in tofacitinib concentrations at baseline versus at the end of induction at week 8 and that tofacitinib concentrations did not differ with clinical remission at specific doses[159].

Further studies are needed to elucidate the role of TDM and the association between drug levels and clinical remission. Additional clinical research will also be essential to establish predictors for mechanistic failure with JAK-inhibitors to guide treatment decisions. However currently dose escalation of both tofacitinib and upadacitinib or in-class switching both represent potential methods of recapturing response.

Ozanimod/S1P receptor modulators-management options for PNR/LOR

Ozanimod and etrasimod are selective S1P receptor modulators of S1P1 and S1P5[160] and S1P1, S1P4 and S1P5[57] respectively. S1P receptor modulators have recently emerged as therapeutic options for induction and maintenance of remission in UC[57,161]. There are no studies evaluating management of LOR and secondary nonresponse with S1P receptor modulators.

DISCUSSION

As with TNF-inhibitor therapy, patients with suspected PNR and LOR to non-TNFi advanced therapy require detailed assessment to exclude other causes of symptoms and to assess disease activity[10,58].

In PNR and LOR to vedolizumab therapy, it appears reasonable to increase frequency of vedolizumab dosing[23,68-77]. While increasing the frequency of vedolizumab 300 mg to 6 weekly and 4 weekly may both be effective strategies[68,72,76], we favour an increase to 4 weekly dosing, if available, in order to maximise likelihood of capturing response and minimise risk of prolonging futile therapy. The role for TDM prior to vedolizumab dose optimisation is not yet established but may be used depending on availability. There is significant heterogeneity in reported drug levels which correlate with clinical remission[75,86,87] and conflicting data regarding the utility of drug levels to predict clinical remission[88,89] and response to dose escalation[70,81]. We propose assessing for response to vedolizumab at approximately 12-24 weeks to allow adequate time for effect of vedolizumab dose escalation[68,70,72,74]. If clinical response is not captured by 24 weeks, we suggest switching therapy (Figure 1).

Once PNR/LOR is confirmed with ustekinumab therapy, options to capture response include increasing dose frequency, intravenous reinduction or a combination of both. While increasing the frequency of ustekinumab 90 mg to 4 weekly or 6 weekly is an effective method of capturing response in the setting of PNR/LOR[41,48,96,98,100-102,107], we favour an increase to 4 weekly dosing, if available, in order to maximise likelihood of capturing response with a view to consider reducing dose at a later stage if remission is achieved and sustained. Intravenous reinduction of ustekinumab is effective for recapturing response in LOR but not PNR[109-112] and consequently in the setting of PNR intravenous reinduction should be combined with increased frequency of ustekinumab[97,99,103-106,113,114]. While ustekinumab levels appear to be positively correlated with response[124-139] there are significant variations in the reporting of levels to achieve clinical remission, which make it more difficult to use levels to guide therapy[140]. Response to ustekinumab should be assessed at approximately 12-24 weeks to allow adequate time for the effect of dose escalation to be assessed [97,99,104-107,109-111,114]. If clinical response is not captured at 24 weeks, we suggest confirming LOR with objective measures and consideration for switching to an alternate therapy (Figure 2).

In the setting of PNR to tofacitinib extended induction to 16 weeks from 8 weeks may be an effective means of inducing clinical response[150]. Where patients have LOR with tofacitinib, dose optimisation to 10 mg BD is an effective means of recapturing response[51,52,148]. We suggest assessing for response can be performed as early as 8 weeks after treatment adjustment given the rapid onset of action of tofacitinib, although some people may take many months to respond as response rates continue to increase up until 12 months after dose escalation of tofacitinib[142,148]. If clinical response is captured at reassessment, we suggest continuing tofacitinib therapy otherwise we suggest utilisation of an alternate therapy.

In the setting of PNR to upadacitinib extended induction to 16 weeks from 8 weeks may be an effective means of inducing clinical response[154]. Following LOR with upadacitinib, dose optimisation to 30 mg daily effectively recaptures response in about[152,153]. An assessment for response can occur as early as 8 weeks, although some patients may take longer to respond and response rates continue to increase to 52 weeks of additional treatment at 30 mg daily, so consideration in the clinical context of whether a patient should continue treatment would be on a case by case basis[144]. We suggest continuing upadacitinib therapy if response is captured at the time of reassessment, otherwise an alternate therapy should be considered.

CONCLUSION

With significant shifts in the treatment paradigm of IBD over the last decade, there remains many unanswered questions regarding the optimal treatment algorithm with non-TNF-i advanced therapy. In this review we propose practical algorithms for the management of PNR and secondary LOR to non-TNF-i advanced therapy. Further clinical research and real-world experience is required to optimise these treatment pathways and to establish the role of TDM to better identify

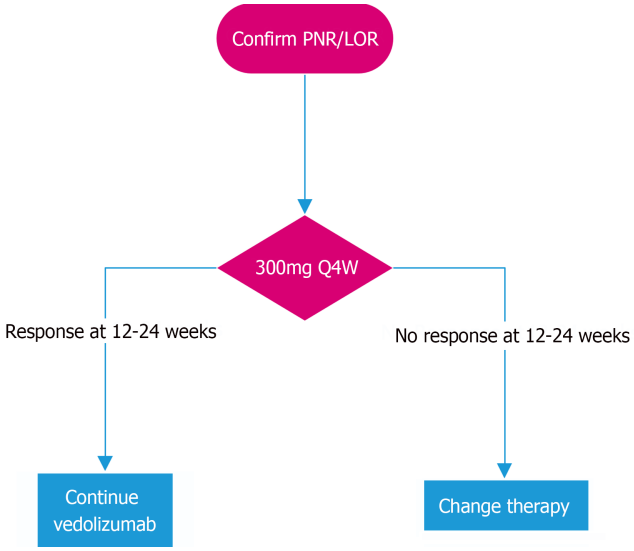

Figure 1 Management of loss of response to vedolizumab. PNR: Primary non-response; LOR: Loss of response.

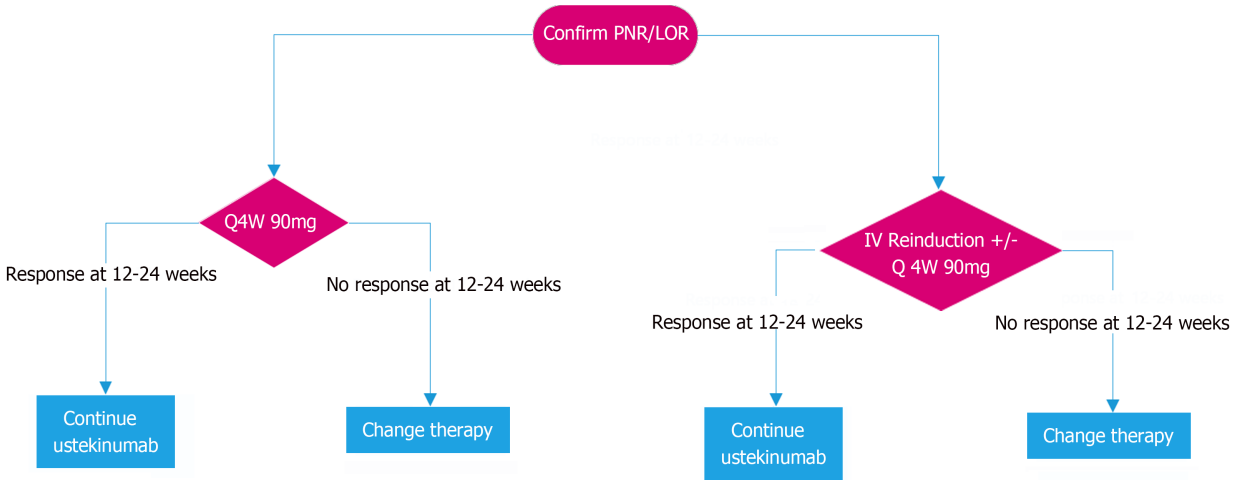

Figure 2 Management of loss of response to ustekinumab. PNR: Primary non-response; LOR: Loss of response.

patients who will not respond to dose optimisation. This knowledge will help minimise risk of prolonging futile therapy with dose escalation while also ensuring advanced therapies are not prematurely discarded in the absence of evidence of irrecoverable non-response.

FOOTNOTES

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LETTER TO THE EDITOR

Is endoscopic ultrasound a promising technique in the diagnosis and treatment of liver diseases?

Enver Zerem, Željko Puljiz, Boris Zdilar, Suad Kunosic, Admir Kurtcehajic, Omar Zerem

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Abstract

Percutaneous ultrasound has been a longstanding method in the diagnostics and interventional procedures of liver diseases. In some countries, its use is restricted to radiologists, limiting access for other clinicians, such as gastroenterologists. Endoscopic ultrasound, as a novel technique, plays a crucial role in diagnosis and treatment of digestive diseases. However, its use is sometimes recommended for conditions where no clear advantage over percutaneous ultrasound exists, leaving the impression that clinicians sometimes resort to an endoscopic approach due to the unavailability of percutaneous options.

Key Words: Endoscopic ultrasound; Percutaneous ultrasound; Liver biopsy; Fine needle aspiration; Focal liver lesion; Liver abscess drainage

Core Tip: Endoscopic ultrasound is crucial in managing digestive diseases. Yet, its application is occasionally advised in scenarios where it lacks superiority over percutaneous ultrasound. This editorial reviews the paper published in the *World Journal of Gastroenterology* in 2024, to discuss its findings and implications.

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TO THE EDITOR

Upon reading the article by Gadour *et al*[1], a comment emerged. The article thoroughly reviews and summarizes the current evidence on the roles of endoscopic ultrasound (EUS) in accurately diagnosing liver disease as well as its therapeutic accuracy and efficacy[1]. They concluded that EUS is a promising technique with potential to be a first-line option for diagnosis and treatment in a subset of liver diseases. This comprehensive review effectively highlights EUS as a safe and effective method in various interventions performed for the diagnosis and/or treatment of liver diseases[1].

The results of this systematic review suggest that EUS may be the method of first choice for the diagnosis and treatment of liver disease and that it has advantages over percutaneous ultrasound (US) in certain diagnostic and interventional procedures. However, direct comparisons between EUS and percutaneous US in the diagnosis and treatment of liver disease are scarce[2-4], and, according to our best knowledge, the only randomized clinical trial directly comparing the two techniques demonstrates the advantage of percutaneous US[5]. Albeit we recognize the robust design and execution, this study[1], also, primarily encompasses retrospective and prospective.

We are certain in EUS' importance in managing digestive diseases[6-8]. However, its application is occasionally advised in scenarios where it lacks superiority over percutaneous US. Having extensive experience in liver disease management[9], we believe that EUS does not surpass conventional percutaneous US in efficacy for liver-related diagnostic and therapeutic procedures and that it can rather rarely be considered as a first-line option during those interventions. Our stance is based on the following considerations:

The liver's location in the abdomen generally allows for better visualization and interventional access *via* percutaneous US compared to EUS, particularly for most of its segments except for possibly segments I, II, and VI. Moreover, segments VII and VIII are positioned such that visualization and the feasibility of conducting interventional procedures using EUS are notably challenging.

For liver lesions, it is preferable to drain pathological contents externally rather than into the gastrointestinal tract, especially if the content is infectious or potentially malignant. The sole exception is bile drainage in cases of obstructive jaundice[9].

Monitoring and catheter manipulation in patients with infectious complications or other drainage issues, irrigating liver abscess collections through a catheter with antiseptic or normal saline, and the cytological, microbiological, and biochemical analysis of the obtained content are considerably challenging or impractical with an endoscopic approach, unlike with percutaneous US procedures[9].

Percutaneous US involves much simpler training compared to EUS, which necessitates proficiency in both endoscopic and US techniques. It is a technically straightforward and cost-effective method, considerably easier to master than EUS which requires comprehensive training in both US and endoscopy[9].

Finally, we would like to highlight that, while EUS is effective, we believe that percutaneous US has more advantages, suggesting it as the first choice in the diagnostic and therapeutic procedures in liver diseases, except for obstructive jaundice cases. EUS is recommended only in rare occasions when percutaneous US is not an option. Future studies, especially randomized clinical trials comparing both techniques, are encouraged to clarify their roles in managing liver diseases more definitively.

FOOTNOTES

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LETTER TO THE EDITOR

Interaction between inflammatory bowel disease, physical activity, and myokines: Assessment of serum irisin levels

Marwan SM Al-Nimer

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Abstract

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, showed a wide spectrum of intestinal and extra-intestinal manifestations, which rendered the patients physically inactive and impaired their quality of life. It has been found that physical activity is a non-pharmacological intervention that improves the quality of life for those patients. Irisin is one member of the myokines secreted by muscle contraction during exercise and could be used as an anti-inflammatory biomarker in assessing the physical activity of IBD patients. In addition, experimental studies showed that exogenous irisin significantly decreased the inflammatory markers and the histological changes of the intestinal mucosa observed in experimental colitis. Furthermore, irisin produces changes in the diversity of the microbiota. Therefore, endogenous or exogenous irisin, *via* its anti-inflammatory effects, will improve the health of IBD patients and will limit the barriers to physical activity in patients with IBD.

Key Words: Irisin; Inflammatory bowel disease; Physical activity; Myokines; Prognostic marker

Core Tip: Irisin is a sports hormone secreted with muscle contraction and serves as an anti-inflammatory biomarker as well as attenuating the intestinal microbiota diversity. Low serum levels of irisin were observed in patients with ulcerative colitis, which can be increased with physical activity. Physical activity is useful in patients presented with extra-intestinal manifestations of inflammatory bowel disease (IBD). Exogenous irisin may overcome the barriers of physical activity in IBD, producing beneficial anti-inflammatory effects and attenuating the microbiota diversity.

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TO THE EDITOR

I read with great interest an elegant editorial by Stafie *et al*[1] who commented on the article published in an issue of the *World Journal of Gastroenterology*[2]. Stafie *et al*[1], made a good comment, and they highlighted certain aspects of the barriers to physical activity (PA) in the relapse of inflammatory bowel diseases (IBD). Recent studies showed that PA can be assessed in laboratories by measuring specific markers named myokines. Therefore, it will be useful to fill the gap on the role of PA in IBD by supplementing the commentary with changes in the myokine levels in IBD patients who were doing any PA.

IBD are emerging as a significant global health concern as their incidence continues to rise on a global scale, with detrimental impacts on quality of life[2]. One of the extra-intestinal manifestations of the IBD is musculoskeletal manifestations that occurred as peripheral arthritis, axial spondyloarthritis (ax-SpA), and enthesitis[3]. It has been found that PA significantly and positively impacts the ax-SpA, improving the quality of life[4]. Therefore, PA is a useful non-pharmacological intervention that combats the SpA in IBD, and it is worth trying to look for a biological marker that indicates the benefit of PA in IBD presented with SpA as a comorbidity of extra-intestinal manifestations (EIMs)[3]. It is possible to use the levels of myokines, notably the serum levels of irisin, as a marker for the training or limitation of PA in patients with IBD. Irisin is a member of the myokines derived from the FNDC5 protein, which is produced by myocytes and secreted into the circulation in response to muscle contraction[5]. It is important to know that the irisin levels increased following the exercise, but they did not maintain their higher levels for the long period that followed the exercise[6].

Figure 1 shows the beneficial interactions between the IBD and their EIMs with the production of irisin by PA or using exogenous irisin. Lower serum levels of irisin were significantly observed in patients with ax-SpA presented with sacroilitis and negative HLA-B27 status and who were treated with non-steroidal anti-inflammatory drugs[7]. Exercises trigger the production of irisin, which is sometimes called sport hormone, and play a role in decreasing the inflammation associated with the risk factors of systematic diseases, *e.g.*, non-alcoholic fatty liver disease[8], obesity[9], heart diseases [10,11], *etc.*

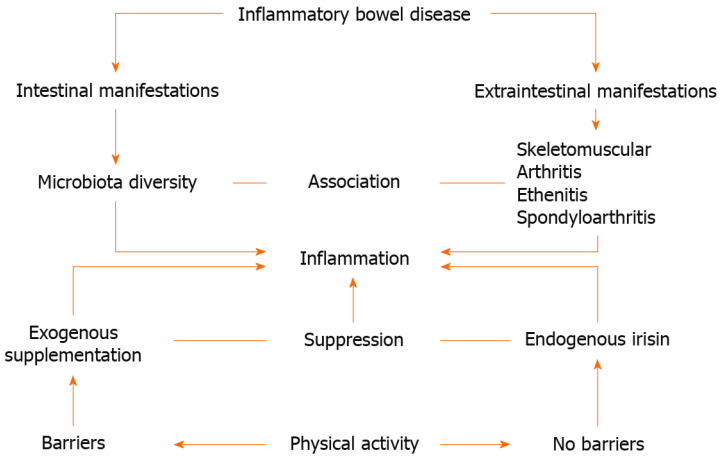

Figure 1 The interactions between irisin, physical activity, and the manifestations of the inflammatory bowel disease.

In an experimental animal model of 2,4,6-trinitrobenzenesulfonic acid colitits fed a high-fat diet, exercised mice showed significantly higher levels of irisin, which is associated with decreased histological changes of the intestinal mucosa, increased colonic blood flow, and attenuation of the plasma levels of inflammatory markers compared with sedentary mice[12]. In an experimental animal model of ulcerative colitis, it has been found that exogenous irisin modulates the intestinal microbiota (by altering the diversity of microorganisms in the stool) and suppresses inflammation in the intestinal mucosa, indicating that irisin has anti-inflammatory properties[13]. It has been suggested that the anti-inflammatory effects of irisin are related to the inhibition of cytotoxicity and apoptosis *via* inhibiting the mitogen-activated protein kinase pathway[14]. The sports activity is a barrier for patients with active Crohn's disease (intestinal manifestations) because it flares up the symptoms[15]. Some authors believe that the barriers to sports medicine are related to psychosocial factors and alterations in the physiological responses to exercise, characterized by a lower sympathetic tone and body temperature[16]. In the scoping review, which included 28 articles, the authors recommended that moderately intense PA is a useful non-pharmacological intervention to improve the quality of life and attenuate the

activity of Crohn's disease[17]. Another scoping review highlighted an important issue about the accuracy of the assessment of the health-related physical fitness status of patients with Crohn's disease due to some limitations in the intensity and type of PA[18]. There is no evidence for using exogenous irisin as an anti-inflammatory medicine in patients with Crohn's disease; therefore, exogenous irisin could be used as a nutriceutical and pharmacological anti-inflammatory medicine[19], as well as a biomarker for certain diseases and PA. In conclusion, PA is a non-pharmacological therapeutic tool in the management of the IBD as it suppressed the inflammation; attenuating the diversity of intestinal microbiota; reliving the symptoms of skeletomuscular complaint. The effects of exogenous irisin, which is still under experimental studies, are similar to the effects of PA and it may substitute the PA in IBD patients with limitations to do exercises.

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