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EDITORIAL

Emerging space for non-polyethene-glycol bowel preparations in inflammatory bowel disease-related colonoscopy: Veering toward better adherence and palatability

Raffaele Pellegrino, Antonietta Gerarda Gravina

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Abstract

Patients with inflammatory bowel diseases (IBDs) require repeated endoscopic evaluations over time by colonoscopy to weigh disease activity but also for different and additional indications (*e.g.*, evaluation of postoperative recurrence, colorectal cancer surveillance). Colonoscopy, however, requires adequate bowel preparation to be of quality. The latter is achieved as long as the patient takes a certain amount of product to have a number of bowel movements suitable to clean the colon and allow optimal visualization of the mucosa during endoscopy. However, significant guidelines recommend preparations for patients with IBD not excelling in palatability. This recommendation originates from the fact that most of the studies conducted on bowel preparations in patients with IBD have been done with isosmolar preparations based on polyethylene glycol (PEG), for which, therefore, more safety data exist. As a result, the low-volume non-PEG preparations (*e.g.*, magnesium citrate plus picosulphate, oral sulphate solutions) have been set aside for the whole range of warnings to be heeded because of their hyperosmolarity. New studies, however, are emerging, leaning in overall for a paradigm shift in this matter. Indeed, such non-PEG preparations seem to show a particularly encouraging and engaging safety profile when considering their broad potential for tolerability and patient preference. Indeed, such evidence is insufficient to indicate such preparations in all patients with IBD but may pave the way for those with remission or well-controlled disease. This article summarizes the central studies conducted in IBD settings using non-PEG preparations by discussing their results.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Bowel preparation; Colonoscopy; Polyethylene glycol; Low-volume

Core Tip: Preparations based on polyethylene glycol (PEG) are most recommended for patients with inflammatory bowel disease (IBD) undergoing colonoscopy. However, these solutions are not always palatable because they often require the intake of large volumes of solution, making it difficult for the patient to complete the entire preparation. This leads to a reduction in the quality of the endoscopic examination. Low-volume non-PEG-based, although excluded in the major guidelines for patients with IBD, are emerging as potentially safe in this setting, especially in remission or mild disease conditions.

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INTRODUCTION

Quality colonoscopy in the inflammatory bowel disease (IBD) patient has adequate bowel preparation as an essential prerequisite. Colonoscopy is, in fact, an imperative examination of IBD and encompasses a long list of indications, among which initial diagnosis, patient follow-up to weigh response to therapy, and colorectal cancer surveillance are recognized [1-4]. Bowel preparation requires the patient to take an oral formulation of varying constitution and volume to obtain a functional number of bowel movements to determine the cleanliness of rectal, colonic and ileal segments that can be explored by colonoscopy[5]. However, new retrograde modalities are emerging (*i.e.* colonic lavage)[6]. The pharmacodynamics of bowel preparations require patient compliance so that the patient ingests the entire formulation and follows any complementary indications (*i.e.* a low-fiber diet).

As a result, it tends to follow that patients' preferred preparations are those with lower volume, good taste (palatable), suitable dose dilution over time (*e.g.*, split dose), and good safety profile such that they do not experience symptoms while taking the product[7].

However, the widely recommended preparations for patients with IBD are low (< 3 L) or high volume (at least 3 L) polyethylene glycol (PEG)-based preparations[5]. This choice, while not axiomatically pursuing the goal of palatability, is necessary because most studies in IBD are available for this type of preparation and because safety studies have shown a significantly better safety profile for PEG solutions than for non-PEG-based solutions (*e.g.*, magnesium citrate plus picosulphate, oral sulfate solutions)[8].

This paradigm, which has been going on for several years, has the potential to change the view of the new studies that are increasingly emerging on non-PEG-based and low-volume solutions.

WHAT PROFILE DO NON-PEG SOLUTIONS HAVE IN IBD?

Non-PEG preparations ordinarily have osmotic power, which partly affects their safety profile compared to isosmolar PEG solutions, especially for electrolyte disturbances[5,9] and mucosal damage[5]. PEG preparations are based on the principle that they, being nonabsorbable and isosmolar fluids, result in minimal electrolyte and fluid absorption or secretion by the gastrointestinal wall. Therefore, to achieve a purgative effect, they must generally be used in large volumes[10]. The opposite principle applies to non-PEG preparations in that their cleansing effect is based precisely on osmotic potency rather than on accumulating nonabsorbable fluids[10]. Despite this, in a general sense, low-volume non-PEG preparations have several potential advantages for the patient employing them for colonoscopy.

First and foremost, these preparations do not have the disadvantage of requiring large volumes of preparation associated with lower adherence and patient preference or gastrointestinal overload symptoms (*e.g.*, nausea, vomiting, abdominal pain) that often prevent completion of the preparation[11]. Additionally, PEG solutions are often poorly palatable due to their salty taste[12]. The more excellent tolerability of non-PEG low-volume solutions compared with PEG-based preparations has also been demonstrated in a large meta-analysis of more than 20 randomized placebo-controlled trials in which, in terms of efficacy, these were also found to be non-inferior to PEG solutions[13].

However, several studies are already available for non-PEG low-volume preparations in IBD (Table 1). These studies have produced compelling results in both clinical trial settings and real-world ones on such bowel preparation efficacy/effectiveness rates and safety.

For example, the prospective CLEAN study in 2019 provided some results about sodium, magnesium and potassium sulphate (trisulphate solutions), sodium phosphate and sodium picosulphate preparations in 119 IBD patients[14]. In all the above regimens, patients had followed a split regimen and a low-fiber diet before colonoscopy in more than half of the cases. In only 18 cases, however, the indication was a flare-up of IBD, and, as a result, most of the patients had a Mayo endoscopic subscore[15] of less than 2 (*i.e.* endoscopically inactive IBD). Picosulphate preparation showed, in this study, a higher mean Boston bowel preparation scale[16] than 2 or 4 L PEG solutions (*i.e.* increased cleaning capacity). The safety profile, within the limit of low numbers, was acceptable in comparison with PEG preparations. Regarding tolerability, however, sodium picosulfate showed substantially more excellent palatability as well as less nausea, vomiting, and bloating.

Table 1 Summary of studies that examined non-polyethylene glycol-based bowel preparations in patients with inflammatory bowel diseases

Ref.	Bowel preparation	IBD sample size	IBD type, *n*	Sample age	IBD duration	Disease activity trend	Split regimen as Y/N or %	Clear diet as Y/N or %
Briot *et al* [14], 2019	MPS, NaP, PicoS	12 (MPS), 26 (NaP), 80 (PicoS)	CD: 8 (MPS), 14 (NaP), 57 (PicoS); UC: 4 (MPS), 11 (NaP), 21 (PicoS); Undetermined IBD: 1 (NaP), 2 (PicoS)	Median: 42.9 (MPS), 41 (NaP), 40.8 (PicoS)	13.9 yr (MPS), 12.9 yr (NaP), 10.6 yr (PicoS)	Remission, mild	58.3% (MPS), 84.6% (NaP), 55.6% (PicoS)	100% (MPS), 100% (NaP), 95.1% (PicoS)
Mohsen *et al*[17], 2021	PicoS + magnesium citrate + PEG	61	N/A	Mean: 39.7	N/A	Unknown	Y	Y
Rueda García *et al* [18], 2023	PicoS	31	CD: 18, UC: 12: Undetermined IBD: 1	Mean: 51.7	N/A	Mild	Y	Y
Kim *et al* [19], 2022	OST	55	CD: 18, UC: 37	Mean: 44.4	93.2 mo	Remission, mild	Y	Y
Lee *et al* [20], 2023	OSS	92	UC: 92	Mean: 47.9	7 yr	Remission, mild	Y	Y

CD: Crohn's disease; IBD: Inflammatory bowel disease; MPS: Sodium, magnesium, and potassium sulphates; N: No; N/A: Not applicable; NaP: Sodium phosphate; PEG: Polyethylene glycol; PicoS: Sodium picosulphate; OSS: Oral sulphate solution; OST: Oral sulphate tablet; UC: Ulcerative colitis; Y: Yes.

Mohsen *et al*[17] also later weighed the efficacy and safety of an osmotically active solution of sodium picosulphate and magnesium citrate (with PEG added) in 56 patients with IBD. These determined less abdominal pain than the PEG-ascorbate comparison, albeit with a greater serum increase in magnesium and no significant differences in efficacy and safety between the groups. This study, however, did not operate a particular stratification by colonoscopy indication type and IBD activity. Another trial (*i.e.* EII-PREP) showed promising results regarding sodium picosulphate but, unfortunately, in only 31 IBD patients[18].

In a subsequent trial targeting patients with inactive IBD, Kim *et al*[19] reported a lower bubble score rate in the novel oral sulphate table preparations and higher palatability (including a willingness to reuse the preparation for subsequent colonoscopy) than the PEG-ascorbate comparison. The problem of bubbles is another technical aspect to consider when discussing mucosal visibility, so much so that the use of simethicone for this purpose is bleached out by European guidelines and also found beneficial for IBD[5,8].

The safety and efficacy profile was comparable. Lee *et al*[20] also reported a similar efficacy and safety profile (even considering changes in serum electrolytes) between novel oral sulphate solution and PEG-ascorbate in 92 patients with inactive ulcerative colitis.

WHAT PROBLEMS PLAGUE NON-PEG PREPARATIONS, AND WHAT IS THE MISSING PIECE OF THE PUZZLE TO ALLOW THEM FULL USE IN IBD?

Studies evaluating non-PEG preparations, specifically in the population with IBD *vs* the counterpart PEG preparations, have shown some homogeneity in reporting good palatability, tolerability, and safety results.

However, there are some drawbacks to consider. Such studies are generally conducted in low sample size settings. This phenomenon poses the problem of requiring more and more evidence from studies with larger samples and, therefore, greater statistical power and generalizability. The absence of recommendations for non-PEG preparations by major guidelines also limits the use of these preparations in clinical practice and thus counteracts the conduct of real-world studies weighing the real-life effectiveness of these preparations by adding new data[5].

In addition, in the available studies, the different disease activity IBD subgroups are not well represented, sometimes unreported and not always weighted by scores widely recognized as usable in IBD (*e.g.*, partial and total Mayo scores, Crohn's disease index of severity, Harvey-Bradshaw index[15]).

Moreover, most available studies enrolled patients with mild or no endoscopic activity. This severely limits interpretation in cases of moderate and moderate-severe endoscopic activity. Indeed, the problem does not arise for severe acute activity since, in those cases, at most, rectoscopy is enough to perform endoscopic evaluation and exclude over-infections (*e.g.*, cytomegalovirus).

One of the reasons for European guidelines to deny the indication of non-PEG solutions in IBD is that they have been described to be associated with a risk of mucosal damage about ten times higher than PEG solutions[5].

However, this recommendation, although seemingly supportable, encapsulates in the definition of IBD the broad spectrum of different degrees of endoscopic activity. Therefore, a conditional stratification of recommendations that

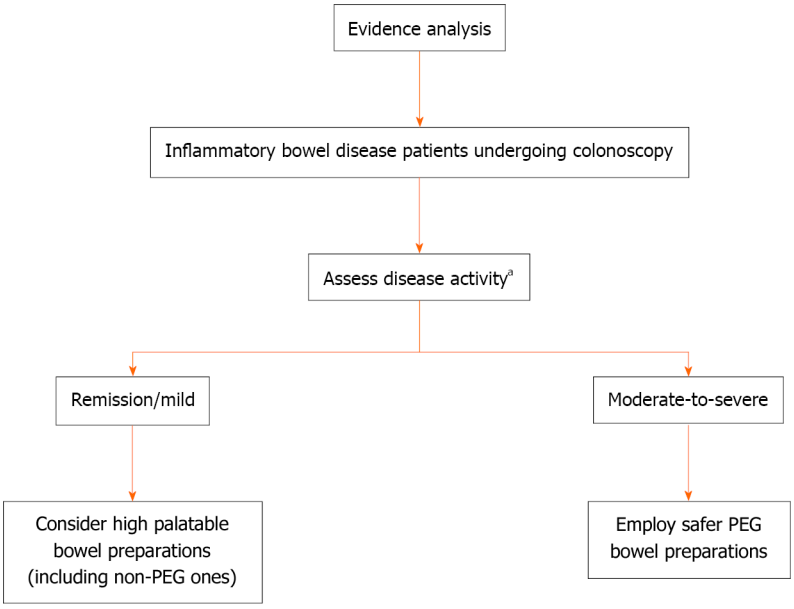

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Figure 1 Stratification hypothesis on the indication of non-polyethylene glycol-based bowel preparations in patients with inflammatory bowel diseases. [a]Disease activity should be determined by instruments explicitly designed for inflammatory bowel diseases (*e.g.*, partial Mayo score, Crohn's disease index of severity, Harvey-Bradshaw index). PEG: Polyethylene glycol.

considers a balance of the efficacy/safety profile for individual indications for colonoscopy should probably be advocated. In other words, one cannot treat an indication for assessment of disease activity (perhaps in a patient with moderate-severe clinical and biochemical activity) and an oncologic surveillance colonoscopy performed in a long-term remission setting in the same way. In the former case, safety weighs more than efficacy since the primary purpose of the endoscopist is to consider disease activity to select treatment, and the mucosal status is already objectively compromised variably. In the second case, where the disease is already well controlled, and the patient has a colon much closer to that of the healthy population, it is undoubtedly efficacy a parameter to observe (especially in patients without safety concerns) as a colonoscopy with a lower quality of bowel preparation may significantly reduce the adenoma detection rate[21]. This evaluation becomes even more relevant compared to high-volume centers performing high-quality chromoendoscopy for surveillance colonoscopy in IBD patients.

A large proportion of patients with IBD receive the diagnosis at a young age and are largely destined for repeated endoscopic evaluations over time. The most recent treat-to-target strategies[22] place endoscopic outcomes among the pillars for eventual IBD treatment discontinuation or switch. For such patients, therefore, under conditions where there are no particular safety red flags, palatable bowel preparations should be reserved, and research should move in this direction. The current evidence, even better if evaluated meta-analytically, could potentially argue for a modification of the recommendations in future guideline updates, probably by including those with IBD in stable remission, or at most in already known mild endoscopic activity, in the pool of patients who can take advantage of low-volume non-PEG preparations. These evaluations are tentative and need to be weighed by *ad hoc* meta-analyses that consider the efficacy-safety ratio of non-PEG low-volume solutions against the current standard of care to assess whether the formulation of recommendations (even with low evidence level) is possible.

CONCLUSION

New evidence has emerged regarding using non-PEG-based bowel preparations for colonoscopy in patients with IBD. Although limited by initial data, these preparations appear to possess sustainable and potentially safe use in patients with IBD in remission or with mild activity with no particular safety concerns of adverse events or post-colonoscopy flare-ups. However, net of this, major guidelines, including the European ones, indicate and recommend only PEG solutions for patients with IBD, encompassing all patients with IBD in this indication without making stratifications based on disease activity. Future guidelines for bowel preparation should weigh whether the currently available studies allow such stratification (Figure 1) by opening the possibility for patients with well-controlled IBD to the use of more palatable preparations for better patient compliance, greater validity of colonoscopy with adequate bowel preparation, and ultimately for greater patient comfort.

FOOTNOTES

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REVIEW

Frailty in end-stage liver disease: Understanding pathophysiology, tools for assessment, and strategies for management

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Abstract

Frailty and sarcopenia are frequently observed in patients with end-stage liver disease. Frailty is a complex condition that arises from deteriorations across various physiological systems, including the musculoskeletal, cardiovascular, and immune systems, resulting in a reduced ability of the body to withstand stressors. This condition is associated with declined resilience and increased vulnerability to negative outcomes, including disability, hospitalization, and mortality. In cirrhotic patients, frailty is influenced by multiple factors, such as hyperammonemia, hormonal imbalance, malnutrition, ascites, hepatic encephalopathy, and alcohol intake. Assessing frailty is crucial in predicting morbidity and mortality in cirrhotic patients. It can aid in making critical decisions regarding patients' eligibility for critical care and transplantation. This, in turn, can guide the development of an individualized treatment plan for each patient with cirrhosis, with a focus on prioritizing exercise, proper nutrition, and appropriate treatment of hepatic complications as the primary lines of treatment. In this review, we aim to explore the topic of frailty in liver diseases, with a particular emphasis on pathophysiology, clinical assessment, and discuss strategies for preventing frailty through effective treatment of hepatic complications. Furthermore, we explore novel assessment and management strategies that have emerged in recent years, including the use of wearable technology and telemedicine.

Key Words: End-stage liver disease; Frailty; Liver cirrhosis; Malnutrition; Sarcopenia

Core Tip: Frailty is a common condition in patients with cirrhosis, and it is associated with increased morbidity and mortality. This review provides a comprehensive overview of the etiology, pathophysiology, assessment, and management of frailty in cirrhosis. It places particular emphasis on the management of frailty during complications, while also delving into the future of managing this condition.

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INTRODUCTION

Frailty is a complex and ever-evolving syndrome that arises from a combination of deteriorating events across various physiological systems. This results in a reduction in the body's physical ability to withstand stressors, leading to decreased resilience and increased susceptibility to adverse outcomes such as disability, hospitalization, and mortality[1-3]. Half of the patients diagnosed with cirrhosis of any cause exhibit frailty[4]. This condition has been shown to have a significant impact on the health outcomes of individuals with liver diseases, leading to higher rates of morbidity and mortality[5]. Despite its importance, there is still a lack of knowledge in the field of frailty in liver cirrhosis and an absence of universal assessment and treatment protocols, especially in the presence of decompensation with ascites and encephalopathy. This review offers an analysis of the pathophysiological mechanisms that give rise to the clinical manifestations of frailty, various assessment tools employed to evaluate frailty in patients with cirrhosis, and highlights the management options available for frail cirrhotic patients including future therapeutic options for this condition.

DEFINITION OF FRAILTY

Although frailty, sarcopenia, malnutrition, and cachexia are distinct terms in literature, they are deeply interconnected [6]. All four terminologies can be used to express patients with muscle loss and measures targeting management of any of these conditions can improve the others[7]. Here is a breakdown of each terminology (Table 1).

PATHOPHYSIOLOGY OF FRAILTY IN END-STAGE LIVER DISEASE

The precise reason for frailty in liver disease is not known, but it is thought to result from the failure of several organ systems, including the neuromuscular, endocrine, immune, and skeletal muscle systems[17] (Figure 1). In this section, we outline a brief overview of different factors that have been cited in literature as potential causes of frailty in cirrhosis[17,18].

Hyperammonemia

Hyperammonemia is a major factor that induces sarcopenia and frailty in patients with liver cirrhosis[19-21]. There are multiple mechanisms through which hyperammonemia can contribute to frailty in individuals with cirrhosis. These mechanisms include upregulation of myostatin expression inhibiting skeletal muscle mass, mitochondrial dysfunction, heightened production of reactive oxygen species that impede protein synthesis, and enhanced proteolysis[22,23].

Hormonal disturbance

Testosterone plays a crucial role in activating the Akt/mTOR pathway, which is responsible for the development and maintenance of muscle tissue[24]. Individuals with cirrhosis often experience low levels of circulating testosterone. This can be attributed to the detrimental effects of cirrhosis on the hypothalamic-pituitary-gonadal axis[25]. Additionally, an increased activity of the hepatic aromatase enzyme converts testosterone into estrogen, further contributing to the decline in testosterone levels and subsequent loss of muscle mass[26]. Moreover, research has shown that androgens suppress the expression of myostatin, a key inhibitor of muscle mass[27,28]. This explains the elevated levels of myostatin in cirrhosis patients which contributes to their muscle mass loss[29].

Insulin resistance is a common occurrence in individuals with cirrhosis, as supported by the literature[30]. Insulin resistance can lead to muscle loss through several mechanisms. Insulin has anabolic effects on muscle tissue. But, when there is insulin resistance, it reduces its ability to stimulate protein synthesis, resulting in muscle mass loss[31]. Insulin resistance can also impair mitochondrial function, leading to decreased energy availability and further promoting muscle loss[32]. Finally, individuals with insulin resistance may be less physically active, which can cause muscle atrophy and a decline in muscle function[33]. All these factors contribute to the development of muscle mass loss and frailty in patients with cirrhosis.

Table 1 Definition of frailty, different types of sarcopenias, malnourishment, and cachexia

	Definition
Frailty	A condition where patients undergo a reduction in their physical abilities and become more vulnerable to health-related challenges, leading to negative health consequences. It is a multifaceted concept that involves different aspects such as physical, psychological, social, and environmental factors[8]
Malnourishment	An imbalance in the consumption of nutrients, whether it be a deficiency or an excess, can have detrimental effects on the body's tissues and overall physical form[9]
Cachexia	A metabolic syndrome that is complex and linked to an underlying illness. It is distinguished by the reduction of muscle mass, with or without a decrease in fat mass[10]
Sarcopenia	A debilitating syndrome that is marked by a gradual and widespread decline in both skeletal muscle mass and strength[11]
Dynapenia	The pre-sarcopenia stage, in which only muscle strength is reduced[12]
Primary sarcopenia	The loss of anatomical skeletal muscle mass in the aging population[13]
Secondary sarcopenia	The loss of skeletal muscle mass in various chronic diseases[14]
Compound sarcopenia	The combination of primary (*i.e.*, age-related) and secondary (*i.e.*, disease-related) sarcopenia. It occurs in older patients with chronic diseases[15]
Sarcopenic obesity	A state of decreased muscle mass in the setting of increased fat mass. The muscle wasting can be obscured by increased muscle mass, making specialized testing and management necessary[16]

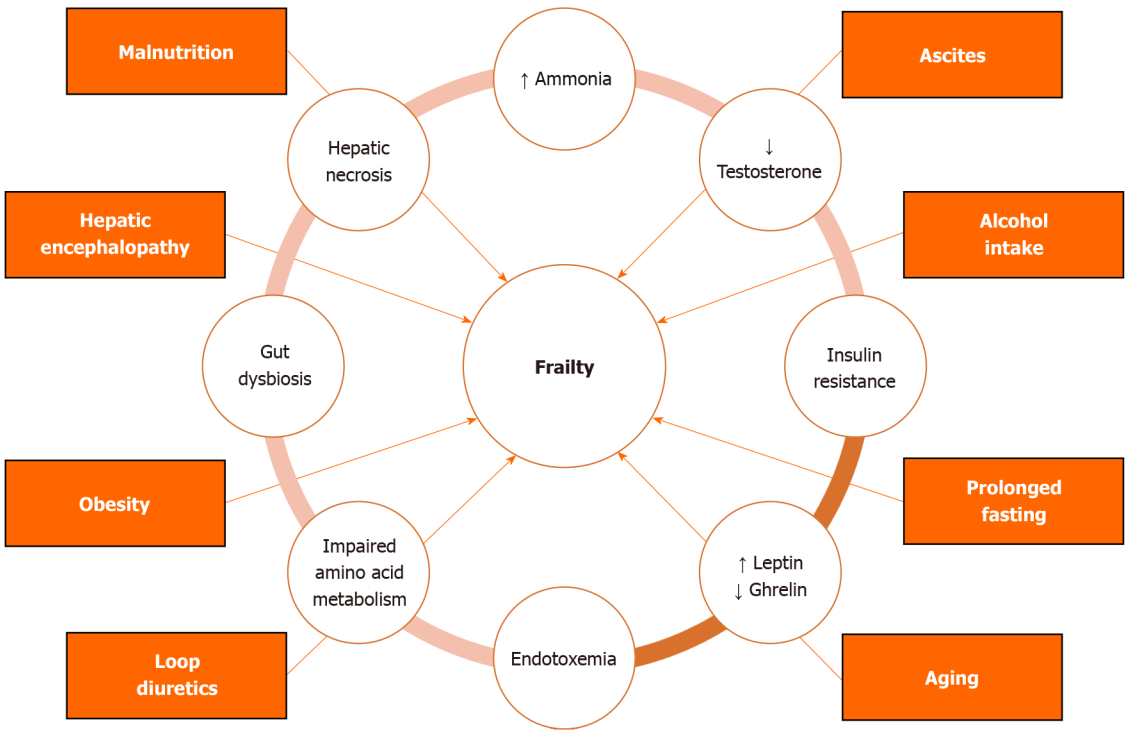

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Figure 1 Pathophysiology of frailty in advanced liver disease.

Leptin and ghrelin are two hormones that play a crucial role in regulating energy balance, appetite, and body weight [34]. Leptin, which is produced mainly by adipose tissue, functions by suppressing hunger and promoting satiety[35]. In individuals with cirrhosis, there is typically an elevation in serum leptin levels, which can contribute to frailty by decreasing appetite, altering energy balance, and causing muscle wasting[36]. Conversely, ghrelin, which stimulates hunger, gastric motility, and gastric acid secretion, is found to be reduced in liver cirrhosis compared to healthy individuals[37,38]. These changes can affect satiety, digestive functions, and muscle mass, which predispose individuals with cirrhosis to frailty.

Proinflammatory mediators

Liver diseases trigger proinflammatory mediators release due to hepatic necrosis and endotoxemia. In advanced liver disease, the death of liver cells triggers the recruitment of immune cells such as macrophages and neutrophils[39]. This

leads to an increase in the production of substances promoting inflammation, such as cytokines, resulting in inflammation both locally and systemically[40]. Additionally, patients with cirrhosis have elevated levels of proinflammatory mediators due to endotoxemia[41]. This occurs when bacterial endotoxins circulate in the bloodstream due to impaired gut barrier function[42], portosystemic shunts[43], compromised Kupffer cell function[44], and altered gut microbiota [45]. The presence of endotoxemia triggers the release of tumor necrosis factor-alpha, interleukin-6, and reactive oxygen species which promote systemic inflammation, cause oxidative stress, and impair mitochondrial function[43,46]. The presence of these proinflammatory mediators can give rise to various frailty components, including muscle wasting, loss of appetite, fatigue, energy deficiency, and impaired immune function[18].

Gut microbiota dysbiosis

The human gut is a complex ecosystem that harbors a diverse array of microbial species, which engage in multifaceted interactions with our body[47]. One of the key benefits provided by the gut microbiota is their remarkable ability to ferment indigestible substances, such as dietary fibers, yielding short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate. Moreover, the gut microbiota plays a pivotal role in generating a wide range of metabolites, including secondary bile acids and indols[48]. These metabolites, along with bacterial components, can circulate throughout the human body, exerting their influence on organs beyond the gut itself[49]. In the context of cirrhosis, there is a notable prevalence of gut dysbiosis, which involves an imbalance in the gut microbiota. This imbalance is marked by a decrease in the diversity of bacterial species and an overall reduction in the number of bacteria present in the gut[50,51].

In cirrhotic patients, dysbiosis plays a significant role in frailty development through various mechanisms[52-55]. Firstly, the presence of a high proportion of harmful bacteria in the gut can lead to systemic inflammation as bacterial lipopolysaccharides translocate through the compromised gut barriers[56,57]. This inflammation can cause muscle wasting and energy deficiency, further contributing to frailty. Secondly, individuals with cirrhosis often have a lower abundance of beneficial gut bacteria, which reduces their capacity to contribute to metabolism. This reduction leads to a decrease in the production of SCFAs, which are not only essential as an energy source but also serve as metabolic mediators in skeletal muscles[58-60]. The decrease in SCFAs may contribute to the observed skeletal muscle loss in cirrhotic patients and further exacerbate the development of frailty[61]. Lastly, small intestinal bacterial overgrowth (SIBO) is common in cirrhosis, and the increased population of gut microbes can lead to heightened competition with the human body for nutrients[62]. This competition can worsen the loss of muscle mass and frailty, as evidenced by the link between SIBO and malnutrition in cirrhosis[63].

Impaired amino acids metabolism

Amino acid metabolism is a crucial process that plays a vital role in maintaining energy balance, promoting muscle growth, and regulating critical processes such as inflammation and insulin sensitivity[64,65]. When this process is disrupted, it can lead to the development of frailty and degenerative diseases[66]. Individuals with liver cirrhosis experience imbalances in body metabolism, resulting in higher levels of fatty acid oxidation and gluconeogenesis. This leads to an imbalance in amino acid metabolism, causing changes in amino acid levels in the blood[67,68]. As a consequence, there are low levels of branched-chain amino acids (BCAAs) in the blood, which are essential for muscle tissue. BCAAs are crucial for protein synthesis in skeletal muscles and serve as a preferred source of energy. Therefore, low levels of BCAAs in the blood can lead to muscle degradation and impaired muscle strength[69]. Moreover, patients with end-stage liver disease (ESLD) have impaired ammonia detoxification in the liver, leading to high levels of ammonia in the blood. To compensate for this, the body breaks down BCAAs stored in skeletal muscles to help eliminate ammonia [70]. This constant consumption of BCAAs further contributes to low levels of BCAAs in the blood, leading to sarcopenia and frailty. Fortunately, supplementing with BCAAs has shown significant benefits for individuals with liver cirrhosis and frailty. In a recent 16-wk randomized controlled trial, BCAA supplementation was found to improve the liver frailty index (LFI), serum albumin levels, and quality of life in frail compensated cirrhotic patients[69]. This finding is consistent with previous studies that have used BCAAs as a therapy for sarcopenia in liver cirrhosis[71,72].

PREDISPOSING FACTORS FOR FRAILTY IN CIRRHOSIS

Malnutrition

Cirrhosis often leads to malnutrition, which is associated with negative consequences[73]. Malnutrition in cirrhosis has various contributing factors, including inadequate oral intake, early satiety caused by ascites, imbalance in ghrelin and leptin levels, maldigestion, malabsorption, gut microbial dysbiosis, and encephalopathy[73,74]. Frailty is strongly associated with malnutrition. Research has shown that malnourished patients have a 3.381 times higher risk of developing frailty compared to well-nourished patients[75].

Ascites

In cirrhotic patients, ascites can cause several symptoms such as loss of appetite, difficulty moving, reduced stomach capacity, and poor digestion[76] (Table 2). These symptoms can ultimately result in malnutrition and frailty. However, therapeutic paracentesis has been shown to effectively counteract these effects and provide several benefits for cirrhotic patients, including improving appetite, decreasing feelings of fullness, enhancing caloric intake, and improving exercise tolerance[77]. Large-volume paracentesis can increase fasting gastric volumes, which leads to better tolerance of nutrient ingestion and improved caloric intake[78]. This could potentially be explained by the procedure providing more space for

Table 2 Pathophysiology, effects, and management recommendations for frailty predisposing factors in cirrhosis

Predisposing factor	Pathophysiology	Morbidity and mortality	Recommendations
Ascites	Loss of appetite; Difficult ambulation; Reduced stomach capacity; Poor digestion	Odds of frailty were higher in ascitic than non-ascitic patients [adjusted odd ratio 1.56, 95% confidence interval (CI): 1.15-2.14][129]. Ascitic patients identified as frail had a 29% waitlist mortality rate, higher than the 17% rate for non-frail patients[129]	Large volume paracentesis with iv albumin; Salt intake not < 5 g NaCl/d to preserve food palatability
Hepatic encephalopathy (HE)	Decreased voluntary oral intake; Decreased capacity for ambulance and exercise	Odds of frailty were higher in HE than in non-HE patients (odd ratio 2.45, 95%CI: 1.80-3.33)[129]. Waitlist mortality was higher for HE patients identified as frail (30%) than non-frail (20%)[129]	Enteral nutrition with precautions to avoid aspiration and hyperglycemia; Parenteral nutrition if indicated; Avoid unnecessary protein restriction
Alcohol intake	Decreased oral intake; Gastrointestinal upset; Vitamin and mineral deficiency; Increased resting energy expenditure; Alcohol direct toxic muscular and neurologic effects	Frail alcoholic liver disease patients had a significantly higher risk of death or liver transplantation compared to non-frail patients ($P < 0.001$)[130]	Alcohol abstinence; Healthy diet with approximately 30 kcal/kg to 40 kcal/kg per day; Small and frequent meals; Enteral feeding in severe disease
Sarcopenic obesity	Challenging to diagnose; Physical disability due to decreased muscle size and high muscle fat	MASLD cirrhotic patients have an increased risk of worsening frailty over time and higher waitlist mortality than non-MASLD patients[131]	Structured exercise program to help preserve muscle mass; If caloric restriction is necessary, maintain adequate protein intake (1.2-1.5 g/kg/d)
Prolonged fasting	Accelerated catabolic state with Increased muscle breakdown		Limit fasting period to a maximum of 12 h; Daily calorie intake should be divided into 4-6 meals; Late evening snacks
Loop diuretics	May worsen muscle mass loss	Loop diuretics inversely correlated with skeletal muscle mass in cirrhotic patients ($P < 0.0001$) and high doses were independently associated with mortality [126]	Regular frailty assessments are recommended for patients who have been on prolonged courses of loop diuretics, particularly when the dosage exceeds 20 mg/d; Spironolactone may be a preferable option for long-term use due to its promising efficacy in treating sarcopenia
Aging	Combined muscle loss due to aging and hepatic illness (compound sarcopenia)	Elderly sarcopenic patients with cirrhosis have longer hospital stays, higher hospitalization costs, and increased risk of in-hospital mortality[15]	Frequent frailty assessment and management in elderly patients with cirrhosis

MASLD: Metabolic dysfunction-associated steatotic liver disease.

the stomach to relax within the peritoneal cavity with albumin infusion helping relieve gastric wall edema[78].

Salt restriction is currently a crucial component of ascites treatment at all stages, as it helps prevent sodium overload and promotes the mobilization of fluid retention[79,80]. Previous studies have indicated that a tight restriction of sodium intake (< 5 g salt daily) can result in a reduced need for diuretics, faster resolution of ascites, and shorter hospital stays [81-83]. However, strict sodium restriction may not always be the optimal approach for managing ascites in cirrhotic patients. A study by Gauthier *et al*[81] provides an example of this. The researchers conducted a trial on patients who were receiving diuretic treatment. They compared the resolution of ascites in a group with strict salt restriction (only 1230 mg salt daily) to a group with no sodium restriction[81]. Surprisingly, despite the rapid resolution of ascites in the restricted salt group at the beginning of the study, there was no significant difference between the two groups after 90 d [81].

While strict sodium restriction has demonstrated short-term benefits, it may increase the risk of sarcopenia and frailty in cirrhotic patients due to the unpleasant taste of food and the additional effort required for food acquisition and preparation, ultimately resulting in a loss of appetite[81,84-86]. This can lead to malnutrition and an increased risk of developing ascites. Two randomized controlled trials have provided strong evidence that adhering to a strict low-salt diet increases the risk of malnutrition and can worsen ascites in cirrhotic patients[87,88]. In a study conducted by Gu *et al*[87], the disappearance of ascites in cirrhotic patients was compared between a group with restricted salt intake and a group with unrestricted salt intake. The results demonstrated that cirrhotic patients in the unrestricted salt group (8.8 g NaCl/d) consumed more calories than those in the restricted salt group (4.2 g NaCl/d), leading to higher albumin levels with better nutritional status and rapidly resolving ascites[87]. These findings suggest that strict salt restriction may not always be the optimal approach for managing ascites in cirrhotic patients. Instead, individualized dietary recommendations are necessary to ensure adequate patient nutrition and prevent complications[84]. For this reason, leading hepatology scientific societies recommend a daily salt intake of no less than 5 g NaCl/d (equivalent to 2 g Na/d) for cirrhotic patients with ascites[79,89-92]. To meet the recommended salt intake, it is highly recommended to avoid consuming canned foods or pre-packaged meals. Instead, prioritize the consumption of fresh, home-cooked dishes that are rich in fruits, vegetables, and dairy products[93]. Furthermore, to enhance the flavor of meals it is advised to substitute salt with a

variety of herbs and spices[84].

Hepatic encephalopathy

Patients with hepatic encephalopathy are at a high risk of malnutrition and frailty due to a decrease in voluntary oral intake[94]. This can result in longer hospital stays, worsening of their condition, and increased susceptibility to infections [95]. When dealing with such cases, enteral nutrition is advised, but it is important to take precautions to avoid the risk of aspiration and hyperglycemia[7]. Parenteral nutrition, on the other hand, should only be used for patients who are unable to tolerate enteral feeding or cannot meet their caloric and nutrient needs orally[7].

It is important to note that protein intake should not be restricted in patients with encephalopathy[7]. While there used to be a debate about whether protein supplementation could worsen hepatic encephalopathy, recent research has shown that protein does not cause encephalopathy and may even improve cognitive function in the long term[96,97]. On the contrary, restricting protein intake could exacerbate frailty[7]. Therefore, to avoid the risk of worsening frailty, it is generally recommended that patients consume protein from a diverse range of sources, including vegetables and dairy products[98]. The American Association for the Study of Liver Diseases (AASLD) suggests that adults with cirrhosis should consume 1.2-1.5 g of protein per kilogram of ideal body weight daily[7,97]. However, for critically ill cirrhotic patients, the recommended protein intake is slightly higher, ranging from 1.2-2.0 g/kg of ideal body weight daily[7]. For children with cirrhosis, a protein intake of up to 4 g/kg of body weight per day is both safe and successful in improving anthropometric measurements without the development of hepatic encephalopathy[99].

Alcohol intake

Alcohol consumption has a significant and complex impact on nutritional status, affecting both nutrient intake and absorption. Initially, alcohol itself contributes to approximately 50% of daily caloric intake, leading to a decreased intake of other essential nutrients[100]. Moreover, alcohol-induced anorexia, nausea, vomiting, and gastritis exacerbate the situation by further reducing oral intake of nutrients. Alcohol also interferes directly with nutrient absorption by damaging the mucosal lining of the stomach and small intestine[101]. This damage impairs the absorption of important nutrients such as protein, vitamins A, B1, B12, folic acid, and zinc, leading to deficiencies of these micronutrients and vitamins in individuals with alcohol-associated liver disease (ALD)[98,100]. Furthermore, chronic alcohol consumption has been found to increase resting energy expenditure, which over time can lead to significant muscle wasting and frailty [102]. These factors cause malnutrition and frailty in alcohol-related cirrhosis, which has a detrimental impact on survival rates and quality of life, with an increased risk of various complications. These include variceal bleeding, development of ascites and hepatic encephalopathy, susceptibility to infections, longer hospital stays, and occurrence of hepatorenal syndrome[103].

Given the multifaceted impact of alcohol on liver diseases and nutritional status, lifelong abstinence is recommended [104]. Additionally, it is crucial to address nutritional deficiencies and promote a healthy diet in individuals with ALD [105]. This can help to mitigate the negative effects of alcohol on nutrient intake and absorption, as well as prevent muscle wasting and frailty. To prevent these issues, current guidelines recommend approximately 30 kcal/kg to 40 kcal/kg per day for these patients, with an emphasis on small, frequent meals as some patients may not be able to tolerate large meals three times a day[106]. In severe cases of ALD, supplementation in the form of enteral nutrition should be considered to ensure adequate nutrition and prevent complications associated with malnutrition[107].

Metabolic dysfunction-associated steatotic liver disease and sarcopenic obesity

Sarcopenic obesity is a condition where there is a simultaneous loss of skeletal muscle and gain of adipose tissue, which is a common finding in patients with cirrhosis[108]. This condition is characterized by a decrease in muscle size and an increase in muscular fat, known as myosteatosis. It can be challenging to diagnose, particularly in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), as the presence of morbid obesity can obscure the signs of sarcopenia, making it difficult to detect[109]. Sarcopenic obesity has detrimental effects on the morbidity and mortality of patients with liver cirrhosis[108]. It poses a greater risk of physical impairment and disability than either sarcopenia or myosteatosis alone, and it is considered a negative prognostic marker for the progression of liver cirrhosis and outcomes of liver transplantation[110]. Additionally, both sarcopenia and myosteatosis are associated with a higher risk of long-term mortality in cirrhosis[108].To manage sarcopenia and MASLD, increasing physical activity and following a healthy diet can be helpful[111].

Currently, there are no specific exercise recommendations available for cirrhotic patients with sarcopenic obesity[112]. However, several studies have indicated that exercise can have positive effects on these patients[113-115]. These studies have shown that exercise can lead to a reduction in body weight and fat mass, as well as an improvement in skeletal muscle mass and physical capacity in patients with cirrhosis. These positive outcomes are particularly advantageous for patients with sarcopenic obesity. In a randomized controlled trial conducted by Román *et al*[114], functional capacity, body composition, and the risk of falls were measured in patients with cirrhosis before and after a moderate exercise program. The results of the study demonstrated that the exercise group experienced significant improvements in functional capacity, increased muscle mass, decreased body fat, and a reduced risk of falls, while no changes were observed in the control group[114]. Studies have also shown that elderly men who engage in moderate-to-vigorous exercise for at least thirty minutes a day have a lower risk of developing sarcopenic obesity[116]. Therefore, it can be concluded that a moderate exercise program can be beneficial for patients with cirrhosis, especially those with sarcopenic obesity. Additionally, while cirrhotic patients with sarcopenic obesity have increased body mass index (BMI) and body fat, it is important to be cautious when recommending weight loss to affected patients, in order not to exacerbate frailty [16]. If caloric restriction is deemed necessary, it is imperative to closely monitor the body composition, muscle strength,

and physical activity levels of these individuals using appropriate assessment tools[117]. Moreover, it is recommended to implement a comprehensive approach that includes ensuring adequate protein intake (1.2-1.5 g/kg/d) and applying a structured exercise program to help preserve muscle mass and promote overall health[7].

Prolonged fasting

Individuals with cirrhosis experience a more rapid breakdown of their body tissues due to starvation than healthy individuals[118]. After an overnight fast, the type of energy sources utilized by cirrhotic patients is comparable to that of healthy individuals who have been fasting for 2-3 d[119]. This implies that cirrhotic patients who undergo medical procedures, such as gastrointestinal endoscopy, with prolonged fasting are at risk of developing a severe catabolic state, which can lead to the breakdown of their body tissues[118]. Therefore, it is recommended that patients with liver cirrhosis limit their fasting period to a maximum of 12 h[120,121]. It is also advised that their daily calorie intake should be divided into 4-6 meals, which can include snacks at night[122,123]. This dietary approach can help maintain stable blood sugar levels and prevent the breakdown of body tissues due to prolonged fasting[118].

Diuretics

The evidence supporting the notion that loop diuretics may worsen sarcopenia and frailty is mounting. For instance, a study discovered that bumetanide and furosemide administration had an adverse effect on myogenic differentiation and exercise-induced muscle hypertrophy[124]. Additionally, loop diuretics have been associated with a decrease in thigh and arm circumference among heart failure patients, regardless of the severity of their disease[125]. Furthermore, a retrospective study involving 266 cirrhotic patients found that high doses of loop diuretics were associated with rapid muscle mass loss and poor survival rates, independent of liver disease severity[126]. This study found that therapeutic dosages of loop diuretics were inversely correlated with skeletal muscle mass in cirrhotic patients, as demonstrated by both simple ($r = -0.27$, $P < 0.0001$) and multiple regression analyses ($t = -3.07$, $P = 0.002$)[126]. Patients receiving more than 20 mg of loop diuretics per day had lower overall survival rates compared to those receiving < 20 mg (median, 66 mo *vs* 97 mo; $P = 0.002$), and higher doses of loop diuretics were independently associated with mortality among cirrhotic patients [hazard ratio, 1.86; 95% confidence interval (CI): 1.03-3.24; $P = 0.039$][126]. Compared to loop diuretics, spironolactone has been suggested to have potential benefits in preventing muscle mass loss, enhancing muscle blood flow, and boosting contractile power[127]. Given these findings, future research needs to investigate the impact of different types of diuretics on muscle health, particularly in patients who are on long-term or high-dose loop diuretic therapy, with regular assessments of frailty.

Aging and compound sarcopenia

The loss of muscle mass due to aging, known as primary sarcopenia, and the loss of muscle mass due to chronic illness, known as secondary sarcopenia, combine to form a health condition called compound sarcopenia[15]. This condition can have a significant impact on the clinical outcomes of older adults with chronic diseases[128]. In patients with hospitalized cirrhotic patients, compound sarcopenia has been associated with increased length and cost of hospital stay with detrimental effects on patient survival[15]. As a result, it is crucial to regularly assess and provide aggressive treatment for elderly patients with sarcopenia.

INFLUENCE OF FRAILTY ON CIRRHOSIS PATIENTS

Depression and reduced quality of life

Frailty is a condition that is associated with reduced cognitive abilities, increased risk of falls, and lower quality of life [132-134]. Depression is a common occurrence in patients with ESLD and is closely linked to frailty, rather than the severity of liver disease[135]. A prospective cohort study was conducted on 542 patients with ESLD who were referred for liver transplantation to investigate the relationship between frailty, depression, and the severity of liver disease[135]. The study found a significant association between frailty and depression, with an odds ratio of 2.78, $P < 0.001$. However, no significant association was found between the Model for End-Stage Liver Disease (MELD) score and depression[135]. This highlights the importance of addressing frailty as a potential risk factor for depression in patients with ESLD.

In another study, the relationship between frailty and disability was examined in cirrhotic individuals receiving outpatient care. Disability was evaluated through the measurement of individuals' capacity to carry out essential activities of daily living (ADLs), such as feeding and bathing, as well as more complex tasks known as instrumental ADLs (IADLs), which encompass activities like shopping and managing finances. The study found a strong link between frailty and disability in patients with cirrhosis[136]. The LFI was used to measure frailty, and each point increase in the LFI was associated with a higher likelihood of experiencing difficulty with ADLs and IADLs[136]. The odds of experiencing current difficulty with at least one ADL and IADL were 3.3-fold and 4.6-fold higher, respectively, for each point increase in the LFI[136]. In participants who initially did not have any baseline disability, the study revealed that for every point increase in the LFI, the odds of having trouble with at least one ADL and IADL after 6 mo were 2.6 times and 1.7 times higher, respectively[136]. These findings suggest that even a slight increase in frailty can significantly impact the ability to perform essential tasks and responsibilities, thereby affecting both patients and their caregivers' quality of life.

Increased risk of cirrhosis complications and hospitalization

Frailty is a distinctive risk factor that is independently associated with a range of cirrhosis-related complications, such as

ascites, encephalopathy, hepatorenal syndrome, and sepsis, which often necessitate hospitalization[129,137,138]. Moreover, frailty has been linked to an increased risk of acquiring nosocomial infections[139]. Patients with significant frailty may require prolonged ICU and hospital stays, and they are more prone to respiratory complications and sepsis [140]. In a prospective study involving 373 pre-transplant patients, researchers found that gait speed, a measure of frailty, played a significant and influential role in the risk of hospitalization for various complications related to cirrhosis[138]. The study found that for every 0.1 m/s decrease in gait speed, there was a 22% increase in the number of hospital days ($P < 0.001$), indicating a robust correlation between frailty and the need for hospital care[138].

Increased risk of non-home discharge

Frailty has been identified as a significant risk factor for non-home discharge among hospitalized patients, which can lead to increased healthcare and financial burden[139]. The results of a prospective study conducted on 211 cirrhotic patients from three Liver transplantation centers revealed that frailty was strongly associated with discharge to physical rehabilitation, a skilled nursing facility, or hospice, rather than being discharged to the patient's home[139]. The study's odds ratio indicated that for every one-point increase in the LFI, the likelihood of non-home discharge increased by 1.81 times, (95%CI: 1.14-2.86)[139].

Increased risk of mortality

Frailty is an established factor that significantly increases the likelihood of severe complications and mortality among liver cirrhotic patients, both before and after liver transplantation[141]. In a comprehensive study conducted across nine transplant centers in the United States, researchers assessed frailty in pretransplant patients on the waitlist and found a significant correlation between the presence of frailty, as measured by the LFI, and an increased risk of mortality. Specifically, patients with frailty had an adjusted risk of death that was nearly twice as high as those without frailty (sub-hazard ratio 1.82, 95%CI: 1.31-2.52)[129]. Furthermore, a systematic review examining the impact of frailty on post-transplant mortality revealed that frailty had a negative effect on post-transplant outcomes. The review suggested that severe frailty was associated with a two-fold reduction in early survival and a 50% reduction in late survival[140].

ASSESSMENT OF FRAILTY IN LIVER DISEASES

The early and prompt assessment of frailty in cirrhotic patients is crucial for healthcare providers to enhance comprehensive care for ESLD patients[142]. Frailty has been observed to be a valuable predictor of outcomes both before and following therapeutic interventions. For instance, frailty has been associated with post-transjugular intrahepatic portosystemic shunt (TIPS) and post-liver transplant morbidity and mortality[143,144]. Additionally, early identification of frailty is also crucial as it is possible to reverse frailty to some extent, and identifying it early on enables healthcare providers to intervene more effectively to enhance the health outcomes of patients with frailty[145]. Therefore, all patients with this ailment need to undergo a frailty assessment to aid in making critical decisions regarding their life and death, including determining their eligibility for critical care and transplantation and prioritizing prehabilitation services such as nutrition, physiotherapy, and psychotherapy[146].

Frailty reassessment is also crucial to monitor the response to treatment of cirrhotic patients who have been diagnosed with frailty. Patients with well-compensated liver cirrhosis should be reassessed at least once a year, while those with decompensated cirrhosis or those receiving active management for these conditions should be reassessed more frequently, every 8 wk to 12 wk[7]. This will help healthcare providers to identify any changes in the patient's condition and adjust their treatment plan accordingly, which can improve the patient's quality of life and overall health outcomes [7].

Assessing frailty in cirrhotic patients requires the use of various assessment tools, each with its own methodology, time requirements, and limitations[146]. It is important to note that clinical interpretation of these tools can also vary among cirrhotic patients. Therefore, healthcare providers should choose the most appropriate assessment tool for each patient and interpret the results accurately. In the following paragraphs, we will summarize the three most used assessment tools for evaluating frailty in cirrhotic patients, including their strengths and limitations.

Fried frailty index

The fried frailty index (FFI) is a commonly used assessment tool for frailty that encompasses both subjective and objective components. It states self-reported fatigue, weight loss, and limited physical activity, along with objective measurements of walking speed and grip strength[8]. It is a quick assessment that can be completed in less than 10 min. The use of FFI has been linked to predicting morbidity and mortality in patients with liver cirrhosis. Higher FFI scores have been associated with elevated MELD scores, reduced albumin levels, ascites, and hepatic encephalopathy[147]. Moreover, the degree of physical weakness observed in individuals on the liver transplant waiting list, as determined by the FFI, is a noteworthy indicator of total hospitalized days per year, regardless of the severity of their liver disease[148]. Additionally, a one-unit increase in FFI leads to a 50% increase in mortality rates among those on the waiting list[149]. Despite these benefits, the accuracy of the FFI may be questionable when assessing frailty in decompensated cirrhosis. In a cohort of 685 pre-transplant patients, the FFI was found to have no association with survival among hepatic encephalopathy patients[147]. This could be attributed to the challenges that HE patients face in reporting subjective FFI components and the suboptimal performance of objective components such as grip strength and walking speed[147].

Clinical frailty scale

The clinical frailty scale (CFS) is a 1-min consistent method utilized to evaluate frailty in patients[150]. It is a comprehensive subjective clinical assessment of frailty that is user-friendly and has demonstrated its ability to anticipate mortality or the requirement for institutionalized care[151]. The scale rates individuals' level of comorbidity, function, and dependence on others for daily activities, ranging from 1 (very fit) to 9 (terminally ill)[151]. Frail patients (CFS > 4) were associated with increased rates of unplanned hospitalization or death among outpatient cirrhotic patients[150]. Additionally, CFS has linked frailty to acute kidney injury and hepatorenal syndrome in patients with hospitalized liver cirrhotic patients[137]. However, the CFS provides only a brief overview of frailty and is not detailed enough to track changes in frailty resulting from therapeutic interventions[146].

LFI

The LFI is a valuable tool for assessing frailty in hepatic patients, as it combines three performance-based evaluations: grip strength of the hand, the duration taken to perform five chair stands, and the duration of maintaining three different balance positions[152]. This quick test (3-5 min) is specifically designed to assess frailty in hepatic patients, making it a reliable and efficient tool for healthcare professionals[152]. A higher LFI score indicates a greater degree of frailty, and an LFI cut-off of > 4.62 has been identified as the most effective in distinguishing between cirrhotic patients who are at high risk for rehospitalization within 30 d and those who are not[153]. This makes the LFI a crucial tool for identifying patients who require additional care and support to prevent rehospitalization. Moreover, healthcare professionals can use the LFI to assess a patient's frailty before transplantation, identifying those who are at high risk for waitlist mortality and prolonged hospital stay after transplantation[154]. Incorporating LFI into the subjective clinical evaluation has been demonstrated to correctly reclassify the survival status of 34% of waitlist patients[154].

In addition to assessing frailty in hospitalized patients, the LFI is also employed to diagnose frailty in out-patient individuals with cirrhosis, making it a versatile tool that can be used in a variety of healthcare settings[155]. Compared to the Karnofsky Performance Status scale, which only measures one aspect of frailty, the LFI is a more comprehensive and accurate tool for assessing the risk of mortality as it captures multiple components of frailty[156].

MANAGEMENT OF FRAILTY IN LIVER DISEASES

In the management of frailty in liver cirrhosis, a continuous process is involved, which includes multiple interventions and regular reassessment of the patient to monitor their response and guide the next steps. In this section, we will provide a summary of the interventions for treating frailty in cirrhosis, as depicted in Figure 2.

Exercise

Recent studies have shown that a sedentary lifestyle is linked to lower survival rates among decompensated cirrhotic patients. In fact, low moderate-vigorous activity has been associated with increased mortality among liver transplant wait-listed patients[157]. Conversely, exercise interventions have the potential to safely improve exercise capacity, peak oxygen consumption, muscle mass and function, and quality of life, while decreasing the hepatic venous pressure gradient in individuals with cirrhosis[158,159]. This can even reverse the process of frailty in cirrhotic patients.

A study was conducted to evaluate the feasibility and benefits of a 6-wk exercise program for cirrhotic patients who were waiting for a liver transplant[160]. The program involved supervised exercise on a stationary bike three times a week. The results of the study showed that the exercise program was both feasible and beneficial for these patients[160]. Specifically, 56% of the patients (9 out of 16) were able to complete the full 6-wk program, and the exercise group showed a significant improvement in oxygen consumption compared to the control group[160].

Although exercise has potential benefits for cirrhotic patients, incorporating it into their routine can be challenging due to the risk of complications. This is especially true for decompensated patients, for whom there have been few studies on the safety and effects of exercise[161]. Cirrhotic patients, especially those who are decompensated, face numerous challenges in performing exercises, such as muscle wasting, fatigue, fluid retention, risks of falls, bleeding tendency, and portal hypertension[162,163]. To fully benefit from exercise, it is crucial to customize the exercise program to the individual patient's needs and risk of complications[7]. For instance, patients experiencing muscle mass loss may benefit from incorporating resistance training into their program, while those with a history of falls should exercise with caution when engaging in aerobic activities[7]. Moreover, while regular exercise has been found to decrease chronic portal hypertension, it is important to note that in acute situations, exercise can lead to an increase in portal pressure. Therefore, it is crucial to apply appropriate primary or secondary prophylaxis for variceal rupture to mitigate any potential risks [162].

To enhance the physical frailty and quality of life of both compensated and decompensated cirrhotic patients, it is generally recommended to incorporate a combination of aerobic and resistance exercises into their routine for at least 12 wk[161]. However, to prevent possible complications and maximize the benefits of exercise, an individualized exercise and nutrition plan should be created based on the patient's degree of frailty. This approach involves categorizing patients into one of three groups: absent/mild, moderate, or severe frailty, and creating an individualized plan for each patient accordingly[164]. For patients with severe frailty, an inpatient rehabilitation program is recommended as they are likely to derive the greatest benefit from it[164]. This approach ensures close monitoring of the patient's progress and helps in avoiding complications. Patients with moderate frailty are advised to participate in home-based exercises, with a focus on enhancing ADLs[164]. For patients with mild or no frailty, it is recommended that they engage in moderate-intensity exercise for a minimum of 150 min/wk[164]. These individuals should gradually work on improving their physical

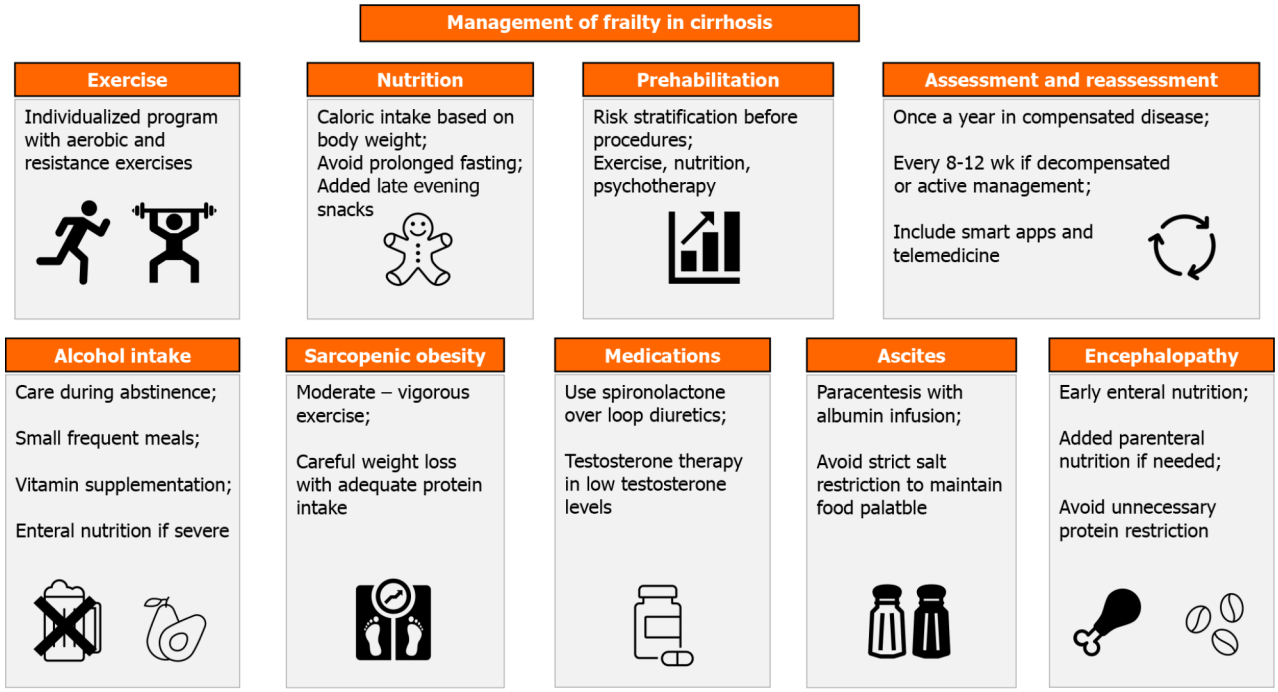

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Figure 2 Different strategies for treating frailty in cirrhosis.

capacity and strength. Regular reassessment of all patients is necessary to modify their exercise programs based on their current state[164]. By following these guidelines, cirrhotic patients can safely and effectively improve their physical health and quality of life.

Nutrition

Studies have shown that interventions aimed at improving nutrition, such as providing nutritional education, protein-energy supplementation, and oral nutritional support, can effectively enhance frailty[165]. The Practice Guidance by the AASLD recommends developing a personalized nutrition plan for all individuals with cirrhosis, considering their current nutritional status[7]. To tailor the nutritional plan for cirrhotic patients, AASLD suggests considering their weight and BMI. For individuals with a BMI between 30-40 kg/m^2, the recommended energy intake is 25-35 kcal/kg/d, while for those with a BMI ≥ 40 kg/m^2, the recommended energy intake is 20-25 kcal/kg/d[7]. Moreover, AASLD recommends a safe protein intake of 1.2-1.5 g/kg/d for adults with cirrhosis, which should come from a diverse range of sources[7]. A recent randomized controlled trial showed that intensive nutrition therapy administered at home for six months can enhance frailty and sarcopenia in patients with decompensated cirrhosis[166]. The study found that the intervention group showed a greater improvement in the LFI compared to the control group (0.8 *vs* 0.4; $P < 0.001$)[166]. AASLD highlights the importance of identifying and overcoming obstacles to proper nutrition for patients with cirrhosis who are frail[7]. This may involve loosening restrictions on salt intake in cases of diet unpalatability, encouragement of enteral feeding in encephalopathy, prevention of prolonged fasting hours, and providing late evening snacks[7].

Prehabilitation

Prehabilitation, also known as preoperative habilitation, involves a range of interventions that are implemented before a medical procedure or treatment to mitigate or prevent any adverse effects that may arise[167]. In the context of liver transplantation, prehabilitation aims to identify high-risk patients as early as possible and enhance their physical capacity before surgery[168]. This is achieved through various interventions, including exercise, nutrition, and psychological stress management[169]. According to a recent systematic review of eight studies, prehabilitation could potentially boost the aerobic capacity of patients who are awaiting orthotopic liver transplantation and is deemed a safe and feasible approach [170]. The review also revealed notable improvements in several metrics, such as VO2 peak, 6-min walking distance, hand grip strength, LFI, and quality of life[170]. Despite the evidence supporting the role of prehabilitation before liver transplantation, there is limited research on the benefits of prehabilitation for frail cirrhotic patients after liver transplantation. While a single study has demonstrated that an exercise training program can lead to post-transplant short-term benefits, such as reduced 90-d readmission rates and shorter hospital stays[171], further research is needed to confirm the potential long-term benefits of prehabilitation after liver transplantation.

Medications

Although pharmacological interventions are not commonly used in frailty treatment, there is evidence to suggest that testosterone supplementation may be a safe and effective option for enhancing muscle mass and strength in males with cirrhosis and low testosterone levels. A 54-wk randomized controlled trial conducted by Sinclair *et al*[172] concluded that

testosterone supplementation can safely enhance muscle mass and strength in this population. However, there is limited information regarding the effect of testosterone therapy in treating frailty after liver transplantation. A single retrospective study suggested that short testosterone therapy may be useful in treating frailty after liver transplantation [173]. In this study, administering a single dose of testosterone replacement therapy along with regular exercise has been associated with patient and graft survival rates of 93.8% and 87.5% at one and five years, respectively[173]. Large randomized controlled trials are necessary to validate the safety and potential benefits of administering testosterone as a treatment for frailty following liver transplantation.

FUTURE APPROACHES IN FRAILTY MANAGEMENT

Emerging information technologies for frailty assessment

Frailty assessment tools are now available online, making it easier to assess frailty in the geriatric population. These web-based tools are user-friendly and can be accessed through internet-connected devices[174]. In addition, smartphone applications have shown great potential in evaluating and quantifying physical activity and patient mobility, which are crucial indicators of frailty. For instance, a recent app was used to prehabilitate liver transplant candidates, and it was found that the app's training level matched that of a physical therapist in 89% of cases[175]. The app also motivated patients through videos and gamification features, leading to a 35% increase in physical activity performance among participants[175]. However, these tools require further advancements to fully comprehend the current patient frailty status, especially in cirrhotic patients who require special clinical evaluation. Validation studies are also needed to ensure that these smart tools can be integrated into clinical decision-making for patients.

A novel tool called the tele-liver frailty index (TeLefI) has been proposed for frailty assessment and follow-up in cirrhotic patients[176]. It utilizes telemedicine to virtually measure frailty in liver transplant candidates with cirrhosis. Wang *et al*[176] introduced this tool by comparing frailty assessment using in-person LFI and then by TelefI assessment tool[176]. The telemedicine-based TeLefI tool has been statistically validated in predicting LFI > 4.4, indicating that it can effectively identify patients who require more frequent follow-up or in-person assessment[176]. This tool has the potential to revolutionize frailty assessment and follow-up in cirrhotic patients, especially those who live in remote or underserved areas. This has the potential to not only decrease healthcare expenses but also enhance patient outcomes. While this tool has shown promising results, more research is necessary to fully understand the benefits and limitations of this novel approach to frailty assessment.

Potential therapeutic targets

Targeting pathways that contribute to the progression of frailty shows promise as a potential treatment approach[17]. In fact, there are several medications that could potentially be used to treat frailty in cirrhosis. Here are some examples (Table 3).

Metformin: In general, the research on the effectiveness of metformin in treating frailty is inconclusive. Although some studies indicate that metformin may not be useful in decreasing the occurrence of frailty[177,178], other studies suggest that it could be advantageous in managing age-related illnesses and ailments including frailty[179-181]. The reason for this protective effect may be attributed to the reduction of insulin resistance, which is involved in the pathophysiology of frailty[182]. Additionally, the correlation discovered between metformin usage and lower levels of proinflammatory cytokines, regardless of blood glucose levels, may also contribute to the mechanism[183]. However, further investigation is necessary to gain a complete understanding of metformin's potential in treating frailty in cirrhosis.

Rifaximin: Rifaximin is an antibiotic that boasts a highly favorable safety profile. Its primary function is to specifically target and eradicate harmful bacteria in the intestinal tract[184]. Due to its low absorption rate, rifaximin is considered an excellent choice for patients who require a safe and effective treatment option[185]. One of the key benefits of rifaximin is its ability to modify the composition of the gut microbiota, resulting in a notable decrease in harmful bacterial taxa. This, in turn, helps to prevent hyperammonemia, bacterial endotoxemia, and translocation, which have been identified as contributing factors to muscle loss in cirrhosis patients[62]. In a recent uncontrolled study, the long-term use of rifaximin in cirrhosis patients had a positive impact on their nutritional status[186]. Furthermore, the study demonstrated that rifaximin enabled these patients to maintain a consistent amount of muscle mass[186]. These findings shed light on the potential of rifaximin as an intervention for addressing malnutrition and potentially mitigating muscle loss in individuals with cirrhosis. However, further research is needed, specifically randomized controlled trials, to establish the efficacy of rifaximin in treating frailty in liver cirrhosis. Additionally, probiotics and fecal microbial transplantation are being explored as potential therapies for frailty induced by gut dysbiosis in liver cirrhosis[62]. However, their effectiveness in human subjects is still under investigation, and there is a lack of comprehensive studies in this area.

Myostatin antagonists: Myostatin is a type of signaling molecule that falls under the transforming growth factor-β superfamily[187]. It has a crucial function in skeletal muscle metabolism, and it works as an inhibitor of muscle mass, leading to a decrease in muscle size[188]. Higher levels of myostatin are linked to poorer survival rates in cirrhosis patients, and increased serum myostatin levels are associated with decreased muscle mass[29]. Studies have demonstrated that blocking myostatin can result in muscle hypertrophy and the reversal of muscle atrophy in both young and old mice[189-191], making it a potential solution to prevent muscle wasting in liver cirrhosis patients[192]. There exist various therapeutic interventions that can counteract the impact of myostatin, such as monoclonal antibodies, myostatin propeptide, and follistatin[190,193-196]. Additional studies are needed to ascertain the efficiency and safety of

Table 3 Comparison of different frailty suggested medications in cirrhotic patients

Suggested medication	Target of action	Side effects	Dose used in clinical trials	Clinical trial results
Metformin	Insulin resistance; Proinflammatory cytokines	Gastrointestinal upset; Non responders[209]	-	-
Rifaximin	Gut dysbiosis	-	1200 mg daily for 24 wk	No significant changes in skeletal muscle index[186]
Myostatin antagonists	Hyperammonemia; Muscle mass inhibition	Spontaneous bone fractures[210]; Vascular (nasal and gum bleeding, telangiectasia)[211]	-	-
L-Carnitine	Hyperammonemia; Proinflammatory cytokines (antioxidant)	Gastrointestinal upset	(1000 mg/d) + exercise for 6 mo [201]	No significant changes in muscle mass, leg, and handgrip strength[201]
L-ornithine L-aspartate	Hyperammonemia	Gastrointestinal upset	6 g three times daily for 2 wk [207]	No significant increase in prealbumin level after use[207]
Testosterone therapy	Testosterone deficiency	Cardiovascular diseases; Prostate cancer; Erythrocytosis[212]	Intramuscular injection of testosterone undecanoate 1000 mg at 0, 6, 18, 30, 42 wk[172]	The intervention group had increased muscle and bone mass with lower fat mass[172]

myostatin antagonists in this specific context.

Carnitine: L-carnitine, an endogenous compound with antioxidant properties, has been shown to promote muscle growth by increasing muscle blood flow[197]. Carnitine also has an essential role in fatty acid metabolism, and its deficiency leads to increased hepatic steatosis, hyperammonemia, cardiac and skeletal muscle disease[198]. Despite its potential benefits, there is limited information available on the effectiveness of L-carnitine in treating frail cirrhotic patients. Two retrospective studies have suggested that taking L-carnitine supplements may help prevent the loss of skeletal muscle mass in individuals with liver cirrhosis[199,200]. On the contrary, a clinical trial involving the administration of a daily dose of 1000 mg of L-carnitine for over six months to liver cirrhosis patients did not result in significant changes in muscle mass, handgrip, and leg strength[201]. Further research is necessary to evaluate the potential benefits of L-carnitine in the treatment of frailty in cirrhosis.

L-ornithine L-aspartate: L-ornithine L-aspartate (LOLA) has been proven to be an effective treatment for hepatic encephalopathy as it helps to reduce ammonia levels[202]. It achieves this by stimulating the production of urea in the liver and promoting muscle glutamine synthesis[203,204]. Administering LOLA to mice with non-alcoholic steatohepatitis has been shown to enhance muscle protein function[205]. By decreasing ammonia levels and improving muscle function in mice, LOLA has been suggested as a potential treatment for sarcopenia and frailty in individuals with cirrhosis[206]. However, a randomized controlled trial administering LOLA of 6 g three times daily for 2 wk to a group of 17 liver cirrhotic patients did not produce a significant increase in prealbumin levels[207]. Therefore, future research is necessary to validate the beneficial role of LOLA in treating frailty in patients with decompensated cirrhosis.

Hormonal therapy: Sinclair *et al*[172] conducted a randomized controlled trial that lasted for 12 mo, which showed notable enhancements in muscle mass, bone mineral mass, and a decrease in total fat mass among cirrhotic patients who received testosterone therapy. Nevertheless, further research is required to ascertain the safety and effectiveness of this therapy, particularly due to potential adverse effects such as an increased risk of hepatocellular carcinoma, cardiovascular diseases, and elevated hematocrit levels[208]. Additionally, the efficacy and safety of testosterone therapy after liver transplantation require further investigation.

TIPS and frailty

There is an ongoing debate surrounding the use of TIPS as a potential therapy for sarcopenia and frailty in liver cirrhosis patients. While several studies have shown promising results in terms of improving muscle mass and nutritional status, as well as reducing the risk of hepatic encephalopathy and mortality in sarcopenic patients[213-215], other studies have raised concerns about the use of TIPS as a therapy for sarcopenia and frailty, particularly in severe cases. These studies have demonstrated that these conditions are associated with a higher risk of post-TIPS complications, such as non-home discharge, prolonged hospital stay, hepatic encephalopathy, and even mortality[143,216,217].

Moreover, while all studies conducted have focused on sarcopenic assessment after TIPS, only one novel study has included the effect of TIPS on frailty parameters[218]. In this study, 12 cirrhosis patients showed improvement in skeletal muscle mass six months after TIPS compared to their baseline measurements before the procedure[218]. However, there was no improvement in LFI, handgrip strength, or physical performance measurements[218]. This study adds to the concerns about using TIPS as a potential therapy for cirrhotic frail patients. To address these concerns and obtain more conclusive evidence, we strongly recommend that future studies on this topic prioritize larger sample sizes and control groups.

CONCLUSION

Frailty is a complex medical condition that arises from multiple predisposing factors in patients with cirrhosis. It has a significant impact on the morbidity and mortality of cirrhotic patients and can even predict the outcomes of therapeutic interventions. Therefore, it is crucial to properly assess, reassess, and intervene in cirrhotic patients to prevent, treat, or even reverse this hazardous process. Looking ahead, future research should explore the possibility of utilizing telemedicine and smart apps for frailty assessment to make clinical decisions for patient treatment and follow-up. This could potentially improve patient outcomes and reduce healthcare costs. Furthermore, future research must investigate the safety and long-term potential benefits of therapeutic strategies, including TIPS, prehabilitation, and medications for managing frailty in cirrhotic patients, especially after liver transplantation.

FOOTNOTES

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MINIREVIEWS

Surgical complications after pancreatic transplantation: A computed tomography imaging pictorial review

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Abstract

Pancreatic transplantation is considered by the American Diabetes Association and the European Association for the Study of Diabetes an acceptable surgical procedure in patients with type 1 diabetes also undergoing kidney transplantation in pre-final or end-stage renal disease if no contraindications are present. Pancreatic transplantation, however, is a complex surgical procedure and may lead to a range of postoperative complications that can significantly impact graft function and patient outcomes. Postoperative computed tomography (CT) is often adopted to evaluate perfusion of the transplanted pancreas, identify complications and as a guide for interventional radiology procedures. CT assessment after pancreatic transplantation should start with the evaluation of the arterial Y-graft, the venous anastomosis and the duodenojejunostomy. With regard to complications, CT allows for the identification of vascular complications, such as thrombosis or stenosis of blood vessels supplying the graft, the detection of pancreatic fluid collections, including pseudocysts, abscesses, or leaks, the assessment of bowel complications (anastomotic leaks, ileus or obstruction), and the identi-

fication of bleeding. The aim of this pictorial review is to illustrate CT findings of surgical-related complications after pancreatic transplantation. The knowledge of surgical techniques is of key importance to understand postoperative anatomic changes and imaging evaluation. Therefore, we first provide a short summary of the main techniques of pancreatic transplantation. Then, we provide a practical imaging approach to pancreatic transplantation and its complications providing tips and tricks for the prompt imaging diagnosis on CT.

Key Words: Diabetes mellitus; Type 1; Pancreas transplantation; Complications; Computed tomography; Diagnostic imaging

Core Tip: Pancreatic transplantation is a complex surgical procedure and, similarly to any major surgical intervention, may lead to a range of postoperative complications that can significantly impact graft function and patient outcomes. Computed tomography offers non-invasive and accurate visualization of the transplanted pancreas and surrounding structures, providing detailed anatomical information and aiding in the detection of complications.

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INTRODUCTION

Pancreatic transplantation is considered by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) an acceptable surgical procedure in patients with type 1 diabetes (T1D) also undergoing kidney transplantation [*i.e.* simultaneous pancreas and kidney (SPK) transplant] in pre-final or end-stage renal disease if no contraindications are present[1]. Pancreatic transplantation has been considered for years the only treatment for T1D that consistently establishes an insulin-independent, normoglycemic state, with 5-year graft survival of 83%, 55% and 70%, in case of SPK, pancreatic transplantation alone (PTA) or pancreas after a kidney transplantation (PAK), respectively [2-4]. The main indication of PTA is presence of T1D and normal or near-normal renal function in patients who suffer from hypoglycemia unawareness, which results in impaired quality of life or with difficulty adhering to the requirement of insulin injection[5]. In few selected cases, transplantation of pancreatic islet – a less invasive procedure consisting in the transplantation of islets of Langerhans in the recipient hepatic portal system – is indicated as an alternative to pancreatic transplantation by ADA and EASD[1]. However, intrahepatic islet transplantation for T1D is limited because of the need of multiple infusions and poor islet viability after transplantation, and more recently intracutaneous transplantation of islets has also been investigated[6]. In a 20-year span from 2000 to 2020, only about 4365 islet allotransplants have been performed according to a recent worldwide survey[7], while the number of pancreatic transplantations in the 10-year span from 2010 to 2019 is of about 23000 procedures[8].

Pancreatic transplantation is a complex surgical procedure and, similarly to any major surgical intervention, may lead to a range of postoperative complications that can significantly impact graft function and patient outcomes[9,10]. The occurrence of postoperative complications may vary depending on factors such as the type of transplantation (SPK, PAK or PTA) and the specific patient population. Cross-sectional imaging – *i.e.*, Doppler ultrasound (US), contrast-enhanced US (CEUS) and computed tomography (CT) – plays a pivotal role in the evaluation of the transplanted pancreas. US is the preferred initial imaging modality for evaluating the transplanted pancreas due to its safe, non-invasive, radiation-free, simple, quick, and repeatable approach. However, US is often affected by factors such as intestinal gas interference and operator proficiency, and partial thrombosis may be easily missed[11]. CT offers non-invasive and accurate visualization of the transplanted pancreas and surrounding structures, providing detailed anatomical information and aiding in the detection of complications. Indeed, CT allows for the identification of vascular complications, such as thrombosis or stenosis of blood vessels supplying the graft as well as bleeding or pseudoaneurysms, the detection of pancreatic fluid collections, including pseudocysts, abscesses, or leaks, the assessment of bowel complications (anastomotic leaks, ileus or obstruction), while it has a limited role in the evaluation of graft rejection[12,13]. Magnetic resonance imaging (MRI) is rarely uncommonly used for examination the assessment of pancreatic graft-related complications, and it is preferred particularly in patients with declining renal function. The main adoption of CT compared to MRI is based on different reasons, including wider availability of CT compared to MRI particularly in the emergency and urgent settings, the lower acquisition time of CT exams compared to MRI which is important in imaging acutely ill and intensively monitored patients, but also to the lower spatial and temporal resolution, creating difficulties in the evaluation of the enteric anastomosis and vascular complications. Contrast medium administration in CT should not be a contraindication in kidney transplant recipients. Fananapazir *et al*[14] demonstrated that the incidence of acute kidney injury in patients with transplanted kidney submitted to CT scans with low-osmolality iodine-based contrast material was 7% when considering the threshold of ≥ 0.3 mg/dL for the increase in serum creatinine levels. The incidence of contrast induced nephropathy after contrast-enhanced CT was similar (6.1%) in a study by Cheungpasitporn *et al*[15]. However, in a study involving

about 6175 patients, McDonald *et al*[16] demonstrated lack of significant difference in the onset if contrast induced nephropathy between patients with a solitary kidney, including kidney transplant recipients (4.1%), and those with bilateral kidneys (4.2%). The assessment of serum creatinine for calculating the estimated glomerular filtration rate is recommended before contrast medium administration within 7 d before CT in patients with an acute disease, an acute deterioration of a chronic disease or in hospitalized patients, and preventive hydration protocols need to be considered in at-risk patients as indicated by guidelines[17-19].

This pictorial review is aimed at illustrating CT findings of surgical-related complications after pancreatic transplantation. A comprehensive knowledge of surgical techniques allows understanding the postoperative anatomic changes that are identified on CT images. Therefore, this review will first a short summary of the main techniques of pancreatic transplantation and, then, will discuss imaging tips and tricks for the prompt diagnosis of complications after pancreatic transplantation on CT.

SURGICAL TECHNIQUES

After organ procurement from a deceased donor, a meticulous graft back-table surgery is necessary before pancreatic transplantation. Main steps are: Splenectomy, removal of the excess fat surrounding the pancreas and ligation of small vessels and lymphatics along the inferior margin of the pancreatic tail, coursing anteriorly around the surface of the neck and head of the pancreas to the proximal duodenal staple line. A suture of the vessels at the root of the mesentery and inferior mesenteric vein is performed followed by an oversewing of the mesenteric staple line. A vascular preparation is necessary using a Y conduit of donor iliac artery which is anastomosed to the superior mesenteric and splenic arteries of the graft (Figures 1 and 2). Assessment of blood supply to the entire pancreas graft exclusively *via* cross-circulation between splenic artery and superior mesenteric artery is mandatory in order to guarantee blood supply to all the pancreas graft. By flushing the superior mesenteric artery and not looking for back-flushing through the gastroduodenal artery is possible to recognize the need for vascular reconstruction of the gastroduodenal artery to guarantee blood supply to head of the pancreas graft and duodenal segment, and possibly reduce the incidence of duodenal complications [20]. A duodenal shortening with stapler and oversewing of the staple line is then completed. At this stage, the graft is ready for implantation.

Through a midline incision, the pancreas allograft is usually placed intraperitoneally, on the right side with the head in a cranial position, and receives arterial inflow from the iliac artery (Figure 1). Venous anastomosis can be performed through systemic vein technique with the graft portal vein (PV) anastomosed to the recipient inferior vena cava or iliac vein, or through the PV technique with the graft PV anastomosed to the recipient inferior vena cava or iliac vein. In the PV technique, the graft PV is connected to the recipient superior mesenteric vein. Systemic drainage theoretically may lead to hyperinsulinemia[21], while portal drainage could allow a more physiological "first pass" effect through the liver since insulin is immediately extracted by the liver. However, the arterial anastomosis to the iliac artery tends to be more difficult using the PV technique and it requires a very long Y graft. Moreover, obesity, thickened mesentery, or an inadequate caliber of the superior mesenteric vein can make the portal drainage even harder[22]. Long-term studies comparing the two techniques have not demonstrated clear metabolic advantages with portal drainage and the use of the PV has remained marginal over the years[23]. For the exocrine pancreas drainage, anastomosis between the donor duodenum and recipient small bowel loop (*i.e.*, jejunal or an ileal loop) is performed side-to-side with a circular stapler. After firing the stapler (trans-oral anvil delivery system EEA), the end of the donor duodenum is closed using a linear stapler. Alternatively, a bladder diversion can be performed[24]. Bladder drainage can be particularly advantageous in case of PTA, for the assessment of the concentration of urinary amylase as a marker of rejection. Disadvantages of this technique include both urologic complications such as hematuria (16%), leaks (14%), reflux pancreatitis (11%), recurrent urinary infections (10%), urethritis (3%), urethral stricture/disruption (3%), and metabolic complications due to the urinary loss of the bicarbonate-rich pancreatic juice, including hyperchloremic metabolic acidosis and dehydration[23, 25]. When these complications became intractable, conversion from bladder to enteric drainage is often necessary[26]. Enteric drainage is currently the predominant technique in pancreatic transplantation[23].

Usually, recipients start receiving immunosuppression during surgery, consisting in antibody induction and a triple drug immunosuppressive therapy is started immediately postoperatively. Most of the Centers utilize a regimen consisting of tacrolimus, mycophenolate mofetil and steroid.

Heparin prophylaxis is recommended with intravenous heparin administered as a single dose during surgery after pancreas revascularization and it is continued after surgery with low molecular weight heparin or continuous infusion, at the discretion of the Transplant Centre.

Some days after transplantation, a CT scan is advisable to early recognize vascular thrombosis or any signs of vascular alterations, not yet clinically relevant.

COMPLICATIONS AFTER PANCREATIC TRANSPLANTATION

Postoperative surgical complications of pancreatic transplantation are still common despite many improvements in surgical techniques, and may be distinguished based on time of onset[27-28]. Postoperative monitoring of the pancreatic graft by CT is requested in about 89% of cases according to a recent series of 230 pancreatic transplantations and is helpful for optimizing patient management[29].

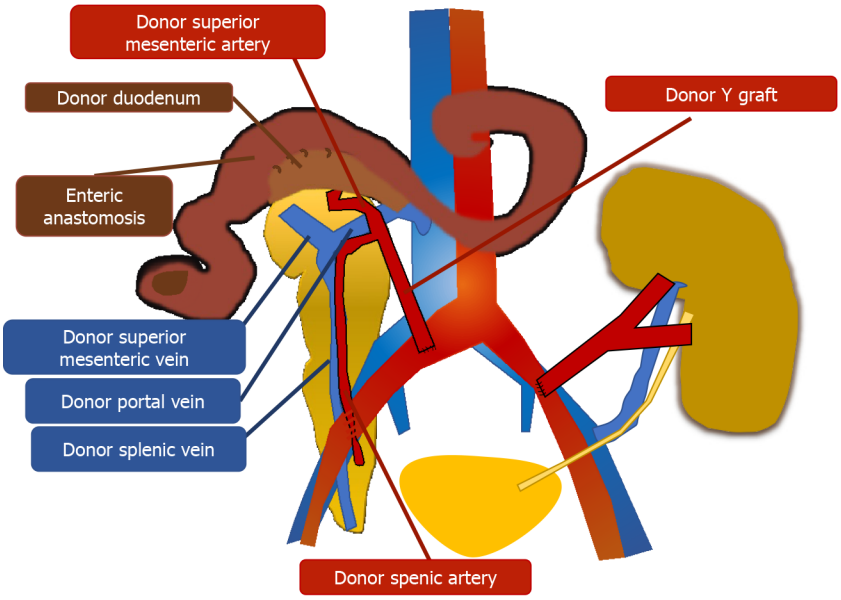

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Figure 1 Schematic imaging representation of simultaneous pancreas and kidney transplantation.

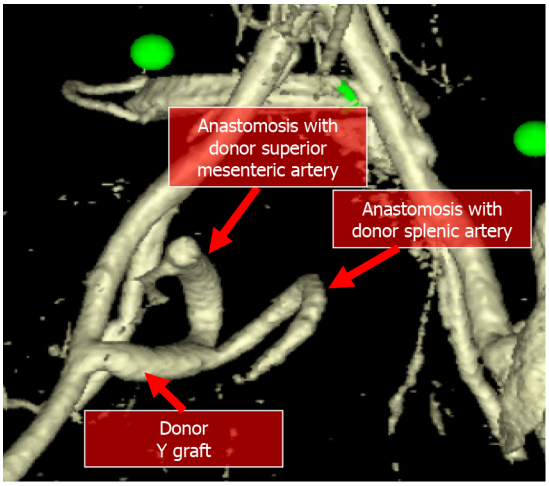

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Figure 2 Volume rendering reformat of computed tomography images in the arterial phase demonstrates the Y conduit of donor iliac artery to the superior mesenteric and splenic arteries of the graft.

The main reasons for requesting imaging are related to the indication per protocol even without acute clinical indication, sudden progressive hyperglycemia, persistent or abdominal tenderness[29]. However, the adoption of CT needs to be patient-tailored particularly in the context of SPK, due to the potentially nephrotoxic effect of contrast agents which is reported to be as low as 5.6% in kidney transplant recipients with the use of hypo-osmolar contrast agent[30].

Initial complications of pancreatic transplantations are largely related to technical factors, including vascular thrombosis, bleeding, enteric anastomotic leak or graft pancreatitis, and urologic complications[8]. Late complications include pseudocyst formation, post-transplant lymphoproliferative disease, pseudoaneurysms, artero-venous fistulas and rejection (Figure 3).

Graft thrombosis is the most common complication after transplant and may lead to graft failure in about 3.7%, 4.1% and 5.9% of SPK, PAK and PTA, respectively[8]. Graft loss due to infection, pancreatitis, bleeding, leaks, and other reasons occur in up to 0.5%, 0.5%, 0.5%, 0.4%, and 0.6%, respectively[8].

Graft thrombosis

Graft thrombosis occurs in 7%-34% of patients after pancreas transplant, with high body mass index being a risk factor, may affect arteries or veins and can be partial or complete[10,12,29,31]. Partial graft thrombosis occurs in about 25% of cases after pancreatic transplantation, is subclinical in the majority of cases, and may resolve spontaneously with medical therapy[29]. Venous thrombosis is far more common than arterial thrombosis, but arterial thrombosis is the most

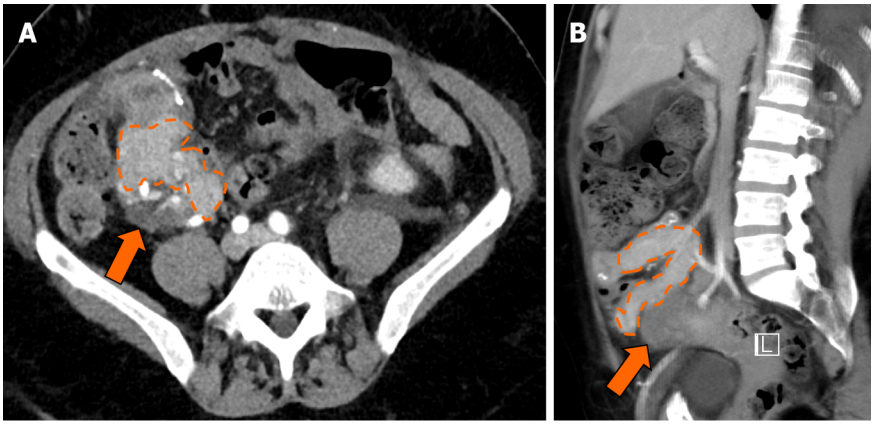

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Figure 3 A 51-year-old woman, one month after simultaneous kidney-pancreatic transplantation is admitted to the emergency department for abdominal pain; final diagnosis at biopsy of the pancreatic graft was rejection. A: Contrast enhanced computed tomography in the axial plane shows a minimally inhomogeneous pancreatic graft (dotted orange line) with peripancreatic fluid (arrows) posteriorly to the graft; B: Sagittal plane of the same contrast enhanced computes tomography.

dangerous leading to rapid graft loss[29,32]. Acute rejection and CT finding of pancreatitis are risk factors for graft thrombosis[12].

Contrast-enhanced CT with angiographic phase and venous phase demonstrates thrombosis as a filling defect in a vessel during the vascular phase, and allows to clearly indicate the extension of the filling defect. Arterial thrombosis (Figure 4) may lead to graft dysfunction, pancreatitis, leakage of pancreatic enzymes, sepsis, necrosis and even emphysematous transformation of the graft if it is left untreated. Pancreatic graft venous thrombi (Figure 5) can remain relatively localized possibly maintaining normal graft function, or may propagate into the PV, iliac vein, or vena cava (in case of systemic venous drainage) or superior mesenteric veins (in case of portal venous drainage). In case of vascular thrombosis, a decreased enhancement of the transplanted pancreas usually occurs dure to the organ ischemia, and the main differential diagnosis between arterial and venous thrombosis is made by direct visualization of the thrombus in the vessel.

Percutaneous thrombectomy, followed by anticoagulation, is considered a therapeutical option to remove the thrombus, with low complication rate[33].

Graft thrombosis may be graded on contrast-enhanced CT based on the system proposed by Hakeem *et al*[12] into:

Grade 0 – Lack of thrombosis.

Grade 1 – Peripheral thrombosis: Thrombus is located at the transected margin of the superior mesenteric vein/splenic vein or superior mesenteric artery and it is present only in a single branch.

Grade 2 – Intermediate nonocclusive thrombosis.

Venous: Thrombus extends into parenchymal vessels/main trunk of the superior mesenteric vein or splenic vein to the superior mesenteric vein/splenic vein confluence but not into the PV.

Arterial: Thrombus extends into the main trunk of the superior mesenteric artery/splenic artery to the "Y" graft but not into the Y graft.

Grade 3 – Central occlusive thrombosis.

Interestingly, despite the diagnosis of vascular thrombosis seems quite straightforward Hakeem *et al*[12] showed some discrepancies among radiologists in the detection with 28 new thrombosis identified on retrospective imaging review, with the grade 1 thrombosis being underestimated at initial diagnosis by the reporting radiologists.

Pancreatitis

Graft pancreatitis is amongst the most frequent complications following pancreatic transplantation, the third most common cause for re-operation following bleeding and pancreas graft thrombosis, and a common histologic feature identified in up to 61% of rejected allografts[34,35]. Graft pancreatitis is distinguished in early if it occurs within 3 mo and later after 3 mo, while physiological acute graft pancreatitis occurs within the first 72 h after reperfusion of the transplanted organ secondarily to an acute inflammatory response related to ischemic reperfusion injury[36].

Common findings in CT include focal or diffuse enlargement of the pancreatic parenchyma, with edematous changes (usually is noted a decreasement in HU value), indistinct pancreatic margins due to inflammation, and surrounding fat stranding (Figure 6). CT imaging allows to differentiate between edematous and necrotizing pancreatitis, to assess the presence of collections and to evaluate long-term evolutions including pseudocyst and walled-off necrosis[37].

Notably, graft pancreatitis and vascular thrombosis may occur simultaneously; indeed, pancreatitis can predispose to vascular thrombosis, and vascular thrombosis can also lead to graft inflammation, thus leading to some overlapping CT imaging features as shown on Figure 7.

Peripancreatic collection and Infection

Infection may occur in the form of peripancreatic fluid collections (Figure 6), pseudocysts (Figure 8), leakage at the level

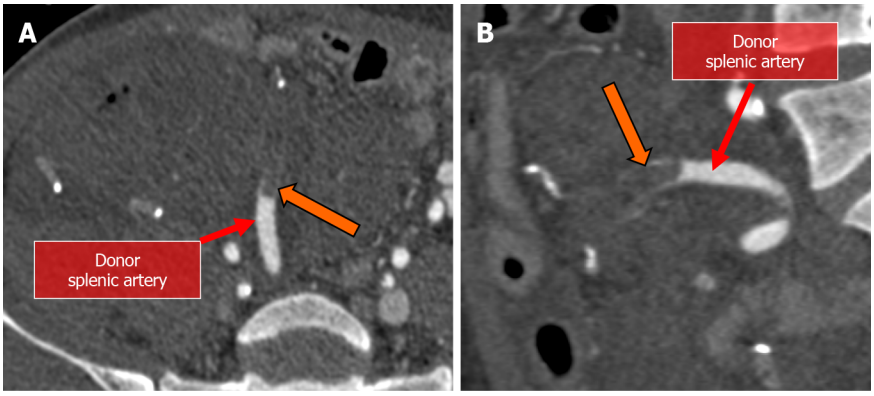

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Figure 4 A 46-year-old woman, few days after surgery had low prothrombin time; final diagnosis was graft arterial thrombosis. A: Contrast enhanced computed tomography in the angiographic phase demonstrated arterial thrombosis of the donor splenic artery. In this patient, the transplanted pancreas was explanted thereafter; B: Coronal plane of the same contrast enhanced computed tomography in the angiographic phase.

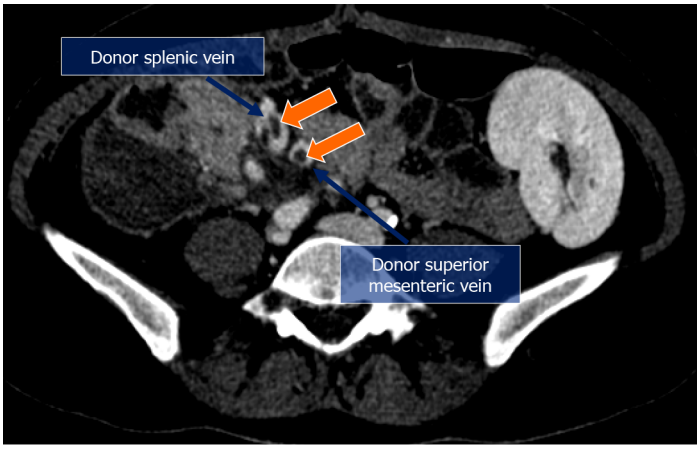

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Figure 5 A 35-year-old woman is admitted to the emergency department for abdominal pain; final diagnosis was venous thrombosis. Contrast enhanced computed tomography in the venous phase demonstrates venous thrombi (orange arrows) in the donor splenic vein and in the donor superior mesenteric vein.

of the enteric anastomosis (Figure 9), or infection of the abdominal wall surgical wound[21,38].

Fluid collections are the most common abnormality after pancreatic transplantation, may occur early or late after transplant, are clinically significant in about 16% of patients, and may lead to superinfection[38,39]. Intraabdominal collections also include seroma, hematoma, lymphocele, urinoma, or pseudocyst[11,38].

CT demonstrates an abnormal fluid collection of low attenuation with surrounding rim-enhancement and possible intralesional gas[38]. Soft tissue edema and fat stranding in the adjacent tissues may also be present. Percutaneous drainage is safe and effective for management of peripancreatic fluid collections after pancreas transplant[38].

Enteric or Pancreatic Leaks

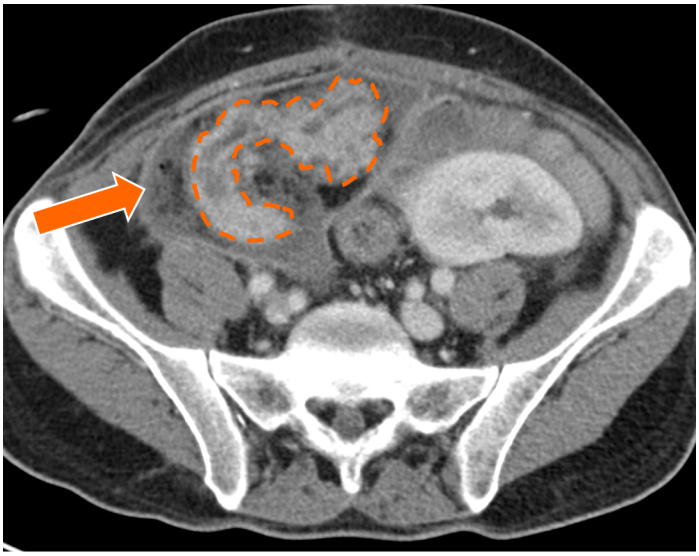
Duodenal leaks represent about 2.5%-2.9% of complications after pancreatic transplantation[40,41] and represent the cause of re-laparotomy in about 2.1% of cases[34]. Enteric leaks after pancreatic transplantation are usually characterized by extravasation of pancreatic juice from the duodenojejunostomy site leading to focal peritonitis and collections (Figure 9), and eventually abscess formation[26]. Duodenal leaks usually occur early in the postoperative course, but may also be seen late post-transplant and increase 6-mo graft loss risk with a hazard ratio of 13.9[40-42]. Pancreatic duct fistula after focal pancreatitis or ischemia leading to duct disruption, may also result in the development of a peripancreatic collection[42].

Bleeding

In the early postoperative period, the occurrence of bleeding is the most common cause of reoperation[29].

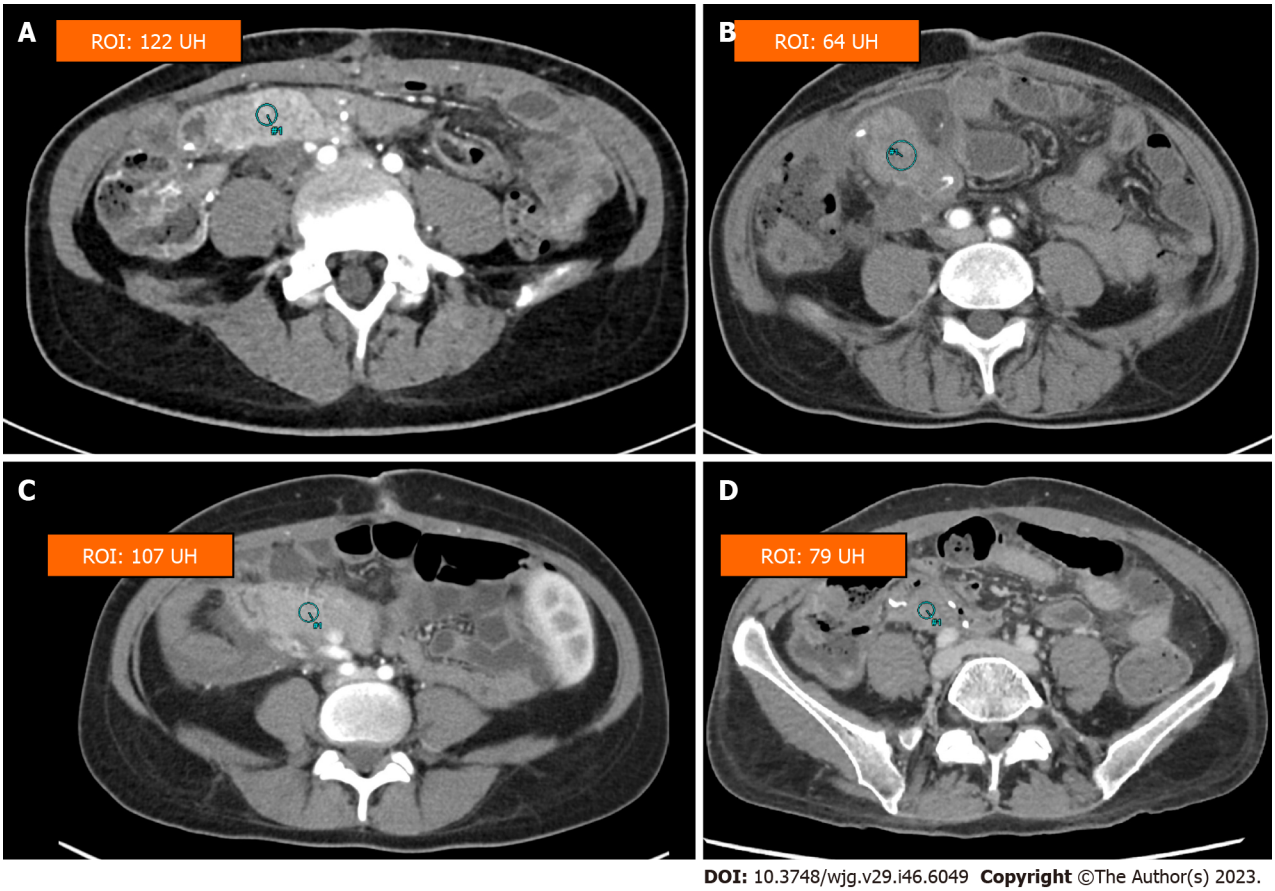
The source of bleeding in the early post-operative period may be:

Intra-abdominal: It is usually related to damage of the peripancreatic vessels or vascular anastomosis, enhanced by the antithrombotic prophylaxis or antithrombotic therapy in patients with vascular thrombosis.



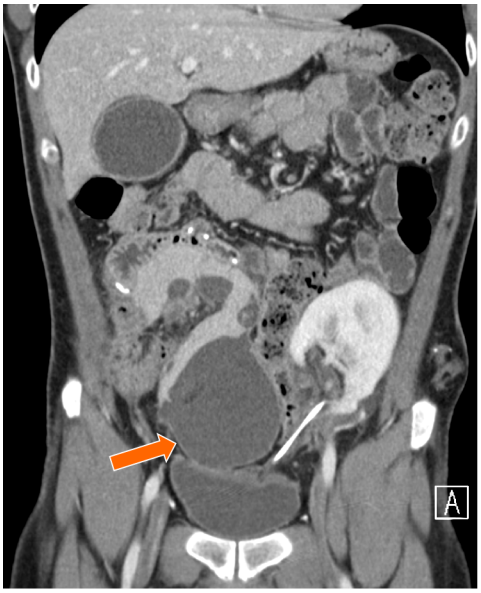
DOI: 10.3748/wjg.v29.i46.6049

Figure 6 A 35-year-old man is admitted to the emergency department presenting hyperpyrexia and abdominal tenderness; final diagnosis was edematous pancreatitis with acute peripancreatic fluid collection. Contrast enhanced computed tomography in the axial plane shows inhomogeneous transplanted pancreas (dotted orange lines) with slightly enlarged Wirsung duct and acute peripancreatic fluid collection (arrow) with thick wall and fat stranding surrounding the transplanted pancreas. A diagnosis of edematous pancreatitis was made.



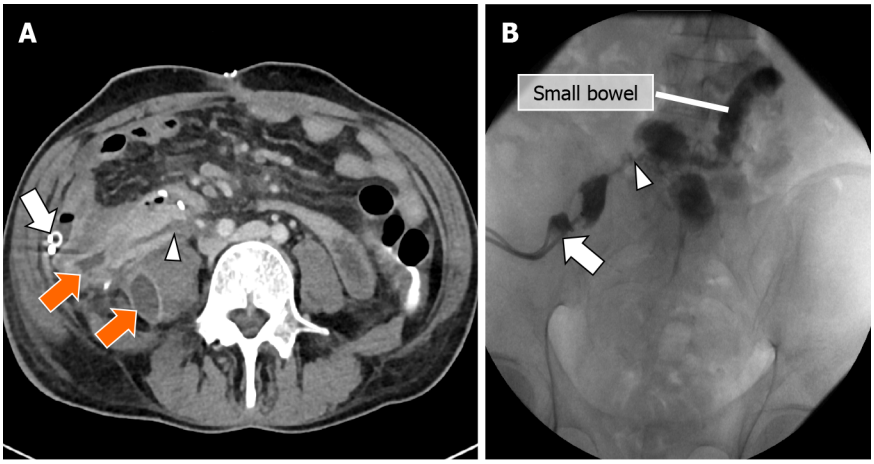
DOI: 10.3748/wjg.v29.i46.6049

Figure 7 Contrast enhanced computed tomography in four different patients after pancreatic transplantation. A region of interest is drawn in the pancreas in the four patients. A: Normal pancreatic parenchyma; B: Inflammatory pancreatitis; C: Decreased parenchymal enhancement from venous thrombosis; D: Decreased parenchymal enhancement from arterial thrombosis.



DOI: 10.3748/wjg.v29.i46.6049

Figure 8 A 35-year-old man after four weeks from edematous pancreatitis. Contrast enhanced computed tomography in the coronal plane shows an encapsulated fluid collection (arrow) of homogeneously low attenuation surrounded by a well-defined enhancing wall consistent with pancreatic pseudocyst.



DOI: 10.3748/wjg.v29.i46.6049

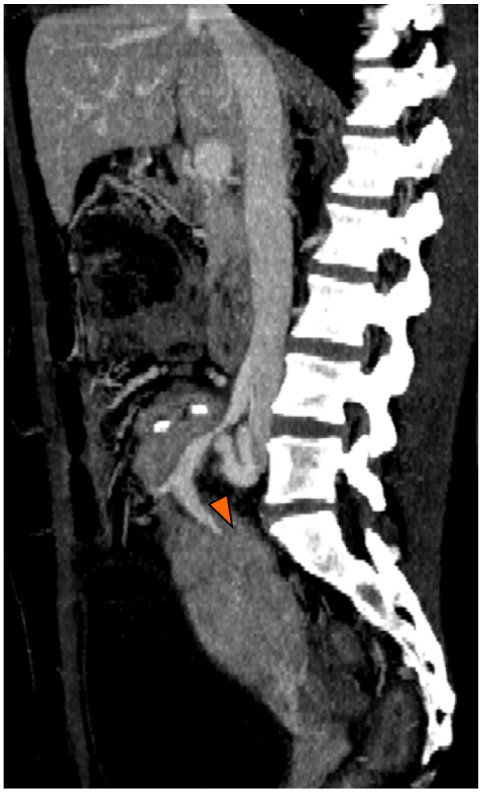
Figure 9 A 43-year-old man admitted to the emergency department for hyperpyrexia and abdominal tenderness; final diagnosis was enteric leakage. A: Contrast enhanced CT demonstrated the presence of an enteric leakage as a fistulous tract (arrowhead) from the small bowel at the level of the duodenojejunostomy, which resulted into fluid collections (orange arrows). Abdominal drainage (white arrow) was inserted and the analysis of the fluid was consistent with the diagnosis of enteric leakage; B: Fluoroscopic image demonstrate the presence of an enteric leakage as a fistulous tract (arrowhead) from the small bowel at the level of the duodenojejunostomy. Abdominal drained is also evident (white arrow).

Digestive: It comes from the digestive anastomosis or the staple line of the duodenal ends. Gastrointestinal bleeding after pancreas transplant usually occur at the duodenojejunostomy due to reduced blood flow to the graft or due to ulcers at the anastomosis. Digestive bleeding may resolve after conservative measures such as correction of coagulation abnormalities, heparin withdrawal and transfusion; surgical revision may be indicated if the bleeding does not resolve.

Precontrast CT may indicate the presence of an acute hematoma as a hyperattenuating (usually above 60 UH) collection on preconstrast CT in case of intrabdominal bleeding or hyperattenuating content in the GI lumen in case of gastrointestinal bleeding. In case of active bleeding, contrast-enhanced CT acquired in the arterial and venous phases demonstrates pooling/extravasation of the contrast agent within the hematoma or within the bowel lumen and may allow to identify the culprit vessel in case of intrabdominal hemorrhage.

Bleeding due to other arterial complications (*e.g.* arterio-venous fistula, pseudoaneurysm, arterioenteric fistula, arterio-ourinary fistula) have been reported but are infrequent, with occurrence of pseudoaneurysm being more common as a late complication[32,43]. Management can be endovascular or surgical and should be individualized[43].

Pseudoaneurysm may develop particularly at the level of anastomoses as a consequence of chemical damage due to leak of pancreatic enzymes[26]. On CT imaging, pseudoaneurysm appears as a saccular enhancing outpouching from the injured artery, with enhancement similar to other arteries, but does not increase in size on delayed phases and follows the



DOI: 10.3748/wjg.v29.i46.6049

Figure 10 A 42-year-old woman admitted in the hospital for elevation of pancreatic amylase 6 mo after transplant; final diagnosis was venous stenosis. Contrast enhanced computed tomography in the sagittal plane with Maximum Intensity Projection reconstruction demonstrates venous stenosis (arrowhead) at the anastomotic site. The pancreatic graft is enlarged with inhomogeneous enhancement which likely reflects graft dysfunction.

blood pool on all phases. Arterio-venous fistula is a very rare complication of pancreatic transplantation[32,43] which may result from the postoperative or post-biopsy laceration of both arterial and venous walls and may potentially lead to major bleeding or graft loss if untreated[43-45]. On CT, arterio-venous fistula will be demonstrated on arterial phase as enlarged Y-graft arteries with an early opacification of the donor draining vein.

Graft vascular stenosis

Vascular stenosis is relatively uncommon with an incidence of about 2.5% and more commonly occur at the anastomotic level[40]. Early detection of vascular stenosis is critical to avoid complications, including thrombosis, ischemia, and graft dysfunction[46]. The multiplanar reconstruction of the vascular tree provides a reliable method of visualizing the entire vascular anastomoses, detecting a focal decrease in caliber of the vessel (Figure 10).

CONCLUSION

In conclusion, pancreatic transplantation is a complex surgery with high morbidity often related to postoperative complications, which may occur during hospitalization, early in the first three months or in the late period. Cross-sectional imaging with CT plays a critical initial role in the diagnosis and management of postoperative complications in many transplanted patients who present to the emergency department for suspected transplant dysfunction. Therefore, radiologists should be aware of surgical techniques and normal imaging appearance of pancreatic transplantation and should be well-trained to recognize identify acute findings and provide key imaging information to optimize patient management.

FOOTNOTES

Author contributions: D'Alessandro C, made the literature search, wrote the first draft of the manuscript, and prepared most of the figures; Todisco M conceptualized the manuscript, helped with figures preparation and provided inputs; Di Bella C and Furian L wrote the first draft of the manuscript for the surgical paragraph, provided inputs and revised the draft of the manuscript; Crimì F provided inputs and revised the draft of the manuscript; Quaia E conceptualized the manuscript, provided inputs, and revised the draft of the manuscript; Vernuccio F conceptualized the manuscript, helped with the literature search, wrote the outline of the manuscript, prepared some of the figures and extensively revised the draft of the manuscript.

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ORIGINAL ARTICLE

Basic Study

Exosome-mediated transfer of circRNA563 promoting hepatocellular carcinoma by targeting the microRNA148a-3p/metal-regulatory transcription factor-1 pathway

Zhuo-Zhen Lyu, Meng Li, Ming-Yu Yang, Mei-Hong Han, Zhen Yang

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Abstract

BACKGROUND

Mesenchymal stem cells (MSCs) exert anti-oncogenic effects *via* exosomes containing non-coding RNA (ncRNA), which play important roles in tumor biology. Our preliminary study identified the interaction of the ncRNA hsa_circ_0000563 (circ563) and the circ563-associated miR-148a-3p in exosomes, as miR-148a-3p and its target metal-regulatory transcription factor-1 (MTF-1) are implicated in hepatocellular carcinoma (HCC) progression.

AIM

To identify the clinical significance, functional implications, and mechanisms of circ563 in HCC.

METHODS

The expression levels of miR-148a-3p and MTF-1 in exosomes derived from MSC and HCC cells were compared, and their effects on HCC cells were assessed. Using a dual-luciferase reporter assay, miR-148a-3p was identified as an associated microRNA of circ563, whose role in HCC regulation was assessed *in vitro* and *in vivo*.

RESULTS

The silencing of circ563 blocked the HCC cell proliferation and invasion and induced apoptosis. Co-culturing of HCC cells with MSC-derived exosomes following circ563 overexpression promoted cell proliferation and metastasis and elicited changes in miR-148a-3p and MTF-1 expression. The tumor-promoting effects of circ563 were partially suppressed by miR-148a-3p overexpression or MTF-1 depletion. Xenograft experiments performed in nude mice confirmed that circ563-enriched exosomes facilitated tumor growth by upregulating the ex-

pression of MTF-1. In HCC tissues, circ563 expression was negatively correlated with miR-148a-3p expression but positively correlated with MTF-1 levels.

CONCLUSION

MSCs may exhibit anti-HCC activity through the exosomal circ563/miR-148a-3p/MTF-1 pathway, while exosomes can transmit circ563 to promote oncogenic behavior by competitively binding to miR-148a-3p to activate MTF-1.

Key Words: Exosome; Cell communication; Noncoding RNA; Metal-regulatory transcription factor-1; Mesenchymal stem cells

Core Tip: We identified the functional implications and mechanisms of exosomal hsa_circ_0000563 (circ563) in hepatocellular carcinoma (HCC). Mesenchymal stem cells suppressed HCC proliferation and invasion *via* their exosomes. The circ563 interacts with miR-148a-3p, a molecule involved in HCC progression, and both are identified at different levels in exosomes. The tumor-promoting effects of circ563 were partially suppressed by miR-148a-3p overexpression or depletion of metal-regulatory transcription factor-1 (MTF-1). Xenograft experiments performed in nude mice confirmed that circ563-enriched exosomes facilitated tumor growth *via* MTF-1 upregulation. Our findings provide new insights into circ563/miR-148a-3p/MTF-1 signaling as a potential therapeutic target for HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a fatal disease and the most common form of primary liver cancer. Although novel chemotherapeutic agents and treatment modalities have been clinically implemented, the survival rate of patients with HCC has not yet improved[1]. Therefore, a deeper understanding of the mechanisms facilitating HCC progression is paramount for the development of more effective therapeutic strategies.

The tumor microenvironment (TME) has been an important aspect of tumor research. Recent studies indicate that mesenchymal stem cells (MSCs) are essential stromal cells in the TME and exert their effects *via* exosomes, as demonstrated by multiple studies[2,3]. Furthermore, the efficacy of therapeutic MSC transplantation has been reported in both experimental and clinical research[4-6]. As a result, MSC-derived exosomes have attracted significant attention due to their implications in intercellular communication.

Exosomes are small extracellular vesicles approximately 30-150 nm in diameter that are formed by cells through a series of regulatory processes. These vesicles are enriched in bioactive molecules like non-coding RNA (ncRNA) with crucial biological functions, whose delivery to recipient cells is involved in various physiological and pathological processes, including carcinogenesis and metastasis[7,8]. Circular RNA (circRNA) is a new class of endogenous ncRNA, which has selectively conserved microRNA (miRNA) target sites and exerts regulatory effects in cancer biology by regulating miRNA gene expression[9,10]. Such interactions between circRNA and miRNA are known as the competitive endogenous RNA theory[11]. miRNAs represent the ncRNA of 20-25 nucleotides, which mediate post-transcriptional gene silencing by binding to the 3'-untranslated regions of target mRNAs. Exosomal circRNA and miRNA are involved in tumor initiation and progression[7,8,12,13]; however, their expression profiles, functions, and dysregulation in HCC require further clarification.

This study found that MSCs suppressed HCC proliferation and invasion *via* their exosomes. The ncRNA circ563 interacts with miR-148a-3p, and both are identified at different levels in exosomes. Metal-regulatory transcription factor-1 (MTF-1) as the direct target of miR-148a-3p is implicated in HCC progression. Therefore, further studies should be performed to determine the possible role and significance of circ563/miR-148a-3p/MTF-1 axis in the development of HCC.

MATERIALS AND METHODS

Cell lines and culture

The human HCC cell lines Hep3B (RRID: CVCL_0326, iCell Bioscience, Shanghai, China) and SNU387 (RRID: CVCL_0250, Procell, Wuhan, China), MSC (Procell, Wuhan, China), and the human embryonic kidney cell line HEK 293T (RRID: CVCL_0045, Cell Research, Shanghai, China) were cultured according to the manufacturer's instructions. The cell

lines used in this study were authenticated, and no cellular cross-contamination or mycoplasma infection was detected.

Isolation and characterization of exosomes

The exosomes were isolated as previously described[14], and their morphology was observed under a transmission electron microscope. The size distribution of exosomes was analyzed using the NanoSight LM10 system (NanoSight, Amesbury, United Kingdom) equipped with fast video capture and particle-tracking software.

Exosome internalization assay

MSCs were modified to express fused CD63-eGFP *via* lentiviral transduction following the manufacturer's instructions. The HCC cells were seeded on glass coverslips coated with poly-L-lysine (Sigma, Shanghai, China). MSC-derived exosomes were co-cultured with HCC cells for 24 h at 37 °C before washing and fixation at room temperature. The uptake of labeled exosomes by recipient cells was observed under a fluorescence microscope (Leica TCS SP8 X, Leica, Shanghai, China).

Western blotting

Exosomes were harvested for protein extraction. Equal amounts of protein were subjected to sodium dodecyl-sulfate polyacrylamide gel electrophoresis and then electroblotted onto a polyvinylidene difluoride membrane (Merck, Nantong, Jiangsu, China) followed by western immunoblotting. Membranes were incubated with primary antibodies overnight at 4 °C, followed by incubation with horseradish peroxidase-conjugated secondary antibody (ZSGB-BIO, Beijing, China). The bands were visualized using a Tanon 5200 Chemiluminescent imaging system (Molecular Devices, Beijing, China) and analyzed using ImageJ software (version 1.52, National Institutes of Health, Bethesda, United States). The following primary antibodies were used: Anti-TSG101, anti-CD9, and anti-CD81 (Abcam, Shanghai, China).

Real-time polymerase chain reaction

Total RNA was extracted using the Ultrapure RNA Kit (CoWin Biotech, Beijing, China) according to the manufacturer's protocol. Equal amounts of the samples were amplified, and real-time polymerase chain reaction (RT-PCR) was performed as previously described[14]. The following primer pairs were used: MiR-148a-3p, forward: 5′-CTCAGTGCAC-TACAGAACTTTGT-3′, reverse: 5′-ATCCAGTGCAGGGTCCGAGG-3′; MTF-1, forward: 5′-GAAAAGCCATTTCG-GTGCGA-3′, reverse: 5′-CAGCCATTACTGGGGCAGAA-3′ (DingGuo Biotechnology, Beijing, China); hsa_-circRNA_0000562 (circ562), forward: 5′-TTTAGTACACAGCATGGCTCA-3′, reverse: 5′-ATTAGCACCCAT-TTTCTTCAGT-3′; hsa_circRNA_0000563 (circ563), forward: 5′-TTGGAATTTAACATGCTTGC-3′, reverse: 5′-GCATTAGCACCCATTTTCTT-3′; hsa_circRNA_00001110 (circ1110), forward: 5′-TCACTTGGGTTCATTCTATTCA-3′, reverse: 5′-GCTTGTCTTTTCTTCTGTTTCC-3′; U6, forward: 5′-GCTCGCTTCGGCAGCACA-3′, reverse: 5′-GAACGCTTCACGAATTTGCGTG-3′; glyceraldehyde-3-phosphate dehydrogenase (GAPDH), forward: 5′-AGAAGGCT-GGGGCTCATTTG-3′, reverse: 5′-AGGGGCCATCCACAGTCTTC-3′; and actin, forward: 5′-CCCTATAAAAC-CCAGCGGCG-3′, reverse: 5′-TCGTCGCCCACATAGGAATC-3′ (Tsingke Biotechnology, Qingdao, China). Data were analyzed using the comparative CT method, and the $2^{-\Delta\Delta Ct}$ method showed the difference between treatment and control conditions.

Transfection assay

Overexpression plasmids of miR-148a-3p, knockdown plasmids of MTF-1, and control empty vectors were obtained from GenePharma (Shanghai, China). Small interfering RNA targeting circ562 (sense: 5′-GGCUCAGCAAAAUG-GAUGAAAdTdT-3′; antisense: 5′-UUUCAUCCAUUUUGCUGAGCCdTdT-3′), circ563 (sense: 5′-GCUU-GCACAAGAAAUGGAUGAdTdT-3′; antisense: 5′-UCAUCCAUUUCUUGUGCAAGCdTdT-3′), and circ1110 (sense: 5′-GGUUCAUUCUAUUCAGUGACUdTdT-3′; antisense: 5′-AGUCACUGAAUAGAAUGAACCdTdT-3′) were synthesized by Hippobio (Zhejiang, China). The cells with stable overexpression of miR-148a-3p (5′-UCAG-UGCACUACAGAA-CUUUGU-3′) or circ563 or with stable knockdown of MTF-1 (5′-GCGGTACCAATGTACCTTTGA-3′) were transfected with lentiviral vectors for *in vitro* and *in vivo* studies. The cells in 6-well plates were transfected using Lipofectamine 2000 (Invitrogen, Shanghai, China), according to the manufacturer's instructions.

Cell viability assay

Cell viability was determined using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The cells were seeded into 96-well plates (approximately 1500 cells/well) before treatment. At the end of each treatment, the MTT reagent was added to the medium. The cells were incubated for an additional 4 h, and the absorbance of the samples was measured at 490 nm using a plate reader (Thermo Fisher Scientific, MA, United States). Experiments were performed in triplicate, and data were expressed as the mean optical density ± SD.

Colony formation assay

The cells (approximately 1000 cells/well) were seeded into six-well plates with different treatments, either simultaneously or subsequently. After 14 d, the cells were fixed with 4% paraformaldehyde and stained with 0.5% crystal violet, and the individual clones (> 50 cells/clone) were counted. Each treatment was performed in triplicate. Data were expressed as the mean ± SD.

Transwell assays

Transwell assays were performed to assess cell invasion and migration abilities in 24-well plates with BD chambers (8-mm pores; BD Biosciences, Shanghai, China). Approximately 1 × 10^5 cells/well were seeded into the upper chambers and cultured in a serum-free medium. The medium containing 30% serum was placed in the lower chambers. After migration through the Transwell membrane, the cells were fixed with 4% paraformaldehyde and stained with crystal violet (Solarbio, Beijing, China). Compared with the invasion assay, the Transwell chambers for the migration assay were not coated with Matrigel. All Transwell treatments were conducted in triplicate.

Flow cytometry

Following different treatments, cell apoptosis was detected using the phycoerythrin (PE) Annexin V Apoptosis Detection Kit I (BD Pharmingen, China) according to the manufacturer's instructions. The cells were harvested after trypsin digestion, centrifuged, and washed with annexin V binding buffer three times. The cells were then stained with PE annexin V and 7-amino-actinomycin D at room temperature for 15 min and analyzed using flow cytometry (BD FACSAria II, Shanghai, China), and the results were analyzed using FlowJo software (version 10; Ashland, OR, United States).

Luciferase reporter assay

A wild-type (wt) or mutant circ563 fragment was constructed and cloned into plasmids containing luciferase. The recombinant circ563-wt/mt plasmids were co-transfected into HEK 293T cells with either a negative control or a miR-148a-3p mimic using Lipofectamine 2000 (Invitrogen Inc., CA, United States). After 48 h, the luciferase activity was measured using the Dual-Luciferase Reporter 1000 Assay System (Promega, Madison, WI, United States). The firefly luciferase enzyme activity was normalized to the Renilla luciferase activity, and the ratio of firefly to Renilla luciferase activity was evaluated. The experiments were independently performed in triplicate.

Patients and specimens

Human HCC tissues and paired tumor-adjacent noncancerous liver tissues were obtained from 14 patients with HCC who underwent tumor resection at the Shandong Provincial Hospital, China. None of the patients had undergone radio- or chemotherapy before surgery. Informed consent was obtained from each participant and approved by the Institutional Review Board. The study was approved by the Institutional Medical Ethics Committee of Shandong Provincial Hospital. Patients aged ≥ 18 years and diagnosed with HCC without any local or systemic treatment were included in the study. By contrast, patients with other types of cancers, liver failure, and taking medications that affect liver function were excluded.

HCC tumor-xenograft mouse model

The animal study was approved by the Animal Ethics Committee of Shandong Provincial Hospital. The animal protocol was designed to minimize pain or discomfort during the experiments. The animals were acclimatized to laboratory conditions (23 °C, 12 h/12 h light/dark, 50% humidity, ad libitum access to food and water) for 2 wk before experimentation. Five-week-old BALB/c nude mice (Provincial Laboratory Animal Center, Jinan, China) were used for this study. Following different treatments, the Hep3B cells were prepared at 3 × 10^6 cells/100 μL. Initially, the HCC-bearing nude mice were prepared to develop subcutaneous tumors. After four weeks, circ563-enriched exosomes (approximately 10^6) were injected intratumorally into the tumor mass twice a week for two weeks. The tumor size was measured weekly, and the tumor volume was calculated using the following formula: Volume (mm^3) = tumor length × $width^2$/2. After six weeks, all mice were sacrificed to compare the tumor volumes and weights. The tumors were fixed in 10% formalin and embedded in paraffin for subsequent immunohistochemical examination.

Immunohistochemistry and scoring

The sections were stained with an anti-MTF-1 sary antibody (Zhongshan Biotechnology Co., Beijing, China). The slides were imaged and analyzed using Aipathwell software (Servicebio, Wuhan, China). The staining intensity was characterized as not present (0), weak but detectable above control (1), moderate (2), and very strong (3). The H-scores were calculated as follows: H-score = ∑(pi × i) = (percentage of weak intensity cells × 1) + (percentage of moderate intensity cells × 2) + (percentage of strong intensity cells × 3). Data were presented as the mean ± SD.

Statistical analysis

Statistical analyses were performed using SPSS 21.0 software. Data were presented in bar plots as the mean ± SD of at least three independent experiments. A P value of < 0.05 (two-tailed) was considered significant. Student's t-test was performed to determine whether the two groups were significantly different. Pearson's correlation analysis was used to assess the correlations between circ563, miR-148a-3p, and MTF-1.

RESULTS

MSCs and MSC-derived exosomes exhibiting tumor-suppressive effects on HCC with corresponding changes in miR-148a-3p and MTF-1 levels

HCC cell proliferation was inhibited by co-culturing with MSCs, which was consistent with the reduced cell viability, migration, and invasion observed under these conditions (Figures 1A-G and Supplementary Figures 1A-G). However, as shown in Figure 1H and Supplementary Figure 1H, apoptosis was induced in HCC cells. To further verify the regulatory role of MSC-derived exosomes in HCC, the exosomes were isolated and characterized by specific marker expression (Figure 1I) and particle size analysis (Figure 1J). In addition, we observed and verified the uptake of labeled exosomes in HCC cells (Figure 1K and Supplementary Figure 1I). MSC-derived exosomes also exerted substantial anti-oncogenic effects in HCC cells by blocking cell proliferation, migration, and invasion while inducing apoptosis (Figures 1L-S and Supplementary Figures 1J-Q). Therefore, MSCs inhibit HCC proliferation and metastasis *via* their exosomes.

A previous study from our laboratory demonstrated that exosomal miR-148a-3p functions as a tumor suppressor in HCC progression, with MTF-1 being its direct target[14]. In the present study, MSC-derived exosomes displayed increased miR-148a-3p and decreased MTF-1 expression levels compared with HCC-derived exosomes (Figure 1T and Supplementary Figure 1R). Co-culturing HCC cells with either MSCs or MSC-derived exosomes led to the corresponding changes in miR-148a-3p and MTF-1 expression levels (Figure 1U and Supplementary Figure 1S). This finding indicates that exosomes contain bioactive materials involved in the regulation of miR-148a-3p and MTF-1 expression in HCC cells.

Characterization of circ563 and its expression in clinical HCC

A search of the CircInteractome databases (https://circinteractome.nia.nih.gov/) yielded three potential circRNAs [circ563, hsa_circRNA_0000562 (circ562), and hsa_circRNA_00001110 (circ1110)] that are most likely to bind to miR-148a-3p based on potential complementary sequences. Further analysis was performed using dual-luciferase reporter assays and RT-PCR. The RT-PCR analyses showed that circRNA was positively correlated with MTF-1 but negatively correlated with miR-148a-3p (Figure 2A). The overexpression of miR-148a-3p considerably inhibited the luciferase activity of circ563-wt. However, the luciferase activity of circ563-mutant-type (mt) cells transfected with miR-148a-3p mimics remained unaffected, thus indicating that miR-148a-3p is a target miRNA of circ563 (Figure 2B). Subsequently, knockdown experiments were performed to investigate whether circ563 affects the biological processes of HCC cells. si-circ563 was transfected into Hep3B and SNU387 cells, both strongly expressing circ563, and the knockdown efficiency was determined by RT-PCR (Figure 2C and Supplementary Figure 2A). Exosomal circ563 (exo-circ563) expression levels were also compared with those of MSCs (Figure 2D and Supplementary Figure 2B). Silencing of circ563 expression blocked the proliferation and invasion of HCC cells and increased their apoptosis rate (Figures 2E-I and Supplementary Figures 2C-G).

Next, circ563 expression was analyzed in human HCC tissues, which showed higher circ563 levels with downregulated miR-148a-3p and upregulated MTF-1 expression levels compared with tumor-adjacent tissues (Figures 3A-C). Correlation analyses further revealed the relationships between circ563, miR-148a-3p, and MTF-1 levels in HCC (Figures 3D-F). These findings suggest that circ563 may be involved in potentiating HCC cell growth and metastasis, considering the observed correlation with miR-148a-3p and MTF-1.

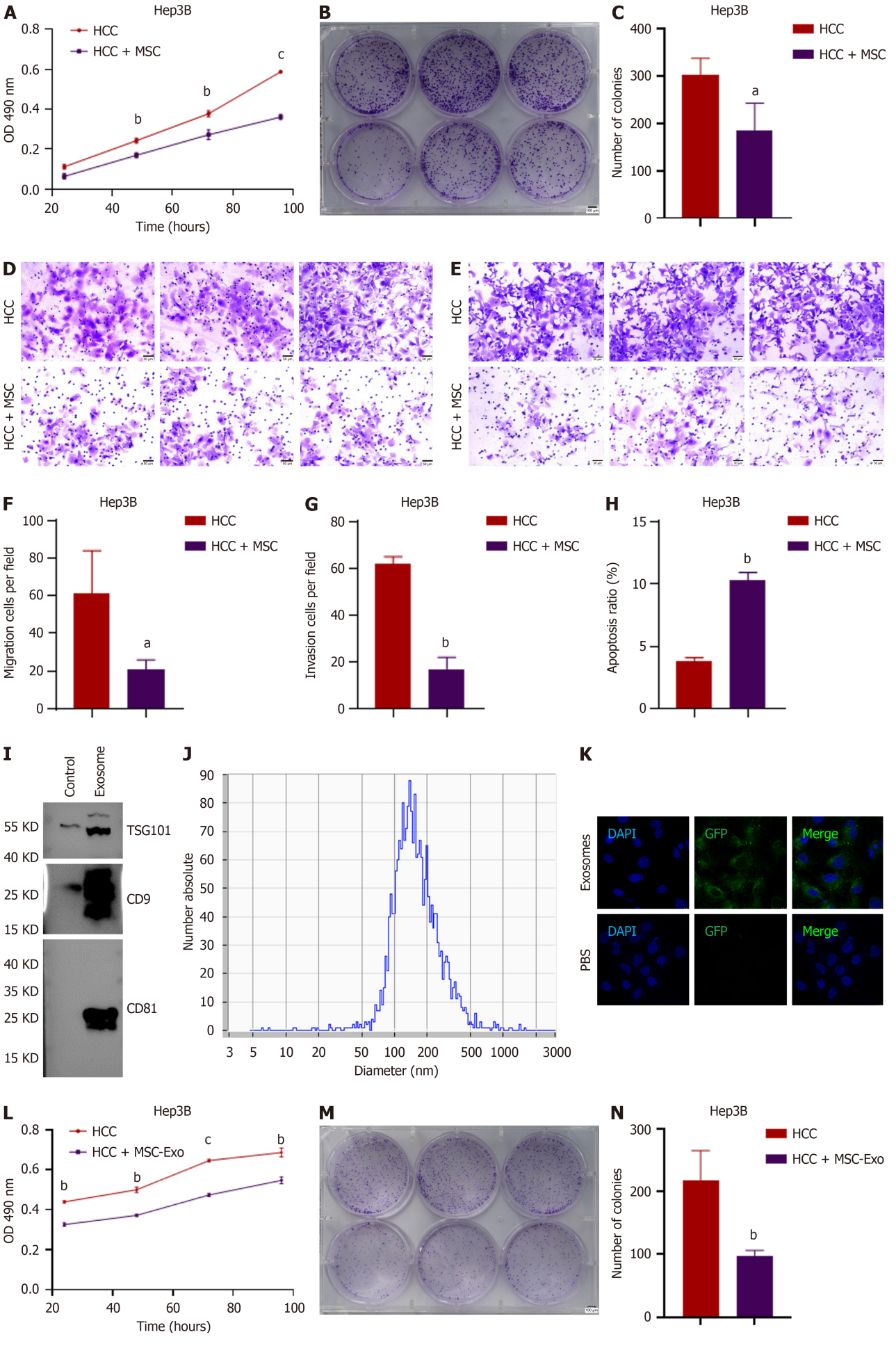
Exo-circ563 potentiating HCC progression by sequestering miR-148a-3p that regulates MTF-1

To further explore whether exo-circ563 exerts an oncogenic role, we suppressed the expression of circ563 in HCC cells and detected a reduction in exo-circ563 levels using RT-PCR (Figure 4A). The HCC cells co-treated with exosomes containing downregulated circ563 levels led to a marked reduction in cell proliferation and invasion and enhanced apoptosis (Figures 4B-I and Supplementary Figures 3A-H).

Consistent with previous results, exo-circ563 overexpression facilitated HCC cell progression. The exo-circ563 overexpression efficiency and upregulation were ascertained through RT-PCR (Figures 4J and K). We co-cultured HCC cells with MSC-derived exosomes following the circ563 overexpression and observed an increase in HCC cell proliferation and metastasis and a suppression of apoptosis (Figures 4L-S and Supplementary Figures 3I-P). These effects were partially prevented by the overexpression of miR-148a-3p or depletion of MTF-1 (Figure 5 and Supplementary Figure 4). These data indicate the involvement of a circ563-dependent mechanism in regulating miR-148a-3p expression as described by the competitive endogenous RNA theory.

circ563 accelerating HCC tumorigenesis in vivo

To further confirm the significance of exo-circ563 in HCC tumorigenesis and progression, *in vivo* experiments were performed. The upregulation of circ563 dramatically accelerated tumor growth in nude mice as evidenced by the detection of larger tumors. This effect could be reversed by miR-148a-3p overexpression or MTF-1 depletion (Figures 6A-C). Therefore, the effects of circ563, by facilitating HCC progression *via* miR-148a-3p and MTF-1 regulation, were also present *in vivo*. Correspondingly, the expression of MTF-1 in murine tumor tissues had changed similarly to tumor growth (Figures 6D and E). All these results show that circ563 accelerates HCC progression by sponging miR-148a-3p to elicit MTF-1-dependent oncogenic effects *via* the circ563/miR-148a-3p/MTF-1 axis (Figure 7).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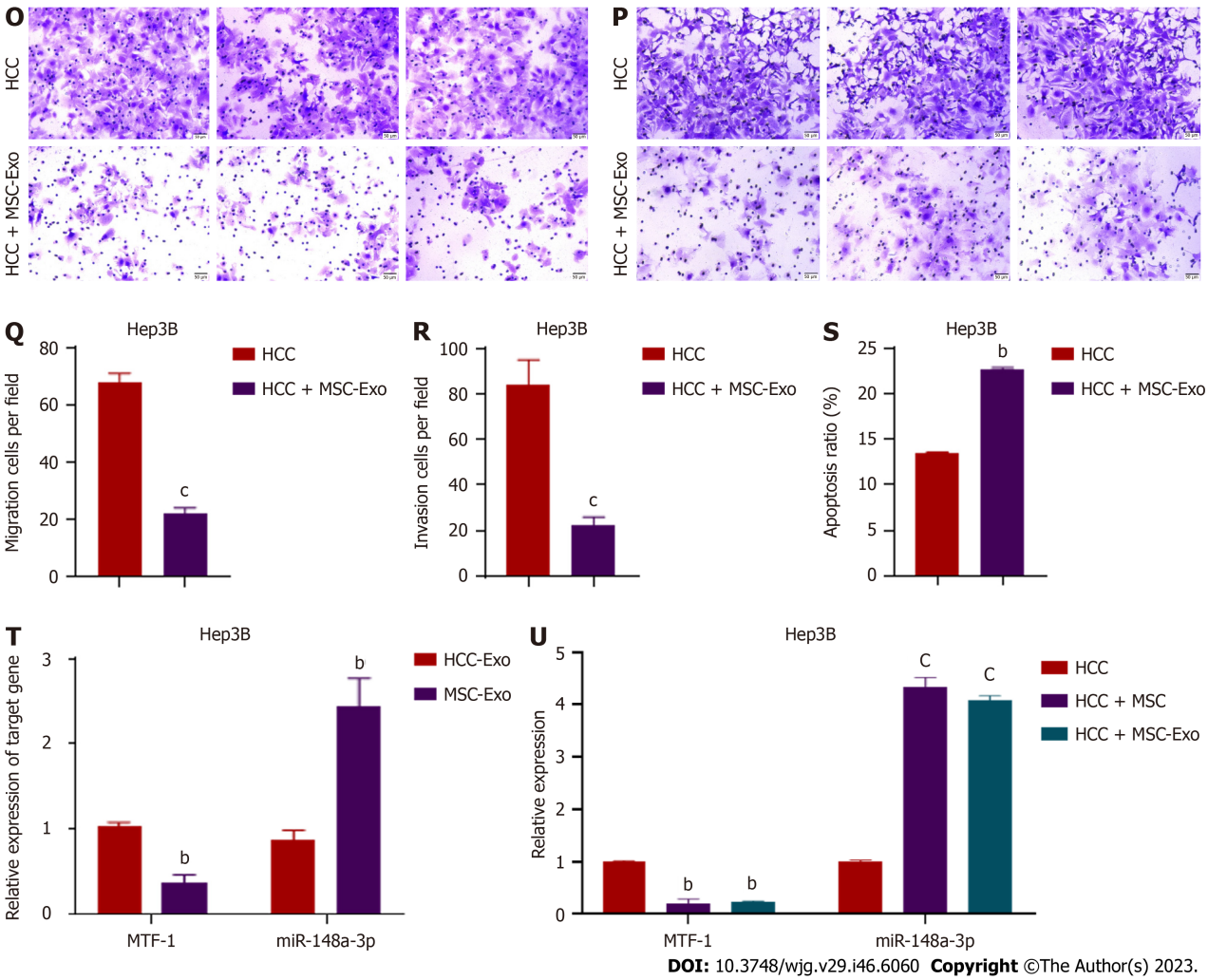

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Figure 1 Effects of mesenchymal stem cells or mesenchymal stem cell-derived exosome co-incubation on Hep3B cells. A-C: The proliferation of Hep3B cells was measured using 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide and colony formation assays; D-G: Invasion and metastasis were determined using the Transwell assay. Scale bar = 500 μm; H: Cell apoptotic rates were detected after co-incubation using flow cytometry; I: Exosomes were isolated, and specific exosome markers were identified using western blotting; J: The particle size analyzer showed that the average diameter of the vesicles was within the diameter range of exosomes; K: The uptake of labeled exosomes was observed and verified; L-S: Hep3B cell viability and metastasis were both suppressed after exposure to mesenchymal stem cell (MSC)-derived exosomes, and apoptosis was enhanced; T: Comparison of miR-148a-3p and metal-regulatory transcription factor-1 (MTF-1) expression levels in MSC- and hepatocellular carcinoma (HCC)-derived exosomes; U: Assessment of miR-148a-3p and MTF-1 expression by real-time polymerase chain reaction in HCC cells co-cultured with MSC and MSC-derived exosomes. Quantitative data from three independent experiments are shown as the mean ± SD (error bars). $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. HCC: Hepatocellular carcinoma; miRNA: MicroRNA; MSC: Mesenchymal stem cell; MTF-1: Metal-regulatory transcription factor-1; PBS: Phosphate buffered saline.

DISCUSSION

Liver cancer remains a global health challenge, and its incidence is expected to reach over 1 million cases by 2025[15]. HCC is the most common primary liver cancer. It is characterized by aggressive progression, broad metastasis, frequent recurrence, and high mortality. Therefore, a better understanding of the processes involved in HCC tumorigenesis and metastasis is urgently needed to discover new treatment strategies and improve patient prognosis.

Recent studies have established a comprehensive role of TME in disease development, making it one of the most promising areas of oncological research[16,17]. Moreover, HCC cells can alter their surrounding microenvironment to promote their growth and metastasis[18,19]. The crosstalk between tumor cells and their microenvironment is important for MSC recruitment to HCC tissues, which has also been observed in HCC animal models[19,20]. Although MSCs were initially considered as oncological delivery vehicles due to their migratory and homing capacity toward tumors[21], increasing evidence suggests that they can modulate tumorigenesis *via* the exosomes[2,3]. In the present study, co-incubation with MSCs inhibited the proliferation and invasion of HCC cells but enhanced their apoptotic capabilities. Further investigation on the mediating role of MSC-derived exosomes in the regulation of HCC cells also led to the discovery of their anti-oncogenic potential by blocking the development of HCC cells. Based on our findings, an exosome-based adjuvant intervention could offer a novel therapeutic approach to HCC by delivering the protected "cargo" directly to the tumor site.

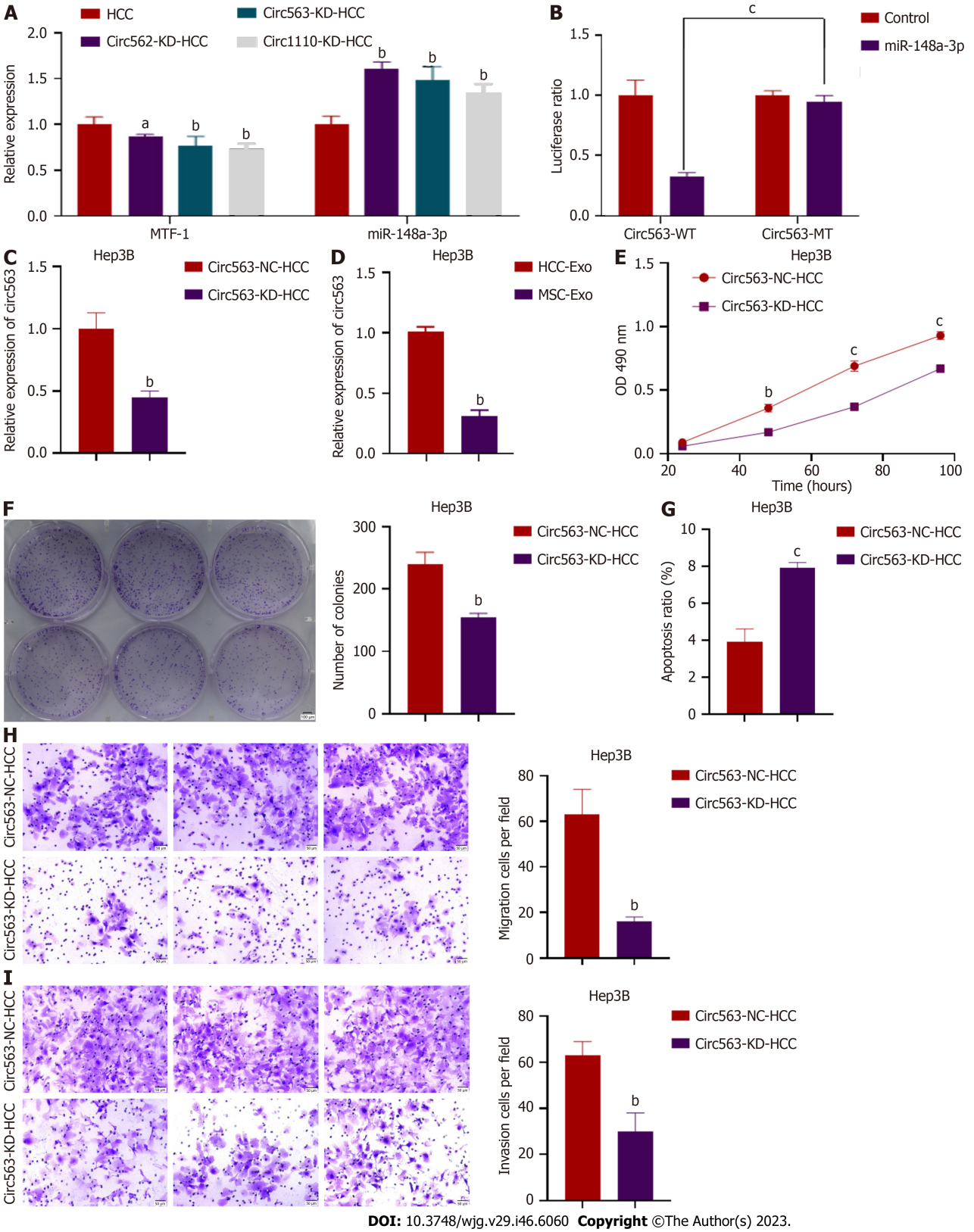

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Figure 2 Identification of hsa_circRNA_0000563. A: Three circular RNAs (circRNAs) (circ562, circ563, and circ1110) were predicted to most likely bind to miR-148a-3p, and the miR-148a-3p and metal-regulatory transcription factor-1 (MTF-1) levels in hepatocellular carcinoma (HCC) cells transfected with the predicted circRNA were detected by quantitative real-time polymerase chain reaction (RT-PCR); B: A dual-luciferase reporter assay was performed to confirm the direct binding between circ563 and miR-148a-3p based on their complementary sequences; C: The knockdown efficiency was verified by RT-PCR; D: The expression levels of circ563 in exosomes were assessed by RT-PCR; E and F: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide and colony-forming assay results showed that circ563 silencing suppressed cell proliferation and reduced the number of colonies; G: Knockdown of circ563 enhanced Hep3B cell apoptosis as determined by flow cytometry; H and I: Transwell assays revealed that reducing the levels of circ563 impaired the migratory potential and invasiveness of HCC cells. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. circRNA: Circular RNA; HCC: Hepatocellular carcinoma; Exo: Exosome.

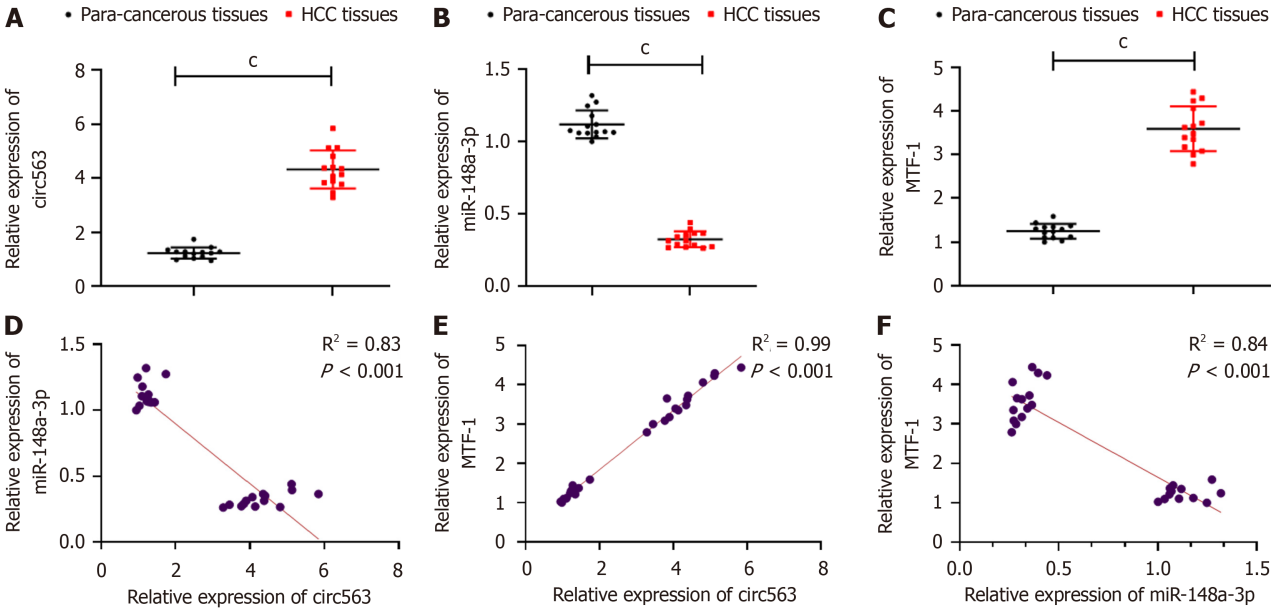

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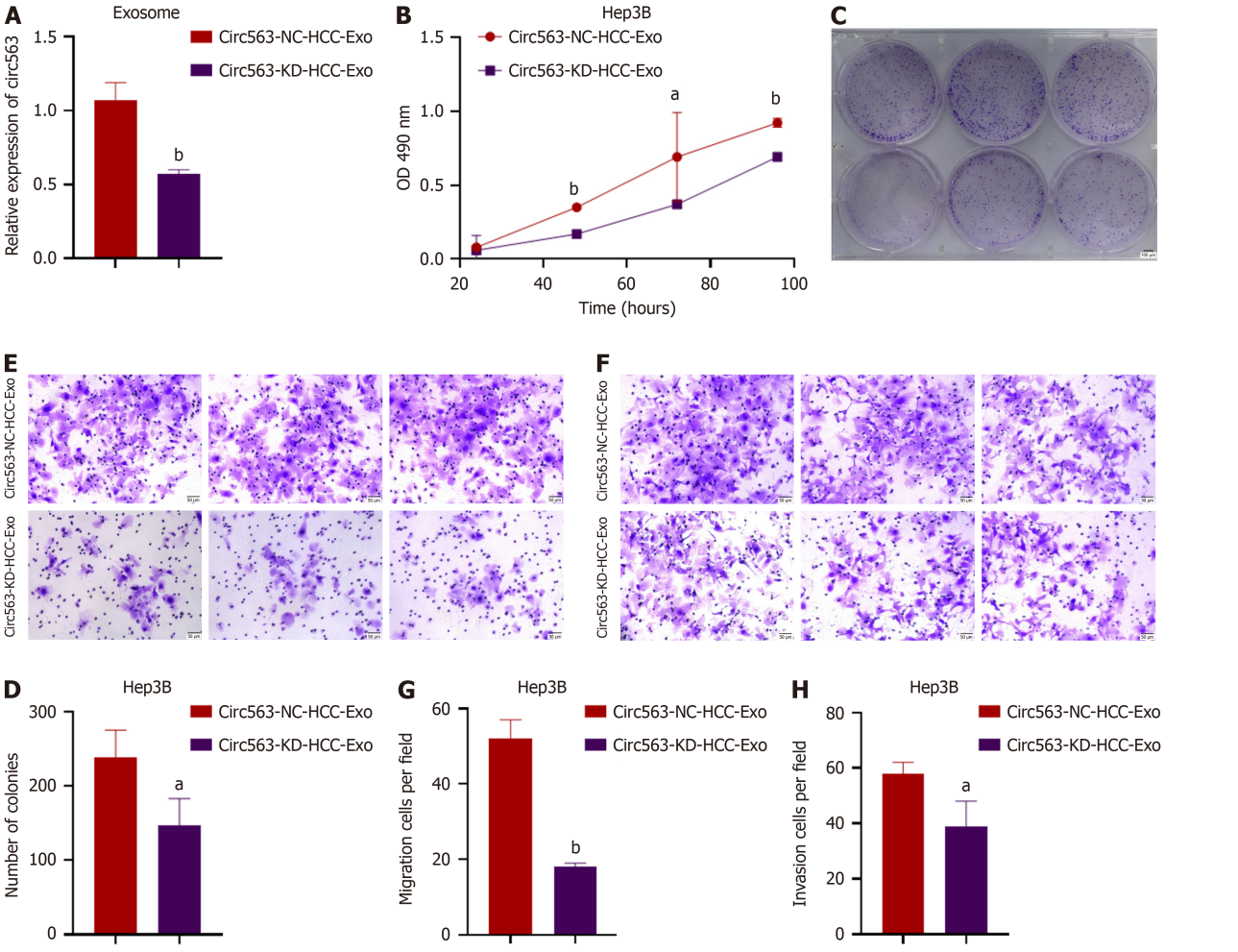
Figure 3 Clinical relevance of circ563 in hepatocellular carcinoma. To further delineate the role of circ563, hepatocellular carcinoma and paired tumor-adjacent tissues were subjected to real-time polymerase chain reaction. A-C: Enhanced circ563 expression in hepatocellular carcinoma (HCC) tissue was detected compared with that in tumor-adjacent tissues, in line with miR-148a-3p downregulation and metal-regulatory transcription factor-1 (MTF-1) upregulation; D-F: Correlation analyses indicated the relationships between circ563, miR-148a-3p, and MTF-1 expression in HCC. °$P < 0.001$. circRNA: Circular RNA; HCC: Hepatocellular carcinoma; MTF-1: Metal-regulatory transcription factor-1.



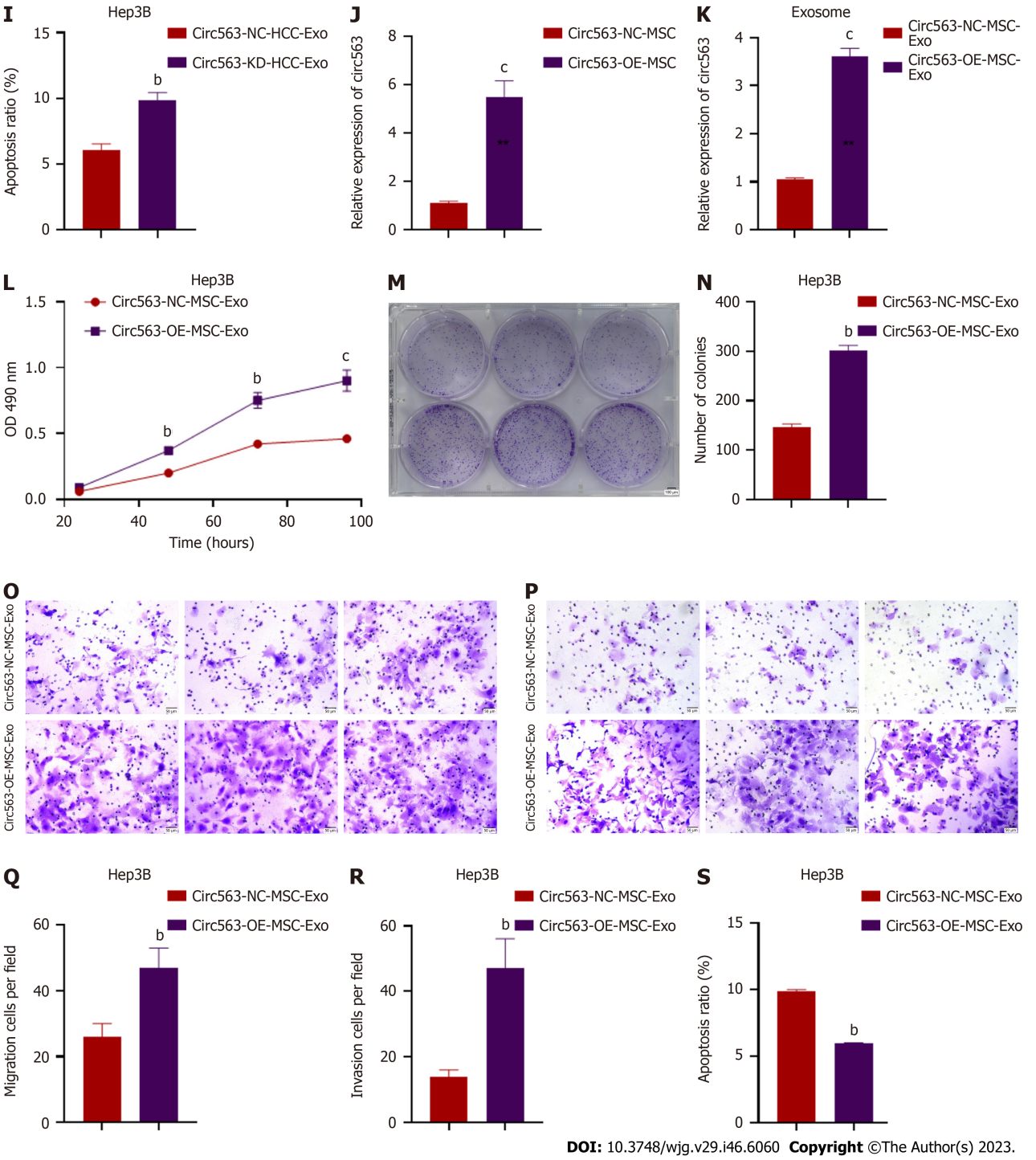


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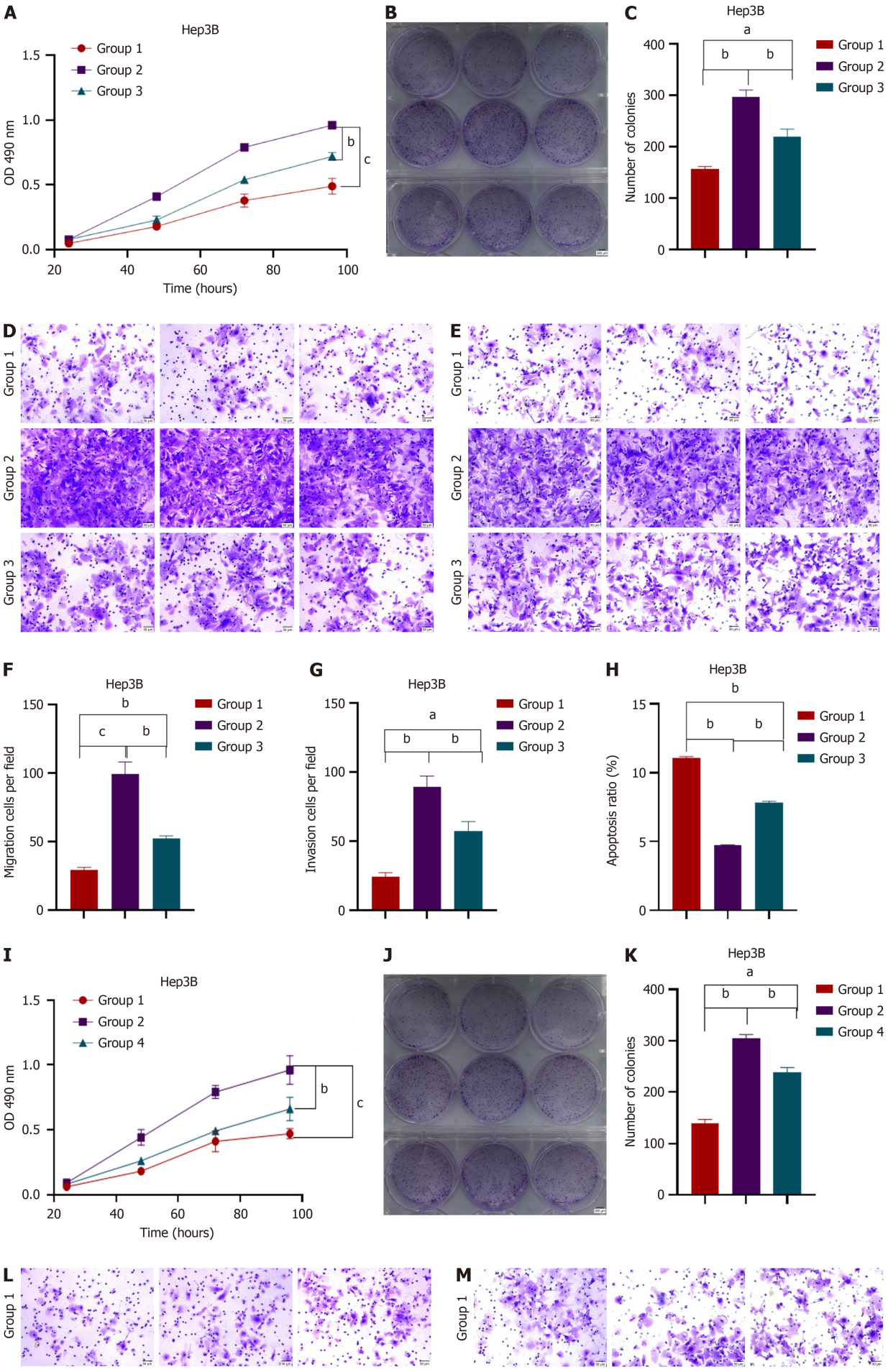
Figure 4 Exosomal circ563 facilitating hepatocellular carcinoma progression. A: First, a knockdown experiment was conducted in Hep3B cells, and the circ563 levels in Hep3B-derived exosomes were quantified by polymerase chain reaction. Hep3B cell function was assessed after co-treatment with exosomes isolated from the culture medium of circ563-knockdown Hep3B cells; B-D: Downregulation of exosomal circ563 (exo-circ563) reduced Hep3B cell proliferation and the number of colonies formed; E-H: Decreased exo-circ563 levels suppressed the migratory activity and invasiveness of the Hep3B cells; I: The downregulation of exo-circ563 was correlated with apoptosis induction; J: The efficiency of circ563 overexpression in the mesenchymal stem cells (MSCs) was determined by quantitative real-time polymerase chain reaction; K: The upregulation of circ563 in MSC-derived exosomes was confirmed; L-R: The hepatocellular carcinoma (HCC) cell proliferation, metastasis, and apoptosis rates were assessed following exosome treatment. Exo-circ563 significantly induced HCC cell proliferation, migration, and invasion; S: Flow cytometry analysis showed that the percentage of apoptotic cells was significantly decreased. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. exo-circ563: Exosomal circ563; HCC: Hepatocellular carcinoma; MSC: Mesenchymal stem cell; Exo: Exosome.

In addition, the exosomes from MSCs have shown tumor-homing capabilities in xenograft mouse models[22]. The uptake of labeled exosomes from MSCs into HCC cells was also reported in the present study. Interestingly, the exosome function most likely depends on the biological materials they encapsulate[23,24]. Mounting evidence suggests that exosomal ncRNAs (miRNA, lncRNA, and circRNA) are actively involved in the initiation and progression of various diseases by regulating cellular proliferation, differentiation, angiogenesis, and immune response[25-27].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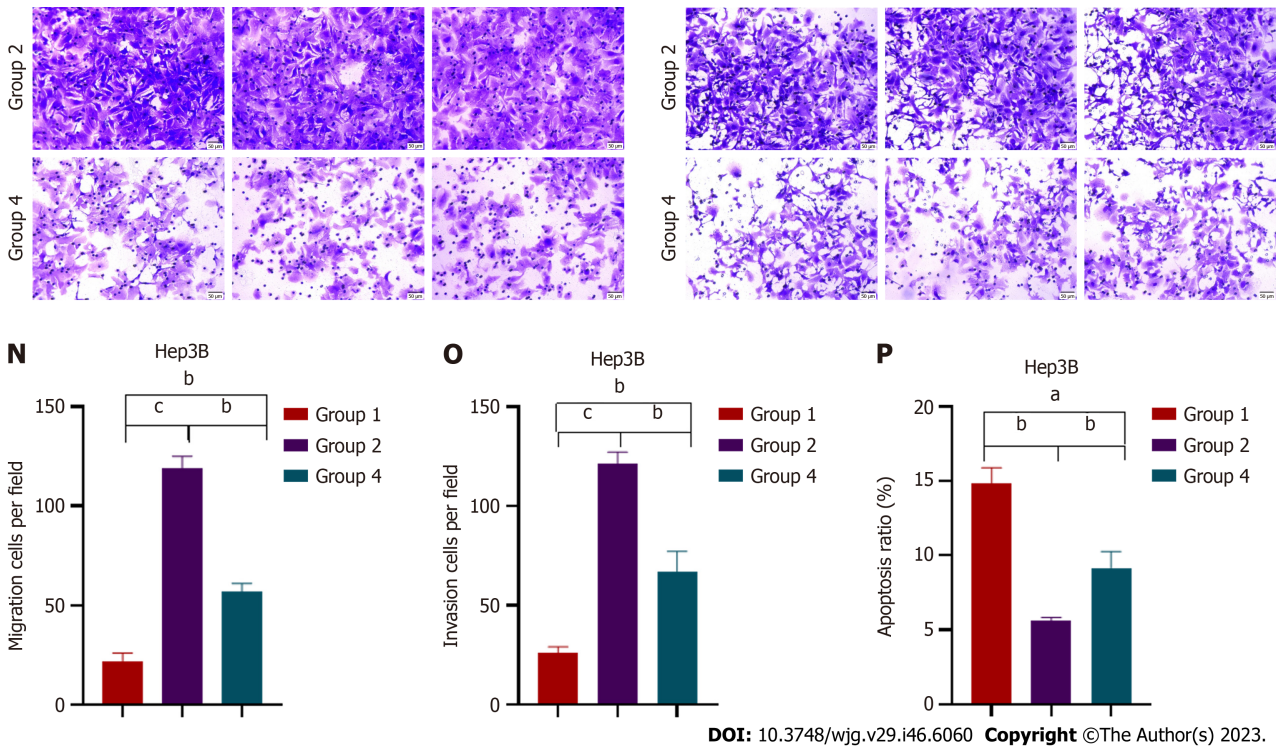

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Figure 5 Oncogenic effect of exosomal circ563 prevented by either miR-148a-3p upregulation or metal-regulatory transcription factor-1 knockdown. A-P: Exosomal circ563 promoted Hep3B cell proliferation and invasion, which were reversed by miR-148a-3p overexpression or metal-regulatory transcription factor-1 depletion. Group 1: Co-culturing Hep3B cells with mesenchymal stem cell (MSC)-derived exosomes; Group 2: Co-culturing Hep3B cells with exosomes derived from circ563-overexpressing MSCs; Group 3: Co-culturing Hep3B cells after miR-148a-3p upregulation with exosomes derived from circ563-overexpressing MSCs; and Group 4: Co-culturing Hep3B cells after metal-regulatory transcription factor-1 knockdown with exosomes derived from circ563-overexpressing MSCs. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$.

circRNAs, a subset of ncRNA that is enriched and more stable in exosomes[28], were differentially expressed in tumor tissues than in normal tissues, suggesting their involvement in tumorigenesis and disease development[29]. *In vitro* and *in vivo* experiments revealed that circRNA commonly sponges miRNA, a major class of small ncRNA closely associated with HCC[30,31], and mediates post-transcriptional gene silencing by binding to the 3′-untranslated region or open reading frames of target mRNA. Previously, our data revealed that exosomal miR-148a-3p functions as a tumor suppressor in HCC with MTF-1 as its direct target. MTF-1 maintains metal homeostasis to protect cells against injury by excess metals and exerts oncogenic potential by manipulating metal or redox homeostasis, enhancing angiogenesis, and inducing tumor development in HCC. The current findings confirmed an increase in miR-148a-3p and a decrease in MTF-1 expression levels in MSC-derived exosomes compared with HCC-derived exosomes. Following HCC cell co-culture with MSC or MSC-derived exosomes, consistent changes were observed in the miR-148a-3p and MTF-1 expression levels. This finding indicates that exosomes may contain specific bioactive materials involved in regulating the expression of miR-148a-3p and MTF-1.

Considering this, we searched the CircInteractome databases and identified hsa_circ_0000563 (circ563) as the specific target that competitively binds to or sponges miR-148a-3p. Circ563 has been implicated in the changes in the pathogenesis of atherosclerosis with significantly lower expression in patients with coronary artery disease than in those assigned as controls. However, the significance and mechanistic function of circ563 in carcinoma, especially in HCC, are yet to be studied[32]. In the current study, the loss-of-function of circ563 in HCC alters cell proliferation, invasion, and apoptosis, as well as miR-148a-3p and MTF-1 expression. Elevated levels of circ563 were correlated with more aggressive tumor behavior, highlighting its oncogenic role in HCC, leading to the conclusion that circ563 activation might be a global event during hepatocarcinogenesis. Intracellularly, circ563 competitively binds to miR-148a-3p, resulting in the activation of MTF-1 in a pattern opposite to that of miR-148a-3p alone. In addition, circ563 enrichment was identified in HCC-derived exosomes with the corresponding changes in the levels of miR-148a-3p and MTF-1. This observation suggests that: (1) Circ563 originating from cells can be delivered by exosomes into the peripheral circulation and recipient cells; and (2) Circ563 affects cell function and accelerates HCC development, given its possible correlation with miR-148a-3p and MTF-1 expression.

Furthermore, rescue experiments demonstrated that the potentiating effects of exo-circ563 could be partially blocked by miR-148a-3p upregulation or MTF-1 knockdown. The oncogenic role of circ563 was verified *in vivo*, as exosomes enriched with circ563 facilitated HCC cell growth in nude mice. Additionally, we assessed the expression patterns of circ563, miR-148a-3p, and MTF-1 in HCC tissues and compared them with those in tumor-adjacent tissues; the trends were consistent with those in HCC cells and exosomes. Collectively, the relative stability, high abundance, and conserved nature of exosomal circRNA across species make them promising candidates as oncogenic biomarkers; a better

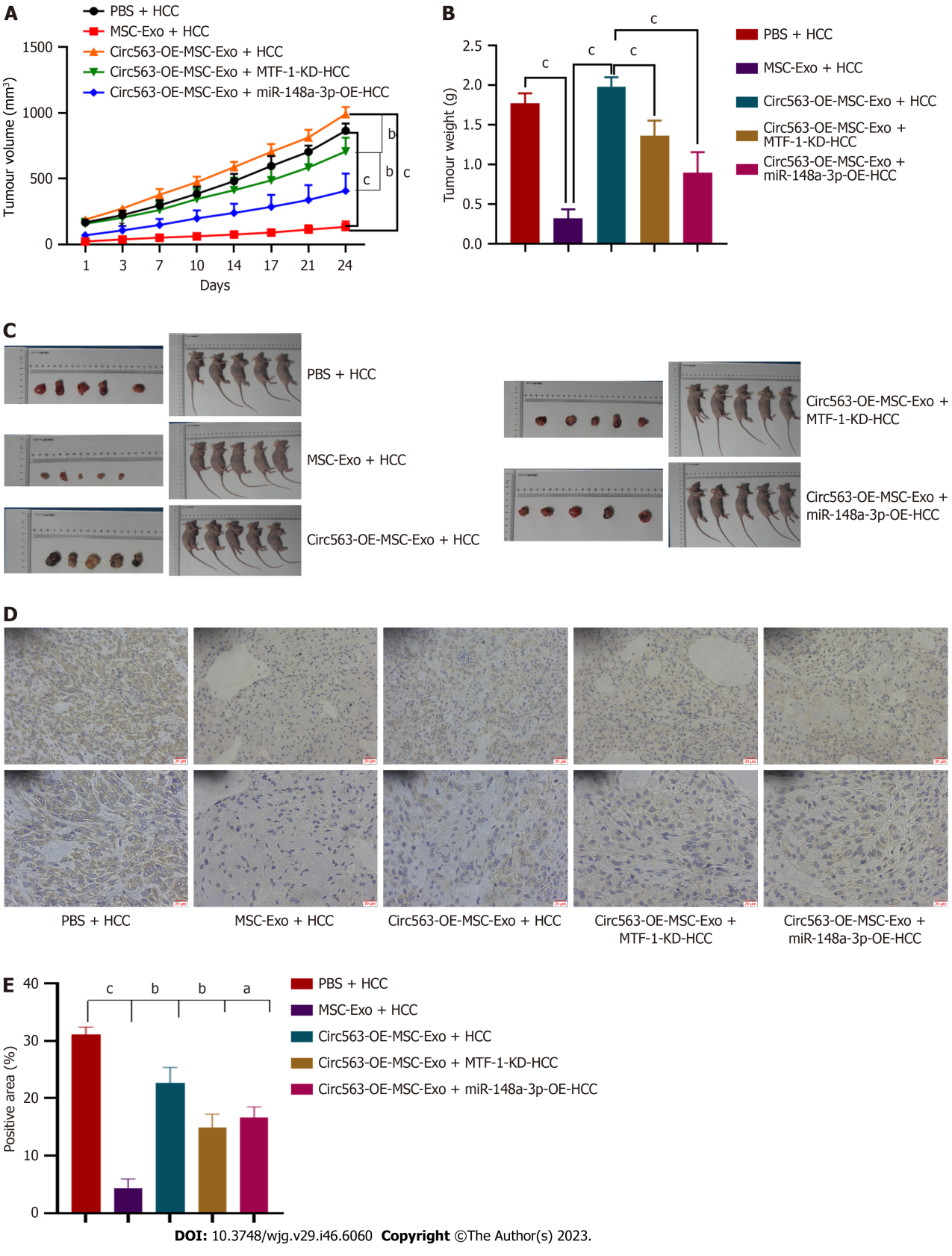

Figure 6 Circ563 promoting hepatocellular carcinoma tumor growth *in vivo*. Mouse xenografts were generated to verify the role of circ563 *in vivo*. Hepatocellular carcinoma cells stably transfected with miR-148a-3p overexpression, metal-regulatory transcription factor-1 knockdown, or control vectors were implanted into the subcutaneous tumors of mice. The xenografts were treated with exosomes after four weeks. A-C: Accelerated growth of circ563-overexpressing Hep3B-derived xenografts is shown with increased tumor volume and weight compared with the control group. Both miR-148a-3p overexpression and metal-regulatory transcription factor-1 (MTF-1) depletion partially reversed the increase in tumor volume and weight; D and E: MTF-1 staining reveals a similar trend with cell growth. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. exo-circ563: Exosomal circ563; HCC: Hepatocellular carcinoma; MSC: Mesenchymal stem cell; Exo: Exosome; MTF-1: Metal-regulatory transcription factor-1.

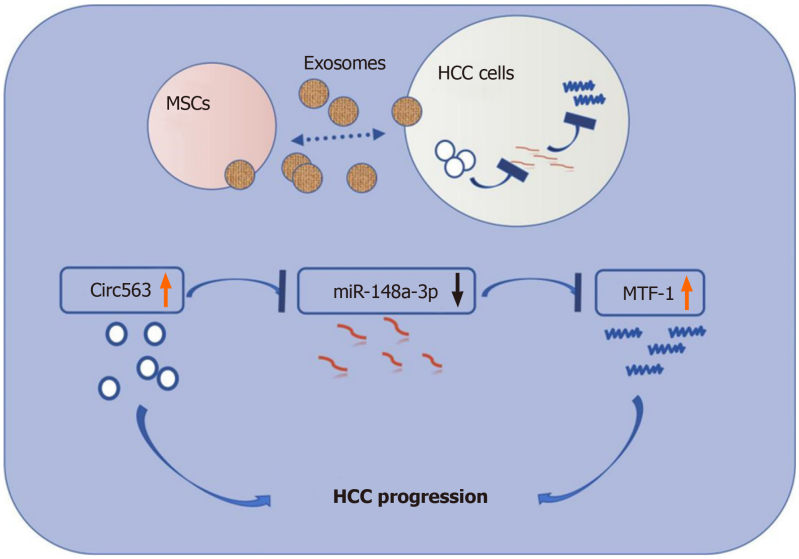

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Figure 7 The schematic model of circ 563/miR-148a-3p/metal-regulatory transcription factor-1 in hepatocellular carcinoma. MTF-1: Metal-regulatory transcription factor-1; HCC: Hepatocellular carcinoma; MSCs: Mesenchymal stem cells.

understanding of the exo-circ563-mediated intercellular network could facilitate the development of therapeutic strategies for patients with HCC.

CONCLUSION

We clarified the regulatory mechanisms of circ563, which can sponge miR-148a-3p to elicit MTF-1-dependent oncogenic effects, eventually acting as a tumor-potentiating factor in HCC. Thus, the ncRNA circ563 could be a promising therapeutic target, and liquid biopsy of serum exosomes targeting circ563 can help diagnose HCC and predict the prognosis of affected patients.

ARTICLE HIGHLIGHTS

Research background

Mesenchymal stem cells (MSCs) exert anti-oncogenic effects *via* exosomes containing non-coding RNA (ncRNA), and the efficacy of MSC-derived exosome therapies has been demonstrated. Our preliminary study identified the interaction of the ncRNA hsa_circ_0000563 (circ563) and the circ563-associated miR-148a-3p which are both enclosed in exosomes, as miR-148a-3p and its target metal-regulatory transcription factor-1 (MTF-1) are implicated in hepatocellular carcinoma (HCC) progression.

Research motivation

This study is to identify the clinical significance, functional implications, and mechanisms of circ563 in HCC.

Research objectives

This study aims to investigate the role of circ563 in modulating HCC functions.

Research methods

The expression levels of miR-148a-3p and MTF-1 in exosomes derived from MSC and HCC cells were compared, and their effects on HCC cells were assessed. Using a dual-luciferase reporter assay, miR-148a-3p was identified as an associated miRNA of circ563, whose role in HCC regulation was assessed *in vitro* and *in vivo*.

Research results

Circ563 silencing blocked the HCC cell proliferation and invasion and induced apoptosis. Co-culturing of HCC cells with MSC-derived exosomes following circ563 overexpression contributed to cell proliferation and metastasis and elicited changes in miR-148a-3p and MTF-1 expression. The tumor-promoting effects of circ563 were partially suppressed by miR-148a-3p overexpression or MTF-1 depletion. Xenograft experiments confirmed that circ563-enriched exosomes facilitated tumor growth by upregulating the expression of MTF-1. In HCC tissues, circ563 expression was negatively

correlated with miR-148a-3p expression but positively correlated with MTF-1 levels.

Research conclusions

Our findings suggested MSCs may exhibit anti-HCC activity through the exosomal circ563/miR-148a-3p/MTF-1 pathway.

Research perspectives

The study presents a new dataset related to HCC. We clarified the regulatory mechanisms of circ563, which can sponge miR-148a-3p to elicit MTF-1-dependent oncogenic effects in HCC. Thus, the ncRNA circ563 could be a potential therapeutic target, and liquid biopsy of serum exosomes targeting circ563 may help predict the prognosis of patients with HCC.

FOOTNOTES

Author contributions: Yang Z designed and coordinated the study, and wrote the manuscript; Lyu ZZ, Li M, Yang MY, and Han MH performed the experiments; Lyu ZZ, Li M, Han MH, and Yang Z acquired and analyzed the data; Lyu ZZ, Han MH, and Yang Z interpreted the data; and all authors approved the final version of the article.

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SCIENTOMETRICS

Hotspots and frontiers of the relationship between gastric cancer and depression: A bibliometric study

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Abstract

BACKGROUND

A significant relationship between gastric cancer (GC) and depression has been found in the last 20 years. However, there is no comprehensive information that helps researchers find popular and potential research directions on GC and depression.

AIM

To determine the research status and hotspots by bibliometric analysis of relevant publications on the relationship between GC and depression.

METHODS

We used the Web of Science Core Collection to search and collate the literature on GC and depression from 2000 to 2022 on 31 May, 2023. Then, visualization analysis was performed using VOSviewer software (version 1.6.19) and the Bibliometrix package in R software.

RESULTS

We retrieved 153 pertinent publications from 2000 to 2022. The annual publication count showed an overall upward trend. China had the most prominent publications and significant contributions to this field (n = 64, 41.83%). Before 2020, most studies focused on "the effect of GC on the development and progression of

depression in patients." The latest research trends indicate that "the effect of depression on the occurrence and development of GC and its mechanism" will receive more attention in the future.

CONCLUSION

The study of "the effect of depression on the occurrence and development of GC and its mechanism" has emerged as a novel research theme over the past two years, which may become a research hotspot in this field. This study provides new insights into the hotpots and frontiers of the relationship between GC and depression, potentially guiding researchers toward hot research topics in the future.

Key Words: Gastric cancer; Depression; Bibliometric analysis; Visualization; Web of Science

Core Tip: Gastric cancer (GC), the most common malignant tumour in the digestive system, has the third-highest mortality rate and the fifth-highest morbidity rate among all cancers. In recent years, some researchers have paid attention to the impact of depression on the occurrence and development of GC and tried to explore the interaction mechanism, which has become an emerging research trend in GC and depression. Bibliometric analysis is a popular and rigorous method for quantitative analysis of large volumes of scientific literature data. It is necessary to investigate the relationship between GC and depression. However, as far as we know, there is no bibliometric study on GC and depression. This study shows the hotspots and frontiers of GC and depression on a global level.

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INTRODUCTION

Gastric cancer (GC), the most common malignant tumour in the digestive system, has the third-highest mortality rate and the fifth-highest morbidity rate among all cancers[1]. As the most common mental disorder, depression is particularly prevalent in cancer patients in recent studies[2-4]. At present, the discussion on the pathogenesis of depression is quite rich, mainly including miRNAs that disorderly expressed[5], receptors and their gene abnormality[6], cerebral structural and functional changes[7]. On the one hand, cancer patients often experience painful emotional reactions, some of which can manifest as depression. On the other hand, depression affects the attitude of cancer patients toward cancer and adherence to drug treatment and the endocrine and immune function, which in turn affects cancer progression[8]. There is increasing evidence that mental disorders such as depression are associated with the incidence and progression of cancer[8-11].

The current research status on the relationship between cancer and depression is still unknown. Studies have focused on research topics such as breast cancer and depression[11,12], lung cancer and depression[13], and colorectal cancer and depression[14]. In recent years, some researchers have paid attention to the impact of depression on the occurrence and development of GC and tried to explore the interaction mechanism, which has become an emerging research trend in GC and depression.

Bibliometric analysis is a popular and rigorous method for quantitatively analyzing large volumes of scientific literature data. Based on the databases of academic publications, such as Pubmed, Web of Science, and Scoups, can reveal the status, hotspots, and emerging trends in a particular research field[15]. It can provide comprehensive information that helps researchers find popular and potential research directions in specific disciplines.

It is necessary to investigate the relationship between GC and depression. However, as far as we know, there is no bibliometric study on GC and depression. Therefore, this study aims to provide an overview of the research status on the relationship between GC and depression by bibliometric analysis. Furthermore, we tried to propose the hotspots, evolution trends, and future research advancement patterns in this field. In addition, future research patterns are forecast based on evaluating bibliometric results in this field.

MATERIALS AND METHODS

Data sources

We selected the Web of Science Core Collection (WOSCC) for the literature collection. WOSCC is the world's leading citation database. It contains records of articles from the highest-impact journals worldwide, including open-access journals, conference proceedings, and books. Notably, the coverage of specific titles extends back to the year 1900[16,17].

This comprehensive and extensive database provides a robust foundation for our bibliometric analysis.

Search strategies

We focused on the WOSCC, collecting the literature on "GC and depression". Then, we searched and exported the relevant articles to the WOSCC on 31 May, 2023. Our search strategy was as follows: Topic = (stomach neoplasm OR stomach cancer OR stomach tumour stomach carcinoma OR gastric carcinoma OR gastric carcinoma or gastric cancer OR gastric neoplasm OR gastric tumour AND TS = depression OR depressive disorder OR depressive symptom. The retrieval time range was from 1 January, 2000 to 31 December, 2022. We included only articles, reviews, and systematic reviews to facilitate further literature content analysis, excluding irrelevant publications.

Bibliometric analysis

We used an Excel spreadsheet to collect bibliometric indicators: The total number of publications, the year of publication, the top ten countries, the Journal Citation Reports (JCR) Quartile rankings of the source journals, the top 5 citations, and the research types.

In addition, we utilized the Bibliometrix package of R-studio software to analyze the included literature data and Biblioshiny for data visualization. In this study, we examined the top ten countries contributing to the field of GC and depression and the annual publication trend for each country.

Visualized analysis

We used VOSviewer software (Version 1.6.19) for keyword co-occurrence analysis to visualize networks of keywords. The network focuses on understanding a particular field's knowledge composition and structure by studying the links between keywords in the article. By drawing the keywords co-occurrence visualization maps, we can identify the hotspots and frontiers in "GC and depression".

Classification of publications

For the classification of publications, we divided the research on the correlation and interaction mechanism between GC and depression into two groups: "GC to depression" and "depression to GC." Based on the above grouping, we used the 2022 JCR Quartile rankings to classify the publications within the two groups. The journal sources not existing in the JCR Quartile rankings were excluded. Additionally, we classified the two research groups according to the classification standard of medical studies[18], which is based on research methodologies.

RESULTS

Analysis of annual publications

In the WOSCC, we retrieved 153 publications on "GC and depression". The number of publications on this topic has generally increased from 2000 to 2022, indicating a growing interest in this field among researchers. A more rapid growth in the number of publications was observed from 2019 to 2021, with 2021 recording the highest annual number of articles (n = 29) (Figure 1).

Top active countries

Over the past 22 years, at least 21 countries have published relevant papers on "GC and depression". The top ten countries issued 140 articles, accounting for 90.32% of the total publications in this field (Figure 2A). The most significant number of publications was from China (n = 64), the total number of publications is 7287986, followed by South Korea (n = 28), the total number of publications is 1368778, and the third was the United States (n = 16), the total number of publications is 210673. From the trend of annual publications of the top ten countries, China has the most significant increase and the fastest growth rate, followed by South Korea and the United States (Figure 2B).

Hotspots and frontiers

We imported the publication related to "GC and depression" in the WOSCC into VOSviewer (version 1.6.19) software, selected all keywords (including author keywords and keywords plus) that occurred more than five times, and divided these keywords into five clusters with a different color (Figure 3). The five cluster are "effect of treatments on GC patients with mental disorders" (cluster 1, red), "epidemiological researches on GC and depression" (cluster 2, green) "diagnosis of GC causing mental disorders and the interaction mechanism" (cluster 3, blue) "outcomes of GC patients" (cluster 4, yellow) and "social support of mental disorders in GC patients" (cluster 5, purple).

In cluster 1, the high-frequency keywords are quantity of life, depression scale, gastrectomy, and chemotherapy. In cluster 2, the high-frequency keywords are risk, prevalence, epidemiology, and mortality. In cluster 3, the high-frequency keywords are diagnosis, anxiety, expression, and apoptosis. In cluster 4, the high-frequency keywords are survivors, symptoms, association, and outcomes. In cluster 5, the high-frequency keywords are adjustment and social support. These results indicate that "GC and depression" included five research directions from 2000 to 2022.

Overlay visualization is shown in Figure 4. The keywords colored purple mean the average year of the appearance of the keyword is earlier than other colors. Keywords colored yellow means the average year of the appearance of the keyword is later. Before 2012, the hospital anxiety and depression scale of patients with GC was the most concerned topic (purple). Then, researchers gradually turned to the psychological adjustment, quality of life, and diagnosis of patients

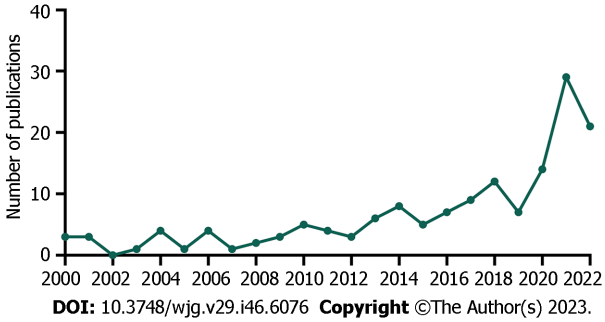

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Figure 1 The number of publications from the Web of Science containing gastric cancer and depression per year from 2000 to 2022.

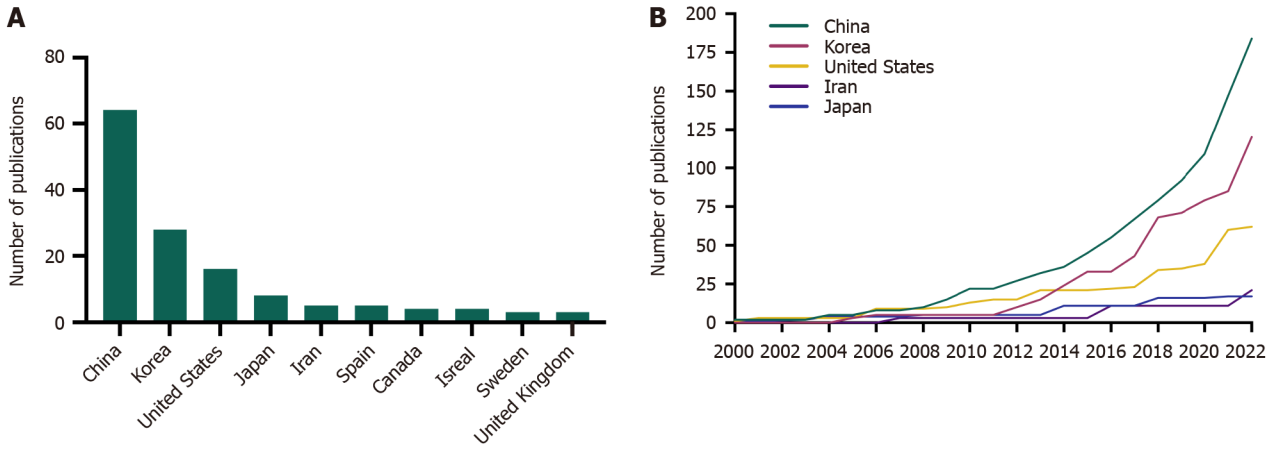

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Figure 2 Top active countries with the most publications on gastric cancer and depression. A: The top 10 most published countries; B: Annual publication trends for the top 5 most published countries.

with GC (green). In recent years, researchers have paid more and more attention to the association between GC and depression, the mechanism of interaction between the two, and the risk factors (yellow) (Figure 4).

Baseline characteristics of publications on the relationship between GC and depression

From 2000 to 2022, the number of publications on "GC to depression" and "depression to GC" showed an increased trend. Compared with the first research on "depression to GC" published in 2004, the research on "GC to depression" published earlier, was published in 2001. In addition, the number of publications of "GC to depression" was higher than "depression to GC" before 2020 and was lower after 2020 (Figure 5).

From 2000 to 2022, the number of publications on "GC to depression" is 48, and "depression to GC" is 27. China is the most active country in both groups, followed by South Korea. Furthermore, China has a higher proportion of publications in "depression to GC" than other countries (n = 17, 63%) (Figure 6).

JCR Quartile rankings and top-cited publications on the relationship between GC and depression

We analyzed the JCR Quartile rankings results for the two groups. The JCR Quartile rankings of publications on "GC to depression" were distributed as follows: Q1 (26%), Q2 (43%), Q3 (17%), and Q4 (14%). However, the JCR Quartile rankings of publications on "depression to GC" were Q1 (43%), Q2 (28%), Q3 (24%), and Q4 (5%). Compared with "GC to depression", there were more publications on "depression to GC" in Q1. Furthermore, publications on "depression to GC" in Q4 only accounted for 5%, which was less than "GC to depression" (Figure 7).

We summarized the top five most frequently cited publications in "GC to depression" and "depression to GC", respectively. Brintzenhofe-Szoc *et al*[19], published in *Psychosomatics* in 2009, had the most cited frequency in "depression to GC" (frequency of cited = 226). Lee *et al*[20], published in the *Journal of Neurogastroenterology and Motility* in 2015, had the most cited frequency in "depression to GC" (frequency of cited = 84) (Tables 1 and 2).

Study types of publications on the relationship between GC and depression analysis

Our analysis revealed that the most prevalent research method in "GC to depression" was the epidemiological research method, among which cross-sectional studies accounted for 40%, followed by cohort studies. In "depression to GC", the most used is the basic research method, including cell, gene, animal, and biochemical research methods (Figure 8).

Table 1 Top cited list of the top 5 highly cited papers related to "gastric cancer to depression" from 2001 to 2020

Ranking	Authors	Title	Journal	Time cited
1	Brintzenhofe-Szoc *et al* [19]	Mixed Anxiety/Depression Symptoms in a Large Cancer Cohort: Prevalence by Cancer Type	*Psychosomatics*	226
2	Nordin *et al*[36]	Predicting anxiety and depression among cancer patients: a clinical model	*European Journal of Cancer*	121
3	Hong and Tian[37]	Prevalence of anxiety and depression and their risk factors in Chinese cancer patients	*Supportive Care in Cancer*	118
4	Tavoli *et al*[54]	Anxiety and depression in patients with gastrointestinal cancer: does knowledge of cancer diagnosis matter?	*BMC Gastroenterology*	98
5	Kim *et al*[40]	Prevalence and prognostic implications of psychological distress in patients with gastric cancer	*BMC Cancer*	68

Table 2 Top cited list of the top 5 highly cited papers related to "depression to gastric cancer" from 2001 to 2020

Ranking	Authors	Title	Journal	Time cited
1	Lee *et al*[20]	The Effect of Emotional Stress and Depression on the Prevalence of Digestive Diseases	*Journal of Neurogastroenterology and Motility*	84
2	Shi *et al*[38]	Catecholamine up-regulates MMP-7 expression by activating AP-1 and STAT3 in gastric cancer	*Molecular Cancer*	72
3	Bica *et al*[39]	Depression as a Risk Factor of Organic Diseases: An International Integrative Review	*Journal of Nursing Scholarship*	38
4	Nan *et al*[55]	Effects of depression on parameters of cell-mediated immunity in patients with digestive tract cancers	*World Journal of Gastroenterology*	23
5	Huang *et al* [44]	Depression accelerates the development of gastric cancer through reactive oxygen species-activated ABL1 (Review)	*Oncology Reports*	21

DISCUSSION

General status, hotspots, and frontiers in the relationship between GC and depression

This study is the first bibliometric analysis of the relationship between GC and depression, providing a potential opportunity to explore the interaction mechanism further. This study analyzed the global publications on GC and depression from 2000 to 2022. The results showed an increasing trend in the annual number of publications in this field. In addition, we could conclude that China and South Korea are the most productive countries in GC and depression. According to the global statistics of GC in 2020, the incidence of GC in China and South Korea is among the top five, and the disease burden is heavy[21]. Therefore, there is more research on GC in China and South Korea than in other countries, and the increase in annual publication volume is relatively significant.

The keyword co-occurrence analysis of the research on GC and depression revealed the distribution of research topics in this field from 2000 to 2022. Combining the overlay visualization, we could present the research hotspots and frontiers in the field. Most researchers focus on which cancer patients are often accompanied by depression and the incidence of depression in GC patients. Kouhestani *et al*[22] estimated the prevalence of depression in GC patients globally based on WHO region classification. They found that 37% of GC patients were accompanied by depression. Regionally, the Eastern Mediterranean region has the highest prevalence of depression in GC patients among all WHO regions. The results suggested that depression is high among GC patients.

Depression could affect the overall health of GC patients. GC patients with depression might significantly impact their quality of life, prognosis, and survival rate[23]. Therefore, researchers have also shown significant interest in the quality of life of GC patients with depression and its improvement. The diagnosis and treatment of GC might impact the psychological condition of patients[24]. Some interventions, such as proper social support[25] and multidisciplinary cooperative continuous nursing[26], could relieve the depression of GC patients.

The research on the interaction mechanism between GC and depression from the perspective of epidemiological[27,28], cellular[29,30], and genetic[30,31]levels became an emerging research topic. This trend might be due to the many kinds of research on hot topics published during this period, revealing innovative explanations emerging from new research fields. For example, the gut-brain axis theory established bidirectional interactions among the brain, the gut, and the gut microbiome[32,33]. Furthermore, many prospective epidemiological studies have shown that depression is a risk factor for cancer[12,34]. In addition, some studies have confirmed that depression is a risk factor for digestive carcinoma and proposed a mechanism for it[35]. These innovative explanations provided new ideas for exploring the interaction mechanism of GC and depression.

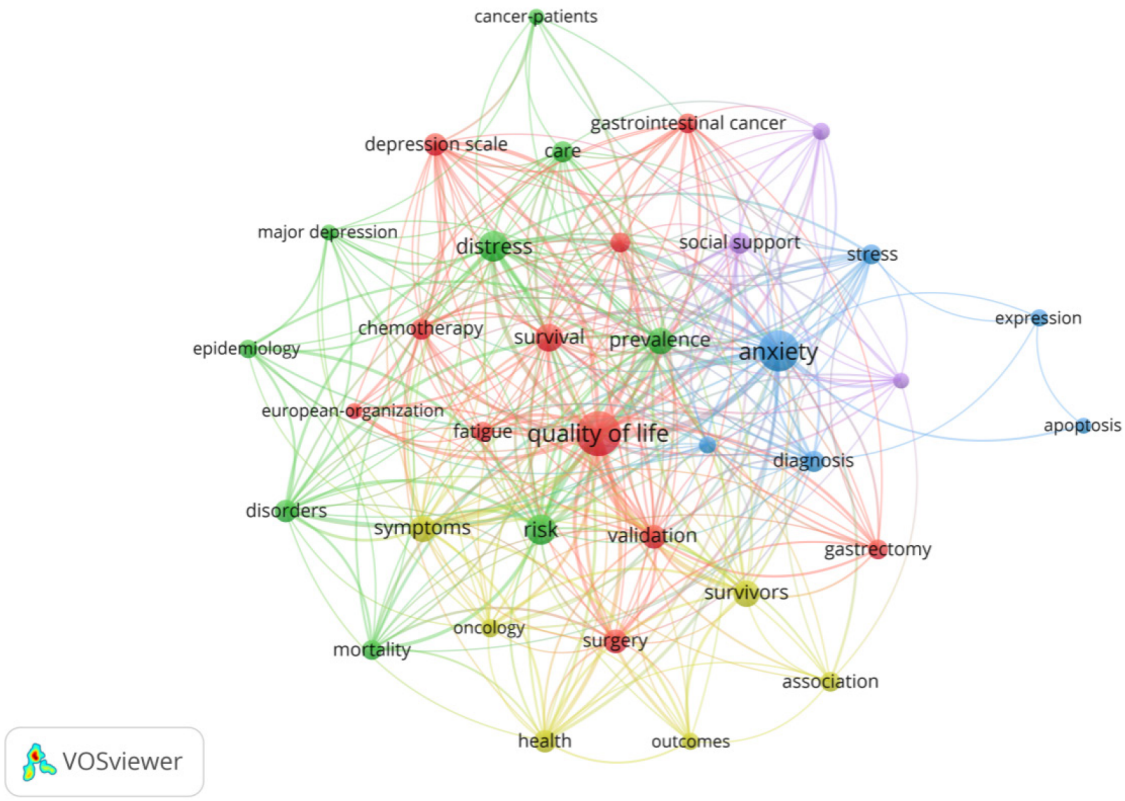

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Figure 3 The network visualization map of keywords co-occurrence in gastric cancer and depression during 2000-2022 based on VOSviewer.

The difference in publications between the two groups

This study indicated that in "GC to depression", the top five most highly cited publications are epidemiological studies, such as the prevalence, mortality, and risk factors of GC patients with depression. This result was also consistent with cluster 2 in the keyword co-occurrence analysis (Figure 3, green). The publication most frequently cited was Brintzenhofe-Szoc *et al*[19], entitled "Mixed Anxiety/Depression Symptoms in a Large Cancer Cohort: Prevalence by Cancer Type", published in *Psychosomatics* in 2009. This study found that mixed anxiety/depression has a high incidence of gastric, pancreatic, head and neck, and lung cancer. The second most cited publication was by Nordin *et al*[36] from the *European Journal of Cancer*. This study indicated that levels of anxiety and depression at diagnosis predict a similar status 6 mo later, and the hospital anxiety and depression scale, combined with a single question about social support, maybe a suitable screening tool for clinical use. The third most cited publication was by Hong and Tian[37] from *Supportive Care in Cancer*. This study showed that depression level was high among Chinese cancer patients. Patients with lung, esophagus, cervix, liver, and stomach cancers were the high-risk groups for depression.

In "depression to GC", researchers mainly focus on the mechanism. The most highly cited was by Lee *et al*[20], entitled "The Effect of Emotional Stress and Depression on the Prevalence of Digestive Diseases", published in the *Journal of Neurogastroenterology and Motility* in 2015. This study showed depression was associated with peptic ulcer disease, adenoma/colon cancer, and GC. Depression was an independent risk factor for gastric adenoma/GC and might be a cause of GC. The second cited publication was by Shi *et al*[38] from *Molecular Cancer*. This study found that up-regulation of matrix metalloproteinase-7 expression through beta 2-adrenergic receptors (AR)-mediated signaling pathway is involved in the invasion and metastasis of GC. The third cited publication was by Bica *et al*[39] from the *Journal of Nursing Scholarship*. This study indicated that mechanisms connecting depression to physical illness appear to involve alterations in the hypothalamic-pituitary axis, unhealthy lifestyle, chronic or acute stressors including posttraumatic stress, an increase in C-reactive protein in men, taking antidepressant medication, and social and emotional loneliness.

We further analyzed the publications on "GC to depression" and "depression to GC". We found that the number of publications in China ranked first in both groups, especially in "depression to GC". Compared with other countries, China focused on the impact of depression on GC patients and the mechanism of it earlier. In addition, we found that research on "depression to GC" was mainly published in Q1 journals, indicating that this research topic might become an exciting research direction in the future.

The difference in research types between the two groups

In "GC to depression", the most research type was epidemiological study, among which 40% were cross-sectional studies. For example, Kim *et al*[40] designed a cross-sectional study and found that depression is common in patients with all stages of GC and is associated with worse outcomes. Kwon *et al*[27] designed a case-control study and identified a

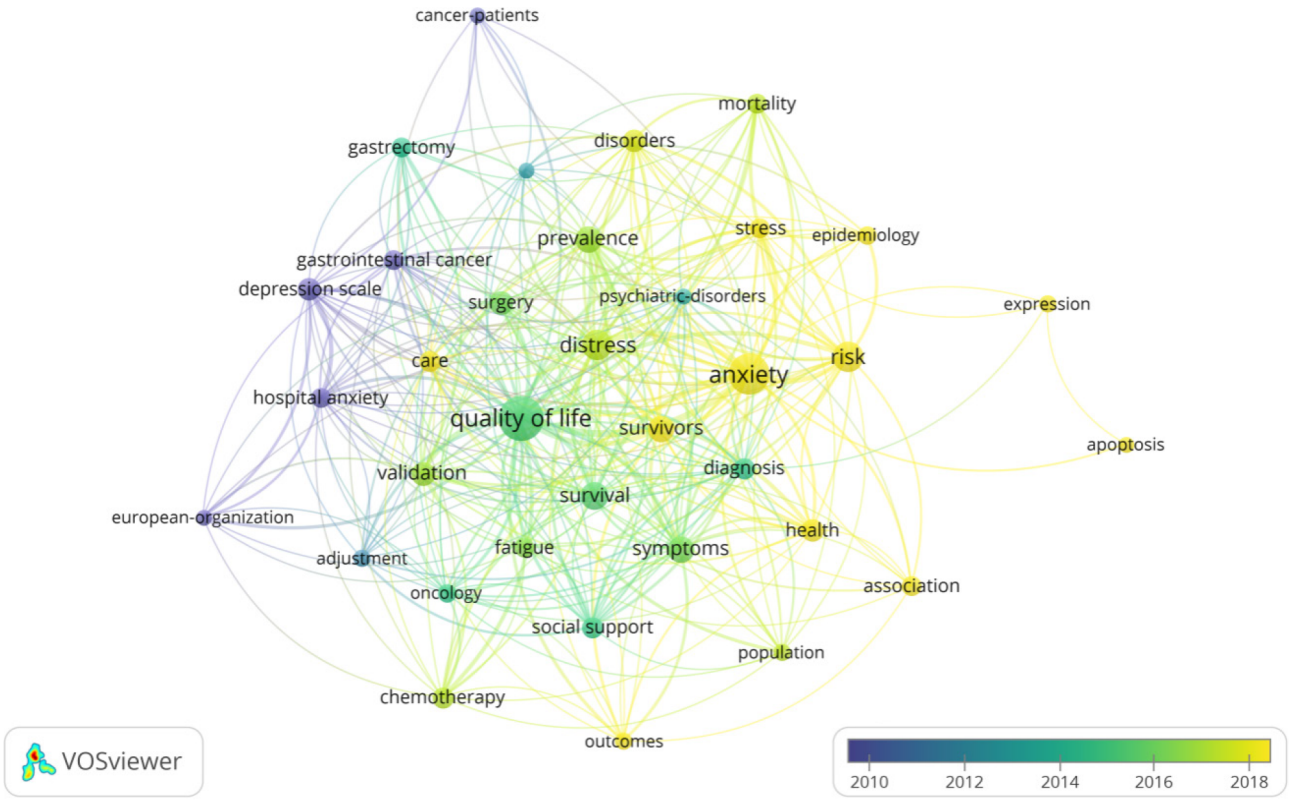

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Figure 4 The overlay visualization map of keywords co-occurrence in gastric cancer and depression during 2000-2022 based on VOSviewer.

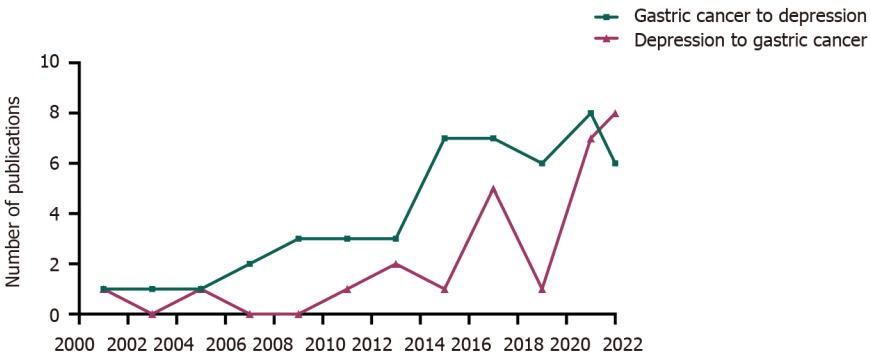

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Figure 5 Comparison of the annually published papers on "gastric cancer to depression" and "depression to gastric cancer".

significant relationship between GC and depression among South Korean adults, especially among female patients between 60 and 69 years old of high income and living in metropolitan regions. In addition, Liu and Wang *et al*[41] conducted a prospective cohort study and found that postoperative depression gradually worsened, relating to poor prognosis, and the degree of malignancy in GC patients is positively correlated with the severity of depression.

In "depression to GC" was mainly basic studies. In recent years, there has been a significantly increased number of publications on the mechanism of depression to GC. This trend might be due to recent epidemiological evidence indicating that mental disorder is a risk factor for GC, but the mechanism is still unclear[20,42,43]. There are four basic study types in "depression to GC": cell study, genetic study, biochemistry, and animal study. This result showed that researchers mainly focused on how depression affects the occurrence and development of GC and conducted research based on animal, cell, gene, and biochemistry levels.

As mentioned above, Shi *et al*[38] confirmed the effect of depression on GC at the genetic level in 2010. Other researchers have found that oxidative stress (OS) is related to GC and depression. Huang *et al*[44] found that high levels of reactive oxygen species (ROS) can activate ABL1 in response to OS. That triggered ABL1 subsequently contributed to the development of GC *via* interactions with the downstream targets and corresponding signaling pathways. Based on this study, they further explored the mechanism and found that ROS-activated ABL1 mediates inflammation by

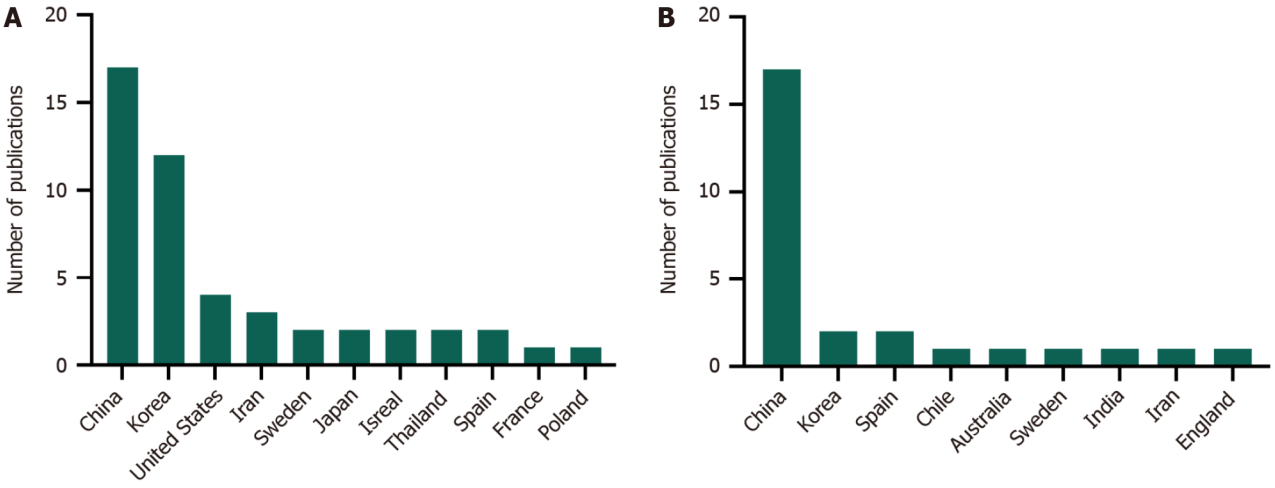

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Figure 6 Comparison of the number of publications on "gastric cancer to depression" and "depression to gastric cancer" in different countries. A: "Gastric cancer (GC) to depression"; B: "Depression to GC".

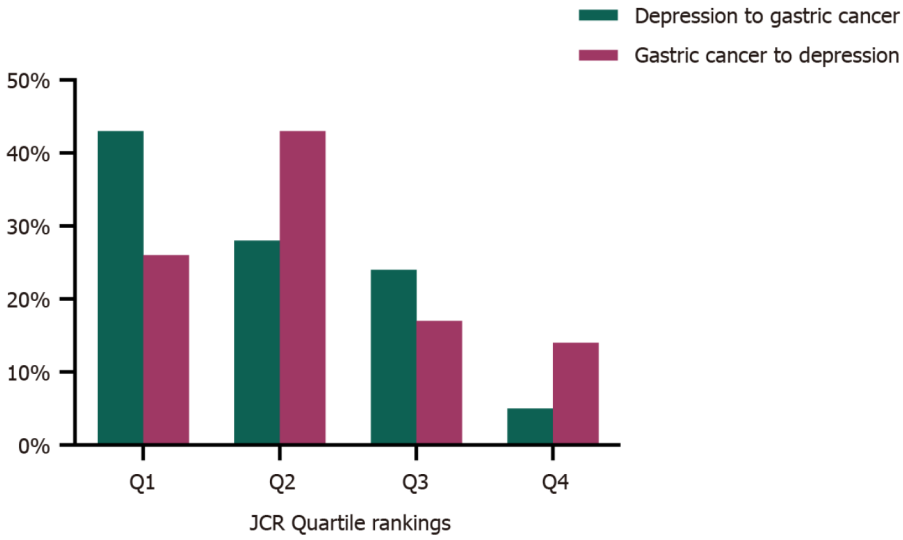

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Figure 7 Published journal sources for "gastric cancer to depression" and "depression to gastric cancer" studies Journal Citation Report divisional statistics. JCR: Journal Citation Report.

regulating NF-kappa B1 and STAT3, which subsequently leads to the development of GC and GC-related depression[45]. In addition, Pan *et al*[46], based on the study by Shi *et al*[38], found that catecholamine-induced neuroendocrine phenotypes of GC cells led to depression-accelerated GC invasion and metastasis *via* the beta(2)-AR/metastasis-associated with colon cancer 1 (MACC1) axis, while beta(2)-AR antagonist or MACC1 silencing could reverse it, showing promising potential therapeutic strategies for improving the outcome of GC patients with comorbid depression. These studies built a foundation for future research on the mechanism of "depression to GC".

Research prospection

The causal relationship between depression and GC merits deeper investigation, which could yield valuable insights into the mechanisms at play. As mentioned above, there have already been population, individual, cellular, molecular, and genetic studies, and some researchers have established animal models. However, there is still a lack of interaction mechanism research on GC and depression at a systematic level. We noticed that depression belongs to the abnormalities of the central nervous system, and GC belongs to the diseases of the digestive system. However, there is still a lack of research on the mechanism of "depression to GC" at the systemic level. As mentioned above, researchers have focused on the association between the central nervous system and other system diseases. For example, Guida *et al*[31] found that changes in gut bacterial composition might cause altered responses in affective behaviors *via* several concurring cellular and molecular mechanisms. Their findings offered the first step towards new insights into microbiota's obscure role in central nervous system functioning. Extricating these pathways may lead to new therapeutic approaches in pathologies

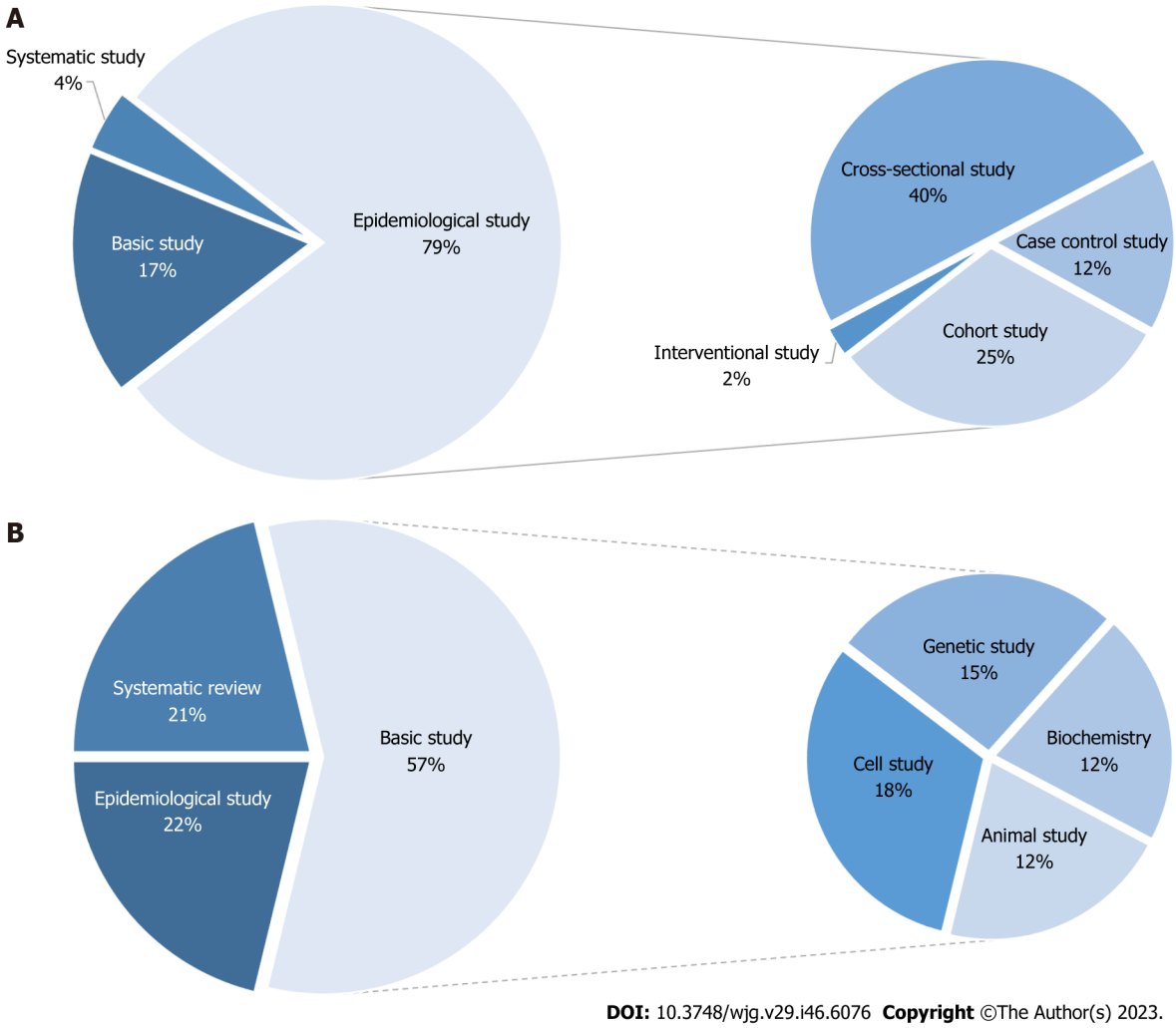

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Figure 8 Classification of "gastric cancer to depression" and "depression to gastric cancer" study types. A: "Gastric cancer (GC) to depression"; B: "Depression to GC".

showing comorbidity between gastrointestinal disorders and psychiatric illness. Van Kessel *et al*[32] found that an abundance of bacterial tyrosine decarboxylase in the proximal small intestine could explain the increased dosage regimen of levodopa treatment in Parkinson's patients. This study suggested that there was an association between the central nervous system and the digestive system. In addition, Mediavilla[47] also found that the importance of gut-brain communication in health and disease, especially the orexin/hypocretin system, bidirectional crosstalk, plays a significant role in various gastrointestinal disorders.

In addition, the nervous system is essential in regulating immune responses to various diseases[48]. Reiche *et al*[49] proposed that stress and depression impair the immune response and might promote the initiation and progression of some types of cancer. Therefore, studying the bidirectional communication between the neuroendocrine and immune systems could contribute to new clinical strategies. Kuol *et al*[50] presented three approaches to the neuro-immune interaction in cancer progression: lymphoid organs innervation, neurotransmitters, and immune cells in cancer, tumor-associated immune cells, and the nervous system. Cortese *et al*[51] indicated that the interaction between nerves and immune cells is critical to cancer growth. There is an interaction between cancer progression and the nervous system[52]. Martyn *et al*[53] showed that Schwann cells, which are the most prevalent neuroglia within the peripheral nervous system, could attract different subsets of immune regulators and augment their ability to suppress the effector T cells and up-regulate invasiveness of tumor cells. These studies provided a new perspective for further exploration[54,55].

Based on this, we speculate that the researcher can also explore the mechanism of depression affecting GC from the perspective of the association between the central nervous and other systems in the future. Furthermore, providing nuanced insights into the severity of depression could enrich the study's findings. Given that depression spans a spectrum ranging from mild to severe, it would be advantageous to elucidate the varying degrees of depression and their potential correlation with the incidence of GC.

CONCLUSION

This study shows the hotspots and frontiers of GC and depression on a global level. According to the increased trend of publications, the number of publications in the future might continue to increase. Between 2000 and 2022, China and South Korea contributed the most to the relationship between GC and depression. The "effect of treatments on GC patients with mental disorders" and "epidemiological research on GC and depression" have always been the research hotspots in the field. The "interaction mechanism between GC and depression" has emerged as a research frontier in recent years, which can be divided into two groups: "GC to depression" and "depression to GC".

The primary research type of "GC to depression" was epidemiological study represented by cross-sectional studies. In contrast, the primary research type of "depression to GC" was basic study, which focused on the mechanism, and it has shown a significantly increased trend in the past two years. "The mechanism of depression effect on the occurrence and development of GC" will be a frontier in the research field of GC and depression in the future. This study is also the starting point for further discussion. At the same time, since its mechanism was still unclear, it shows the necessity of further analysis.

ARTICLE HIGHLIGHTS

Research background

Depression is particularly prevalent in cancer patients in recent studies, and gastric cancer (GC) is the most common malignant tumour in the digestive system. There is increasing evidence that mental disorders such as depression are associated with the incidence and progression of cancer. Some researchers have paid attention to the impact of depression on the occurrence and development of GC, which has become an emerging research trend in GC and depression.

Research motivation

Present the research status and explore the hotspots for frontier studies using bibliometric analysis of relevant publications on the relationship between GC and depression.

Research objectives

We focused on the Web of Science Core Collection, collecting 153 pieces of literature on "GC and depression". The retrieval time range was from 1 January, 2000 to 31 December, 2022. We included only articles, reviews, and systematic reviews.

Research methods

We used an Excel spreadsheet to collect bibliometric indicators. In addition, we utilized the Bibliometrix package of R-studio software to analyze the included literature data and Biblioshiny for data visualization.

Research results

The annual publication count showed an overall upward trend. China had the most prominent publications and significant contributions to this field. The effect of depression on the occurrence and development of GC and its mechanism will receive more attention in the future.

Research conclusions

The effect of depression on the occurrence and development of GC and its mechanism may become a research hotspot. This study provides new insights into the hotpots and frontiers of the relationship between GC and depression.

Research perspectives

This study shows the number of publications on GC and depression in the future might continue to increase. This study is the starting point for further research on the mechanism of depression's effect on the occurrence and development of GC. Since the mechanism was still unclear, it shows the necessity of further analysis.

FOOTNOTES

Co-first authors: Jia-Yu Liu and Ji-Qi Zheng.

Co-corresponding authors: Jian-Ning Zhang and Wen-Pei Tang.

Author contributions: Liu JY and Zheng JQ were responsible for literature search, study design, data collection, data interpretation, and writing; Zhang JN, Tang WP and Yin CL were responsible for study design and provided feedback on all manuscript texts. Liu JY and Zheng JQ contributed equally to this work as co-first authors; Zhang JN and Tang WP contributed equally to this work as co-corresponding authors. The reasons for designating Liu JY and Zheng JQ as co-first authors, and Zhang JN and Tang WP as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete

the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Liu JY and Zheng JQ contributed efforts of equal substance throughout the research process. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Zhang JN and Tang WP as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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L-Editor: A
P-Editor: Yuan YY

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LETTER TO THE EDITOR

Albumin-bilirubin score in non-malignant liver diseases should be properly validated

Andrea Pasta, Francesco Calabrese, Maria Corina Plaz Torres, Giorgia Bodini, Manuele Furnari, Edoardo Vincenzo Savarino, Vincenzo Savarino, Edoardo Giovanni Giannini, Elisa Marabotto

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Abstract

The albumin-bilirubin (ALBI) score to assess the risk of decompensation in patients with initially compensated cirrhosis may improve their prognostic evaluation. This letter critically evaluates the research, which utilizes the ALBI score to forecast decompensation in cirrhosis patients over a three-year period. This score was initially developed to assess liver function in hepatocellular carcinoma, its prognostic utility for non-malignant liver diseases has now been explored, recognizing decompensation as a pivotal event that significantly affects patient's survival. Some concerns regarding the methodology of this research may be raised, particularly the exclusive use of radiological diagnosis, potentially including patients without definite cirrhosis and thus skewing the decompensation risk assessment. The reported predominance of variceal bleeding as a decompensating event conflicts with established literature, that often reports ascites as the initial decompensation manifestation. The letter highlights the absence of details on esophageal varices and their management, which could introduce bias in evaluating the ALBI score's predictive power. Furthermore, the letter points out the small sample size of patients with high-risk ALBI grades, potentially compromising the score's validity in this context. We suggest prospective future research to investigate the dynamic changes in the ALBI score over time to reinforce the validity of the ALBI score as a predictor of decompensation in non-malignant liver disease.

Key Words: Albumin-bilirubin score; Decompensated cirrhosis; Liver disease; Non-

malignant liver disease; Portal hypertension

Core Tip: The albumin-bilirubin (ALBI) score was initially proposed to evaluate liver function in patients with hepatocellular carcinoma. It proposed to validate the ALBI score to assess the risk of decompensation in patients with compensated cirrhosis. We provide a comment to highlight the preliminary nature of the evidence reported by the authors. Further studies are needed to validate the ALBI score to predict decompensation in patients with cirrhosis.

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TO THE EDITOR

We read with great interest the study by Navadurong *et al*[1], who identified the albumin-bilirubin (ALBI) score for predicting decompensation in patients with initially compensated cirrhosis in a 3-year period.

The ALBI grade was initially proposed by Johnson *et al*[2] to assess liver function in patients with hepatocellular carcinoma; subsequently, it has been proposed as a prognostic tool in patients with non-malignant liver diseases. Here, the occurrence of decompensation in patients with cirrhosis is important in the prognostic assessment because after the first episode of decompensation, the patients' survival significantly declines compared to patients with compensated cirrhosis, with a median survival of 19 and 107 mo in patients with decompensated and compensated diseases, respectively[3].

We would like to commend the authors for the effort. However, we believe that some methodological issues may have limited the strength of the study's conclusion. First, relying solely on radiological tools to diagnose cirrhosis overlooks the comprehensive assessment of this complex condition, which should include clinical, laboratory, and histological data for a more accurate diagnosis and treatment plan. Hence, patients without definite cirrhosis, in whom the decompensation risk is inconsistent, may have been included.

Second, the study reports variceal bleeding as the main cause of decompensation. This result is somehow conflicting with the literature, as ascites is most frequently reported as the first decompensating event[4,5]. We observed that the inclusion criteria did not consider the presence and characteristics of esophageal varices, such as their size, presence of red marks, and prophylactic measures for first bleeding (beta-blockers, elastic band ligation). Hence, it is impossible to ascertain whether the association of ALBI grade with decompensation risk remains independent from these potential biases. As some studies previously suggested that the ALBI grade is correlated with hepatic venous pressure gradient, we believe that future studies aimed at assessing more on this correlation and clinical outcomes could be an area of interest [6].

Lastly, as reported by the authors, the number of patients with high-risk ALBI grade and occurrence rate of decompensating events were few. This limitation could have decreased the validity of the score in this setting. Therefore, it might have been of interest to assess whether longitudinal modifications of the ALBI score, as previously reported for other well-established prognostic indexes, could have gauged its prognostic relevance[7].

We believe that using the ALBI grade as proposed by the authors is fascinating; however, the study conclusions may be regarded as preliminary, and we concur with the authors' suggestion that the role of the ALBI grade in non-malignant liver disease as a predictor of decompensation should be confirmed in prospective, larger studies before being considered a validated tool.

FOOTNOTES

Co-first authors: Andrea Pasta and Francesco Calabrese.

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LETTER TO THE EDITOR

Paying attention to the value of thrombelastography and the impact of postreperfusion syndrome on outcomes of liver transplantation

Yu-Li Wu, Lu Che, Yi-Qi Weng

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Abstract

Only limited information is available about the connection between massive blood transfusion and postoperative survival rates in pediatric liver transplantation. The aim of Gordon's study was to examine the potential impact of perioperative transfusion on postoperative complications and death in young children receiving pediatric living-donor liver transplantation (PLDLT). The authors concluded that transfusion of a red blood cell volume higher than 27.5 mL/kg during the perioperative period is associated with a significant increase in short- and long-term postoperative morbidity and mortality after PLDLT. However, viscoelastic coagulation monitoring was not utilized in the study; instead, only conventional coagulation monitoring was conducted. Overall, the choice of blood coagulation monitoring method during blood transfusion can have a significant impact on patient prognosis. Several studies have shown that the viscoelastic coagulation testing such as thrombelastography (TEG) is highly sensitive and accurate for diagnosing coagulation dysfunction. Indeed, a TEG-guided blood transfusion strategy can improve prognosis. Moreover, postreperfusion syndrome is one of the most common complications of liver transplantation and an important factor affecting the prognosis of patients and should also be included in regression analysis.

Key Words: Liver transplantation; Child; Blood transfusion; Thrombelastography; Reperfusion Injury; Prognosis

Core Tip: The influence of blood transfusion strategies based on different coagulation testing methods on the outcomes of pediatric liver transplantation cannot be ignored. Additionally, postreperfusion syndrome during liver transplantation can have an important impact on the prognosis of pediatric patients and should be accounted for when studying risk factors for postoperative mortality.

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TO THE EDITOR

We read with interest the recent article by Gordon *et al*[1] titled "Perioperative blood transfusion decreases long-term survival in pediatric living donor liver transplantation (LDLT)". The original study sought to ascertain whether blood transfusions are related to early and late postoperative complications and mortality in children undergoing LDLT. The authors concluded that in pediatric LDLT, perioperative red blood cell transfusions exceeding 27.5 mL/kg are a direct cause of reduced patient and graft survival as well as an independent risk factor for death. We are grateful for the contribution of the authors, who performed a long-term postoperative follow-up and collected a large amount of data, providing important information that avoiding or reducing blood transfusions improves postoperative survival in children with liver transplantation, which can help to inform clinical decision-making. However, we believe that the following aspects need to be discussed.

In the study, viscoelastic coagulation monitoring was not used, and only conventional coagulation monitoring was carried out, and we think that this may have a certain impact on the results. The conventional coagulation test (CCT) includes the international normalized ratio (INR), prothrombin time, activated partial prothrombin time, thrombin time, and platelet count, among others. The viscoelastic coagulation test is used to measure and analyze the viscoelastic properties of blood clot formation. It involves measuring and converting the viscoelasticity produced by the interaction between fibrin strands and platelets during the blood coagulation process into digital data, which are then graphically plotted for analysis. Currently, there are two types of equipment available for conducting viscoelastic coagulation tests: classical thrombelastography (TEG) and rotational thromboelastometry. The coagulation system is responsible for maintaining the balance between clot formation and dissolution in the blood, and monitoring the coagulation process during a blood transfusion is crucial to ensure proper blood clotting and minimize the risk of complications such as bleeding or clotting disorders. Studies have shown that TEG during liver transplantation can effectively monitor the hypercoagulable state of patients and the subsequent risk of embolism; in contrast, the ability of the INR to monitor the hypercoagulable state and predict the risk of embolism is poor[2]. A randomized controlled trial showed that in patients with liver cirrhosis and severe coagulation dysfunction before invasive surgery, the TEG-guided transfusion strategy significantly reduced the use of blood products and did not increase bleeding complications compared with the standard strategy (blood transfusion guided by the INR and platelet count)[3]. In another randomized clinical trial, Bonnet *et al*[4] found that a transfusion algorithm based on thromboelastometry coagulation assessment reduced the total number of blood product units transfused during liver transplantation, especially the amount of fresh frozen plasma transfused. Therefore, the value of the CCT in liver transplantation is questionable; it is time-consuming and cannot fully reflect the complex changes in coagulation in patients with liver disease over time. Viscoelastic coagulation tests can provide comprehensive information from coagulation initiation to fibrinolysis, clot strength, and stability; they are more sensitive and accurate than the CCT in the diagnosis of coagulation disorders and can help to prevent complications and improve patient outcomes.

Like any other test, TEG has certain limitations. It measures blood coagulation outside the body, rather than the coagulation of blood while it is flowing within the vasculature; therefore, TEG does not reflect the function of the endothelium in coagulation[5]. In addition, the TEG testing equipment is costly and requires more professional training for operators to use it effectively. The factors mentioned above may limit the prevalence of TEG usage. However, the viscoelastic coagulation assay was recommended in the recent clinical guidelines by the European Society of Anesthesiology to reduce the rate of blood product transfusion during liver transplantation[6]. This guideline pointed out that the preoperative viscoelastic coagulation assay might help to predict blood loss and blood transfusion during liver transplantation[6].

In addition, the Gordon *et al*[1] study did not include all events that had an impact on prognosis in regression analysis, such as postreperfusion syndrome (PRS). PRS is defined as a significant decrease of over 30% in the mean arterial pressure compared with that at the end of the anhepatic phase, and this decrease has to last at least 1 minute and occur in the first 5 min after liver graft reperfusion[7]. Decreased body temperature in children before reperfusion and prolonged graft cold ischemia time are independent risk factors for PRS in pediatric liver transplantation[7]. Metabolic acidosis, hyperkalemia, hypocalcemia, and the release of many proinflammatory cytokines into the systemic circulation by the transplanted liver releasing after reperfusion are possible mechanisms for PRS[8]. PRS is one of the most common complications during liver transplantation and can lead to delayed recovery of graft function, prolonged hospitalization, and increased mortality and seriously affect quality of life in the postoperative period[7,9]. Therefore, we believe that PRS

may have an important impact on the prognosis of children and should be included in regression analysis.

In summary, considering the advantages of viscoelastic coagulation monitoring, we should pay attention to the value of using TEG in liver transplantation. Additionally, PRS can have an important impact on the prognosis of pediatric patients who undergo liver transplantation and should be considered when exploring risk factors for postoperative mortality.

FOOTNOTES

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