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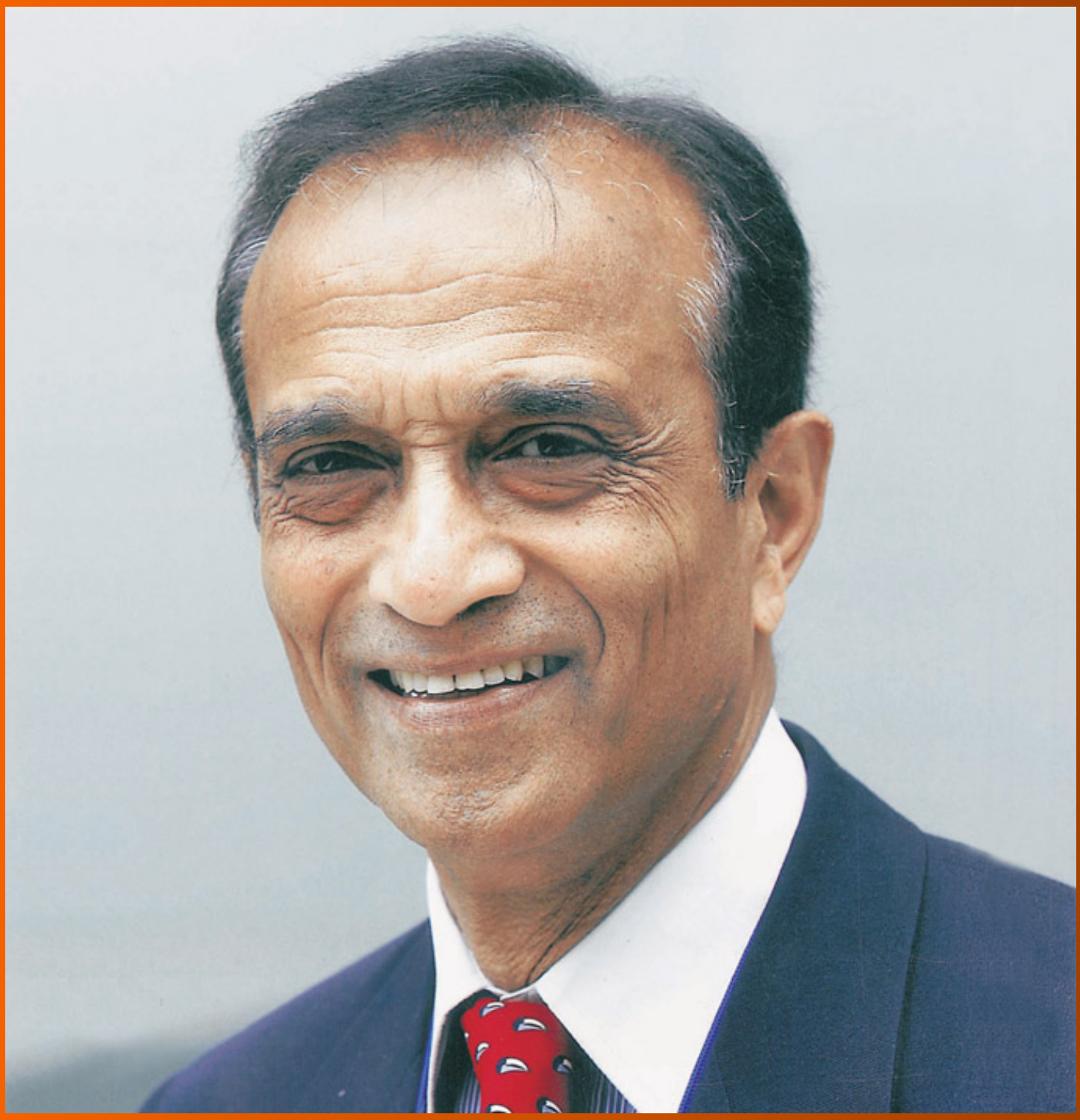

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EDITORIAL

Role of sodium-glucose co-transporter-2 inhibitors in the management of nonalcoholic fatty liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent cause of chronic liver disease worldwide. NAFLD is considerably more frequent in patients with type 2 diabetes mellitus (T2DM) than in the general population and is also more severe histologically in this group. Sodium-glucose co-transporter-2 (SGLT2) inhibitors, the newest class of antidiabetic agents, appear to represent a promising option for the management of NAFLD in patients with T2DM. In a number of studies, treatment with SGLT2 inhibitors resulted in a reduction in hepatic steatosis and in transaminase levels. However, existing studies are small, their follow-up period was short and none evaluated the effects of SGLT2 inhibitors on liver histology. Accordingly, larger studies are needed to verify these preliminary results and define the role of SGLT2 inhibitors in the treatment of NAFLD in patients with T2DM.

Key words: Nonalcoholic fatty liver disease; Type 2 diabetes mellitus; Sodium-glucose co-transporter-2 inhibitors; Steatosis; Fibrosis; Transaminases

Core tip: Nonalcoholic fatty liver disease (NAFLD) is more frequent and more severe in patients with type 2 diabetes mellitus (T2DM) than in the general population. Sodium-glucose co-transporter-2 (SGLT2) inhibitors appear to represent a promising option for the management of NAFLD in patients with T2DM. However, existing studies are small, their follow-up period was short and none evaluated the effects of SGLT2 inhibitors on liver histology. Accordingly, larger studies are needed to verify these preliminary results and define the role of SGLT2 inhibitors in the treatment of NAFLD in patients with T2DM.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent cause of chronic liver disease worldwide and is defined as increased intrahepatic fat accumulation, in the absence of a history of alcohol abuse, intake of steatogenic medications and other causes of chronic liver disease[1]. NAFLD covers a wide range of histological and clinical disorders, from nonalcoholic fatty liver, which refers to isolated steatosis affecting hepatocytes, to nonalcoholic steatohepatitis (NASH), where inflammation and fibrosis coexist with steatosis and might progress to cirrhosis and hepatocellular carcinoma (HCC)[2-4]. The current prevalence of NAFLD is proportional to the increasing rates of obesity and is estimated to affect 24%-46% of the general population[4,5]. On the other hand, the prevalence of NAFLD is considerably higher in patients with type 2 diabetes mellitus (T2DM) than in the general population, ranging between 50%-75%[4,6,7]. Moreover, NAFLD appears to be more severe histologically in patients with T2DM[4,6,7]. Importantly, T2DM is a risk factor not only for NASH but also for the development of cirrhosis and HCC[8,9]. Indeed, NAFLD is considered as the hepatic phenotype of metabolic syndrome, a prediabetic disorder related to insulin resistance and abdominal obesity[10]. The pathogenesis of NAFLD also involves the increased efflux of free fatty acids to the liver as well as with oxidative stress, inflammation, mitochondrial dysfunction and hepatocellular apoptosis[11]. Notably, both T2DM and NAFLD are associated with increased risk for cardiovascular disease, which represents the leading cause of death in both diseases[12,13]. Currently, there are no approved pharmacological treatments for NAFLD and the mainstay of management is lifestyle changes, including diet and exercise[1]. Among antidiabetic agents, limited data suggest that glucagon-like peptide-1 receptor agonists might exert a beneficial effect on NAFLD whereas other classes do not appear to be effective[1]. Given the frequent coexistence of NAFLD and T2DM as well as the increased liver- and cardiovascular-related morbidity associated with their coexistence, there is a pressing need to develop effective therapeutic interventions for patients with T2DM-associated NAFLD.

ACTIONS OF SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS

In this context, emerging evidence suggests that sodium-glucose co-transporter 2 (SGLT2) inhibitors might represent a useful tool for the management of these patients. SGLT2 inhibitors are the newest class of oral hypoglycemic agents and reduce blood glucose levels by inhibiting renal tubular glucose reabsorption[14]. This results in increased urinary glucose excretion without stimulating insulin release and hence without a risk of hypoglycemia. In addition to their hypoglycemic action, SGLT2 inhibitors induce weight loss by inducing urinary glucose excretion and osmotic diuresis[14]. They also reduce blood pressure by stimulating urinary sodium excretion[15]. Notably, recent large randomized controlled trials showed that SGLT-2 inhibitors reduce cardiovascular morbidity in patients with T2DM[16,17].

EFFECTS OF SGLT2 INHBITORS ON NAFLD

Regarding the effects of SGLT2 inhibitors on NAFLD in patients with T2DM, a number of small studies (n = 16-84) with a relatively short follow-up (12-24 wk) yielded encouraging results[18-23]. Indeed, a reduction in hepatic fat content was observed as evaluated with magnetic resonance imaging or computed tomography[18-21,23]. A decrease in transaminase levels was also recorded in most studies[18-22]. Moreover, a reduction in markers of hepatocellular apoptosis (cytokeratin 18-M30 and 18-M65) was observed[18]. A small study (n = 16) reported a decrease in type IV

collagen 7S levels, a marker of hepatic fibrosis, after treatment with dapagliflozin for 24 weeks[22] but another study (n = 40) reported no change in type IV collagen 7S levels or in other markers of fibrosis (Fibrosis-4 index and NAFLD fibrosis score) after treatment with luseogliflozin for 24 wk[21]. Weight loss, a reduction in blood pressure, a decrease inHbA_{1c} and fasting glucose levels as well as an improvement of the lipid profile were also recorded[18-23]. Treatment with SGLT2 inhibitors was generally well-tolerated, apart from an increased incidence of genitourinary tract infections[18-23]. Interestingly, in a comparative study, ipragliflozin was as effective as pioglitazone in the reduction of hepatic steatosis[19]. Moreover, in another comparative study, luseogliflozin was more effective than metformin in reducing hepatic steatosis[23].

Several mechanisms appear to be implicated in the beneficial effects of SGLT-2 inhibitors on T2DM-associated NAFLD (Figure 1). Weight loss is an important mediator of the improvement in hepatic steatosis[18-21,23]. Furthermore, a relative increase in fatty acid oxidation instead of carbohydrate oxidation could also play a role in the reduction of hepatic fat accumulation and might also suppress hepatic inflammation[14]. Moreover, data from animal models support a direct positive effect of SGLT-2 inhibitors on insulin resistance and an inhibitory effect on liver injury and lipotoxicity[24,25]. Importantly, a recent preclinical study also showed that canagliflozin reduces the risk for hepatocellular cancer in an animal model of NASH[26].

CONCLUSION

SGLT2 inhibitors appear to represent a promising option for the management of NAFLD in patients with T2DM. However, existing studies are small, their follow-up period was short and none evaluated the effects of SGLT2 inhibitors on liver histology. Moreover, these agents induce a notable increase in non-serious adverse events, particularly urinary and genital tract infections, and their glucose-lowering benefit might have been overestimated[27]. In addition, even though the pharmacokinetics of SGLT2 inhibitors are unlikely to be affected by the presence of hepatic impairment, there are limited data regarding the safety of these agents in patients with severe liver dysfunction (*e.g.*, Child-Pugh grade C)[28-30]. Therefore, close monitoring is required during the administration of SGLT2 inhibitors in patients with advanced cirrhosis, particularly in patients with ascites who are receiving diuretics. Overall, larger studies are needed to verify the preliminary findings suggesting a benefit of SGLT2 inhibitors in NAFLD and to define their role in the treatment of this common comorbidity in patients with T2DM.

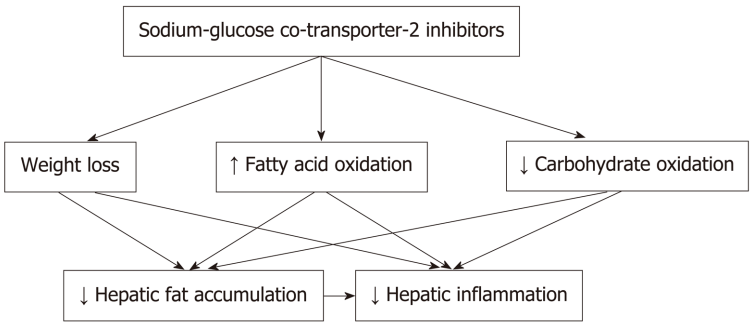

Figure 1 Mechanisms implicated in the beneficial effects of sodium-glucose co-transporter-2 inhibitors on type 2 diabetes mellitus-associated nonalcoholic fatty liver disease.

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OPINION REVIEW

Importance of fatigue and its measurement in chronic liver disease

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Abstract

The mechanisms of fatigue in the group of people with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis are protean. The liver is central in the pathogenesis of fatigue because it uniquely regulates much of the storage, release and production of substrate for energy generation. It is exquisitely sensitive to the feedback controlling the uptake and release of these energy generation substrates. Metabolic contributors to fatigue, beginning with the uptake of substrate from the gut, the passage through the portal system to hepatic storage and release of energy to target organs (muscle and brain) are central to understanding fatigue in patients with chronic liver disease. Inflammation either causing or resulting from chronic liver disease contributes to fatigue, although inflammation has not been demonstrated to be causal. It is this unique combination of factors, the nexus of metabolic abnormality and the inflammatory burden of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis that creates pathways to different types of fatigue. Many use the terms central and peripheral fatigue. Central fatigue is characterized by a lack of self-motivation and can manifest both in physical and mental activities. Peripheral fatigue is classically manifested by neuromuscular dysfunction and muscle weakness. Therefore, the distinction is often seen as a difference between intention (central fatigue) *versus* ability (peripheral fatigue). New approaches to measuring fatigue include the use of objective measures as well as patient reported outcomes. These measures have improved the precision with which we are able to describe fatigue. The measures of fatigue severity and its impact on usual daily routines in this population have also been improved, and they are more generally accepted as reliable and sensitive. Several approaches to evaluating fatigue and developing endpoints for treatment have relied of biosignatures associated with fatigue. These have been used singly or in combination and include: physical performance measures, cognitive performance

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measures, mood/behavioral measures, brain imaging and serological measures. Treatment with non-pharmacological agents have been shown to be effective in symptom reduction, whereas pharmacological agents have not been shown effective.

Key words: Fatigue; Chronic liver disease; Non-alcoholic fatty liver diseases; Non-alcoholic steatohepatitis; Measurement; Patient-reported outcomes

Core tip: Fatigue is prevalent, persistent and complex in people with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. Fatigue can be analyzed in terms of peripheral and central fatigue, increasing precision of evaluation while elucidating causes and improving treatment. The liver is central to the pathogenesis of fatigue, which in our view, is dependent upon energy regulation. Biosignatures for fatigue are being tested that reflect metabolic and inflammatory pathways of relevance. Non-pharmacological treatments including weight loss, aerobic and resistance exercise are effective in treating fatigue in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. Pharmacological agents to date have not been shown to have a significant/reliable effect in reducing fatigue.

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INTRODUCTION

Fatigue is a critical component of chronic liver disease (CLD)[1]. It is common, complex, confusing and challenging to treat. It is thought to be the hallmark of certain diseases, including autoimmune diseases and chronic congestive heart failure, and is known to accompany many chronic illnesses including cancer, primary biliary cholangitis, sclerosing cholangitis and other cholestatic types of CLD. Relatively recently, investigators have identified that fatigue may also associate with non-alcoholic fatty liver diseases (NAFLD) and non-alcoholic steatohepatitis (NASH)[2]. This lag in recognition of an association with NAFLD/NASH is, in the opinion of the authors, in part because NAFLD/NASH have only recently been described as a clinical entity, and it is considered a "silent" disease with low symptom burden. Additionally, the role of the liver in the pathogenesis of fatigue has not been well understood, and it has been attributed to other causes such as autonomic dysfunction, sedentary behavior and sickness behavior/hypothalamic-pituitary axis dysfunction[2,3].

Our point of view, based on our and others' research with patients with chronic hepatitis C (CHC) and NAFLD/NASH, leads us to a somewhat different perspective. That is, that while the mechanisms of fatigue are protean in the group of people with NAFLD/NASH and CHC, the liver is central in its pathogenesis. It uniquely regulates much of the storage, release and production of substrate for energy generation. It is exquisitely sensitive to the feedback controlling the uptake and release of these energy generation substrates. Metabolic contributors to fatigue, beginning with the uptake of substrate from the gut, the passage through the portal system to hepatic storage and release of energy to target organs (muscle and brain) are central to understanding fatigue in patients with CLD and possibly others.

In addition to energy needs for normal function, the level of inflammation either causing or resulting from CLD contributes to fatigue, although inflammation has not been demonstrated to be causal. It is this unique combination of factors, the nexus of metabolic abnormality and the inflammatory burden of NAFLD/NASH and CHC that creates pathways to different types of fatigue (*i.e.*, central and peripheral fatigue which will be discussed below). These pathways, in our opinion, create guidance for assessment, endpoints for treatments and possible interventions.

Primary fatigue, which is fatigue not associated with an accepted underlying fatigue-causing disease mechanism such as tumor, heart failure, anemia, thyroid

dysfunction or medications, is especially difficult to treat. Frequently, depressive symptoms accompany fatigue, and people with CLD are treated for depression or are treated for insomnia. These may be effective in treating primary depression or insomnia but are not shown to be effective for treating fatigue. These observations lead us to support the view that exercise is among the highly specific and effective treatments for fatigue associated with NAFLD/NASH and CHC.

Why are we writing this opinion piece? We are attempting to provide a context in which fatigue is understood and can be clinically evaluated so that it can be distinguished from somnolence, mood disturbance or other co-morbidities often associated with fatigue. New approaches on how to measure fatigue include use of objective measures and patient reported outcomes (PROs). These measures have improved the precision with which we are able to describe fatigue. The measures of fatigue severity and its impact on usual daily routines in this population have also been improved and more generally accepted as reliable and sensitive.

This paper will discuss fatigue in CLD and possible mechanisms, review which treatment approaches may be effective in controlling symptoms and will discuss future opportunities for research that may lead to biosignatures such as performance and serological measures to assess fatigue.

FATIGUE AS A CONSTRUCT

Fatigue is common and experienced by virtually everyone during the course of their lives[4]. However, fatigue is difficult to characterize and define because it encompasses a complex interaction between biological, psychosocial and behavioral processes[5]. Therefore, it is important to differentiate it from other related constructs, such as sleepiness, while still creating clear definitions for fatigue[6]. To follow along with this example, sleepiness is simply the propensity to fall asleep, while fatigue can be overall tiredness that is not corrected by sleep. Clear distinctions can be drawn when exact definitions and terminology are utilized. Fatigue needs to be differentiated from symptoms of somnolence (*i.e.*, the quality or state of being drowsy), dyspnea (*i.e.*, difficult or labored respiration), boredom and weakness.

The most common types of fatigue that are used in the literature are central and peripheral[7]. However, it is important to be aware that these types of fatigue are defined differently across disciplines[8]. Again, clear and exact terminology is important when types of fatigue are discussed. In our research, we have been able to demonstrate clear distinctions between mental (central) and physical (peripheral) fatigue[9]. Central fatigue is characterized by a lack of self-motivation and can manifest both in physical and mental activities. Peripheral fatigue has been classically manifested by neuromuscular dysfunction and muscle weakness[7]. Therefore, the distinction has been about intention (central) *versus* ability (peripheral). It is important to also consider the types of activities. Fatigue can be experienced differently when performing a physical task *versus* performing a mental task[10].

For those with CLD, both dimensions of fatigue have been shown to be present[11]. However, this one categorization may not be sufficient to provide sensitive assessment of fatigue. In our qualitative work, we were able to show additional dimensions of fatigue that might be useful for treatment and research purposes[12]. Capacity across both the central and peripheral domains was an important distinction for patients. Fatigue and energy level were intricately linked and therefore capacity became a way for patients to describe their access to energy (access), their rapid depletion of energy (depletion) and their ability to restore energy once it was used (restoration). We believe that the inclusion of these concepts (access, depletion and restoration) would help to add depth to our understanding of fatigue across the central and peripheral domains. Recently, there have been many reviews of fatigue in the context of liver disease (see Table 1 for a summary of recent reviews). Fatigue has a profound effect on patients' quality of life[2]. There is a need to increase the depth of our understanding of fatigue in order to be able to better treat it.

FATIGUE IN LIVER DISEASE

Prevalence

Estimates of the prevalence of fatigue differ across different studies. However, in the general population it ranges from 5%-7%[13]. For patients within a primary care practice, the prevalence increases to between 10%-25%[13], and in individuals with chronic illness the prevalence ranges widely depending on the illness (from 20%-60%)[14]. In CLD, the prevalence ranges between 50%-85%[11]. Fatigue is the most

Table 1 Summary of recently published reviews specifically on fatigue in liver disease

Article title
Fatigue in chronic liver disease: New insights and therapeutic approaches[3]
Fatigue complicating chronic liver disease[95]
Depression, fatigue and neurocognitive deficits in chronic hepatitis C[96]
Patient-Reported outcomes and fatigue in patients with chronic hepatitis C infection[21]
Future directions for investigation of fatigue in chronic hepatitis C viral infection[97]
Fatigue, depression and chronic hepatitis C infection[98]
Fatigue in cholestatic liver disease-a perplexing symptom[99]
Fatigue in liver disease: Pathophysiology and clinical management[11]
Understanding and treating fatigue in primary biliary cirrhosis (cholangitis) and primary sclerosing cholangitis[19]
Liver-brain interactions in inflammatory liver diseases: implications for fatigue and mood disorders[30]
Fatigue in primary biliary cirrhosis (cholangitis)[100]
Complications, symptoms, quality of life and pregnancy in cholestatic liver disease[101]
Fatigue in primary biliary cirrhosis (cholangitis)[102]

commonly reported symptom in CLD, and it is also the symptom that most often gets individuals to visit their doctors[15]. In addition, the severity of fatigue does not seem to be associated with biochemical or histological parameters of liver disease severity, although the data are mixed on this point[16].

Measurement

Although there is a proliferation of measurement tools to assess fatigue, there is no instrument that can provide both specificity and sensitivity for measuring fatigue. The lack of a tool is part of the problem that leads to under diagnosis, under recognition, and under treatment of fatigue in CLD patients. Part of the issue is that the tools that are currently used do not adequately capture the complexity and dimensionality of fatigue[17]. None of the commonly used tools address all aspects of fatigue. Commonly assessed areas include: Descriptions or characterizations of fatigue, feelings of distress associated with fatigue, presumed causes of fatigue and consequences of fatigue[18]. It is important to recognize what components of fatigue are being assessed and what components of fatigue should be assessed. Because there are no tools that address all of these components, it is important for researchers to consider what it is about fatigue that is relevant to the current research or patient and use that to drive the selection of a specific measure[17]. Please see Table 2 for a summary of instruments.

SYMPTOMS OF FATIGUE

Fatigue in liver disease is a well-described syndrome and is recognized as prevalent, persistent and problematic. It is the hallmark of primary biliary cholangitis[19], other forms of cirrhosis[20] and has been associated with CHC[21]. In fact, suggestions have been made that clinically significant fatigue should be an indication for anti-viral therapy[22]. Unlike cancer and myalgic encephalomyelitis/chronic fatigue syndrome (MECFS), there are no specific criteria for a "liver related fatigue" syndrome. However, much of the fatigue literature in hepatology does derive from the excellent work done by the National Cancer Consortium Network in an effort to raise awareness of cancer-related fatigue and to define it[23]. The field has also been influenced by the Centers for Disease Control and Prevention, who has championed the cause of devising criteria for diagnosis of MECFS and the National Institutes of Health, who has spearheaded the need for using common data elements in developing a standard approach to evaluation and performing research into MECFS[24]. These efforts have led to consensus that chronic fatigue is a persistent perception of tiredness that interferes with function, needed and desired activities and is often distressing and difficult to treat[25,26].

One important observation from one of our studies[27] is that the descriptive variables (PRO profiles as well as the serum analytes) differed between people with central fatigue compared with peripheral fatigue. These differences may help in planning treatment.

Chronic fatigue implies fatigue most days for at least a duration of 3 mo. Additionally, it is a multi-dimensional symptom and may be experienced as tiredness

Table 2 Commonly used measures of fatigue

	Type of assessment	Domain(s) assessed	Length	Used in liver disease?
Fatigue assessment scale[103]	5-point Likert scale	Severity	10 items	Rarely
Fatigue severity scale[104]	7-point Likert scale	Severity, Impact	9 items	Often
Fatigue impact scale[105]	5-point Likert scale	Physical, Cognitive, Psychosocial	40 items	Sometimes
Fatigue scale[106]	4-point Likert scale	Physical, Mental	11 items	Rarely
Multidimensional Assessment of Fatigue[107]	Visual analog scale	Severity, Distress, Impact on Activities	14 items	Rarely
Multidimensional fatigue inventory[108]	5-point Likert scale	General, Physical, Activity, Motivation, Mental	20 items	Sometimes
Visual analog fatigue scale[109]	Visual analog scale	Energy, Fatigue	18 items	Rarely
Functional assessment of chronic illness therapy fatigue scale[110]	5-point Likert scale	Severity, Impact	13 items	Often
Sf-36 vitality scale[111]	5-point Likert scale	Energy	4 items	Often
Chronic liver disease questionnaire fatigue scale[112]	7-point Likert scale	Energy	5 items	Often
PROMIS®-fatigue[113]	5-point Likert scale	Severity	Variable[1]	Rarely

[1]PROMIS® is a computer adaptive test where the specific questions and number of questions is tailored to the individual using item response theory techniques. Usually the number of items will range between 4-12.

in the musculoskeletal system, cognitive decline or fuzzy thinking , muscle fatigue, poor recovery from exercise and decreased motivation for usual activities. See Table 3, which was taken from the International Classification of Disease 10th edition for diagnosis of cancer related fatigue.

The experiential aspects of fatigue may be influenced by age, culture, comorbidities, pain, mood, sleep and affect[28]. In fact, there is a significant interest in the possibility of symptom clusters, such as pain, fatigue, anxiety, depression and insomnia having a common etiology or genetic basis[29]. This is understandable given the overlapping nature of many of the symptoms. This presents a diagnostic and therapeutic dilemma because of the overlap between depressive symptoms and fatigue[30]. In fact, it is believed by some investigators that the word "fatigue" may be used interchangeably or may be a residual sign of depression[31,32].

The relationship between depression and/or depressive symptoms and fatigue suggests additional overlap because of the reported findings of changes in serotonin levels and abnormalities with tryptophan pathway regulation that is common in the depression and fatigue literatures[27,33-37]. Not only does this create diagnostic confusion, but it often leads to treatments for depression, which may not be helpful for reducing fatigue.

Additionally, we rely upon patients and research participants to "fit" their symptoms into standardized evaluations that have specific descriptors about level of intensity. Responses are stereotyped and not personalized, and as a result we get a limited amount of information about what individuals are truly experiencing. Our research group attempted to learn about how people with liver disease are likely to express their symptoms of fatigue (as discussed above)[12]. In this study we provided groups with CHC infection an opportunity to describe their fatigue using any adjective or metaphors they chose. They spoke of the dimensions of the fatigue in terms of intensity, frequency and duration. There were references to having limited capacity to do the things they wished to do. Further, that their energy stores often depleted rapidly without having the restorative power to recharge. Or they were unable to access the energy in order to do things they wished or needed to do. The presentation of their perceptions of fatigue and its impact helped us understand what they were experiencing and how central fatigue influences their functioning and well-being. Other investigators have made similar points about how important fatigue is to an individual[38].

Despite the fact that there is no unique signature describing fatigue associated with liver disease, many of the symptoms patients report are consistent with fatigue syndromes previously reported by investigators assessing cancer and MECFS. Interestingly, as in these other diagnoses, fatigue may associate with other symptoms in clusters of pain, anxiety, depression and insomnia. But with recent advances, there

Table 3 Fatigue symptoms for diagnosing pathological fatigue

The symptoms must have been present every (or nearly every) day over a 2-wk period during the past month	
Necessary	Significant fatigue
	Diminished energy
	Increased need to rest disproportionate to level of activity
At least five of these symptoms must be present	Experience of limb heaviness of generalized weakness
	Diminished concentration or attention
	Decreased motivation or interest to engage in usual activities
	Insomnia or hypersomnia
	Experience sleep as unrefreshing or non-restorative
	Perceived need to struggle to overcome inactivity
	Marked emotional reactivity to feeling fatigued
	Perceived problems with short term memory
	Post-exertional malaise for several hours

are published data supporting the constructs of central and peripheral fatigue, whose symptoms and impact are very different. Data are also pointing to serological measures (pro- and anti-inflammatory cytokines and growth factors) that are linked to symptoms of fatigue that can be distinguished using self-reports[9]. A summary of associated symptoms is provided in Table 4.

MECHANISMS OF FATIGUE

Fatigue may be attributed to a mechanism such as neuromotor dysfunction associated with muscle weakness, an organ specific explanation such as hypothyroid state or congestive heart failure. More often, fatigue is used as a non-specific term by patients, and many health care professionals treat it as such without producing a differential diagnosis or seeking a cause for it. Therefore, making the investigation of potential underlying mechanisms of fatigue is an important area.

Central and peripheral fatigue are experienced and measured differently and may be indicators of how the underlying mechanisms of fatigue differ as well. Central fatigue, is mediated by the central nervous system and is characterized by a failure to transmit motor impulses or perform voluntary activities[39], or the inability or reduced ability to perform attentional tasks. Peripheral fatigue, in comparison is a reduction in the ability to exert muscular force after exercise[40] and maintain a maximal force because of muscular limitations[8]. This implies that the source of the fatigue is independent of the muscular apparatus and originates above the neuromuscular junction[41]. A theoretical case can be made for a role for the autonomic nervous system as well[42]. Nonetheless, fatigue has been linked to many specific conditions including: anemia, cancer, cardiac, pulmonary, renal, liver disease, hypothyroid states, nutritional status and medication (Table 4). The assumption is that a deficit or disorder is the cause of the fatigue and correcting the deficit or disorder is likely to reverse the fatigue. When evaluating patients with chronic or "pathological" fatigue, it is advantageous to obtain a full work up to identify possible causative factors of fatigue and/or comorbidities that may contribute to its persistence.

However, there are many possible contributions the liver specifically makes in the pathophysiology of chronic fatigue. One recent review discussed the central role of the liver in metabolism and generation of energy[43]. It creates substrates for the production of ATP responsive to two conditions: (1) When eating and carbohydrate is available, the liver metabolizes glucose into glycogen and fatty acid; and (2) In the fasting state, when it produces energy by metabolizing glycogen *via* glycogenolysis or *via* gluconeogenesis. The liver can also metabolize fatty acid into ketone bodies for energy, but this is less efficient and occurs when glycogen is depleted from the liver[44].

The data supporting the central role of glucose to fatigue has been the result of studies in people with diabetes. This group of patients were studied to assess the relationship between blood glucose level and fatigue as well as the fluctuation in blood sugar levels over time[45,46]. This is an important observation because it supports the view that metabolic homeostasis is likely to be important for sustained physical and cognitive activity and because of the highly correlated conditions of type 2 diabetes and CLD (NAFLD/NASH).

Table 4 Established associations among physical findings, diagnoses and fatigue

Adrenal insufficiency	
Anemia	
Auto-immune diseases	
Cancer	Especially in breast, pancreatic, pulmonary
Cardiac failure	
Deconditioning	
Electrolyte imbalance	
Hypo/hyperthyroidism	
Infection	
Malnutrition	
Medication	Anti-emetics, anti-histamines, anxiolytics, chemotherapy, opioids, radiation, sedatives
Pulmonary	Chronic obstructive pulmonary disease, cystic fibrosis
Renal failure	
Sarcopenia	
Stress	Physiological, hypercortisolism
Symptoms Contributing	Depressive symptoms, insomnia, pain
Syndromes of unknown etiology	Lyme disease, chronic fatigue syndrome
Vitamin deficiency	Especially B complex

The liver is closely connected to extra-hepatic tissues in order to signal energy needs (skeletal muscle, brain), storage (adipose tissue) and substrate (gut). These responses are regulated through hormonal and neuronal networks. The hormonal signaling results from insulin, which stimulates glycolysis and lipogenesis. It suppresses gluconeogenesis and glucagon inhibits the effects of insulin. With respect to the nervous system, both the sympathetic and parasympathetic nervous system are important. The former stimulates and the latter inhibits gluconeogenesis.

In addition, control of liver metabolic processes depends upon several key transcription factors (FOXO1, PGC-1a and others) that control enzyme expression, which in turn controls hepatic metabolic processes[43]. The disruption of energy production and utilization has a profound impact on insulin sensitivity, development of type 2 diabetes and fatty liver. These changes in metabolic status are likely to be related to fatigue.

As mentioned above, the liver is in continual communication with extra-hepatic tissue, and with respect to fatigue it communicates through neuronal and hormonal networks. There are important gastrointestinal hormones that influence hepatic glucose production. Glucagon-like peptide is one that stimulates insulin secretion, and serotonin found in the gut stimulates gluconeogenesis in hepatocytes in the fasting state. Absorption of food and possibly microbiota release substrate through the gastrointestinal tract that send signals to the central nervous system (CNS) *via* the vagus nerve[47-49]. The sympathetic nervous system and parasympathetic nervous system both work through the CNS (hypothalamus) to regulate hepatic glucose production. Sympathetic nervous system activity increases glucose production and mobilizes substrate to extra-hepatic tissue (*e.g.*, muscle, brain) and parasympathetic nervous system inhibits it[50]. Insulin signaling has an effect on the hypothalamus to stimulate interleukin (IL)-6 production, which suppresses gluconeogenesis[51]. The role of this pro-inflammatory cytokine is also thought to contribute to the progression of steatosis to steatohepatitis[52]. IL-6 is involved in inflammatory and metabolic changes that may stimulate synthesis of other cytokines that induce cell migration and initiate healing processes, including fibrosis development of steatohepatitis[53]. Skeletal muscle has endocrine properties and has been shown to be able to secrete myokines, which are inflammatory peptides. Myokines are involved in the inflammatory response, and physical activity plays a key role in down-regulating their release[54].

Many peripheral factors at the gut, liver and skeletal muscle level, central factors involving a variety of hormones including leptin and growth hormone regulate gluconeogenesis and insulin resistance. The latter is critical to the development of NAFLD and/or type 2 diabetes. Both conditions are associated with metabolic imbalances, metabolic stress and energy production inefficiencies (all of which promote insulin resistance in the liver)[55]. The CNS plays a key role in the perception of fatigue. It is likely that changes in neuronal signaling within the brain gives rise to changes in perceptions of fatigue and influences behavior. Swain *et al*[3] suggested in a

recent review that there are several possible peripheral pathways by which liver inflammation can relay information to the brain that enhances fatigue perception. Signals include inflammation of: (1) The neural pathways *via* vagal nerve afferents; (2) Direct effect *via* transport through the circulation of pro-inflammatory cytokines; and (3) *Via* immune cells in the liver (Kupffer cells, stellate cells, natural killer cells) and recruited neutrophils, monocytes and macrophages[56]. They further suggested that there is evidence linking the basal ganglia to central fatigue[3]. Others identify a critical role for the hypothalamic pituitary adrenal axis (HPA axis). A recent review of its potential mechanisms that contribute to fatigue in cholestasis is available[57].

Because the HPA axis controls many functions of the liver through neuroendocrine pathways as well as mediating inflammation, it is thought to influence cellular and molecular processes in the liver. Fatigue, asthenia and muscular weakness, which can get worse during stress and infection[58], have been correlated with an impaired stress response due to HPA axis dysfunction. Interactions of the HPA axis with the liver also stimulate release of pro-inflammatory cytokines that stimulate release of glucocorticoids by the adrenals and block bile acid efflux impairing glucocorticoid metabolism[59]. In chronic inflammation, the HPA axis function is suppressed. Some investigators suggest that the common symptoms reported by people with CLD, such as fatigue, asthenia, lack of motivation and depressive symptoms are similar to symptoms associated with chronic fatigue syndrome and are suggestive of suppressed HPA axis[60].

Recent data[33] suggest that the monoamine transmitters are elevated in patients with CHC and persistent fatigue. Specifically, in patients taking direct acting anti-viral agents, serotonin levels were significantly decreased at post treatment week 4 compared with baseline. Compared with baseline, there were significant decreases in IL-10 levels at end of treatment and 4 wk post-treatment. Changes in dopamine and tryptophan levels at the end of treatment correlated with increasing emotional health scores. Changes in monocyte chemoattractant protein-1 at end of treatment and IL-8 at 4 wk post-treatment correlated with increasing mental health scores. These data support the view that cytokines are involved in the well-being of patients with CHC. Others have reported significant roles for neurotransmitters, including the tryptophan pathway[34,61].

Borrowing from the literature[25,26] and using our own patient base with CHC and NAFLD/NASH, we have observed that patients display some similar symptoms. These include post-exertional malaise and an aversion to physical exercise/activity. They experience mental fatigue, sleep disruption, mood changes consistent with anxiety, depressive symptoms and decreased quality of life[62,63]. Some have difficulty concentrating and processing information. Most of this resolves with viral eradication shortly after completion of anti-viral therapy[11,27]. However, these symptoms persist in 23%-26% of those who achieve sustained viral eradication (SVR)[27]. When evaluating who within the group with CHC continued to have fatigue after achieving SVR, it was the group that had higher baseline depressive and other affective symptoms[27] and who had a higher number of comorbidities. Additionally, the change in cytokine profile after achieving SVR may be clinically meaningful. High baseline serum levels of interferon-g were associated with fatigue. Reductions in levels of chemokine (C-C motif) ligand 2 were associated with persistent fatigue after 12 wks of SVR. With respect to predictors of fatigue, there are no predictors of central fatigue at baseline if one controls for the diagnosis of depression. However, with respect to peripheral fatigue the best predictors at baseline for peripheral fatigue are IL-10, IL-8 and TNFα. TNFα continues to remain a strong predictor of persistent moderate/severe peripheral fatigue after treatment[27]. The contribution of tryptophan pathways and serotonin to fatigue[27,35] and recently to cognitive deficits[64] demonstrate that there are dynamic changes in the central nervous system within the hypothalamus-hippocampal circuit that cause central fatigue. These changes are associated with increased tryptophan-kynurenic acid pathway activity that causes reduced cognitive function, impaired spatial cognitive memory accuracy and increased hyperactivity and impulsivity[64].

POSSIBLE FATIGUE BIOMARKERS/BIOMARKER SIGNATURES

Current clinical and translational research has led to discussions about possible endpoints for treatment trials and clinical outcomes in managing fatigue. There is interest in the research community to develop objective measures, biomarkers or biomarker signatures for self-reports. According to the National Institutes of Health, "a biomarker is a defined characteristic that is measured as an indicator of normal

biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions. A biomarker signature is a combination of multiple variables to yield a patient-specific indicator of normal biological processes or responses to an exposure or intervention including therapeutic interventions. Biomarker modalities are diverse, and can include genetic, protein, cellular, metabolomics, imaging, behavioral, and physiologic endpoints"[65].

Fatigue is a symptom or state that is multi-dimensional. Hence measures of and outcomes for treating fatigue would benefit from the use of a multidimensional construct, such as the World Health Organization's International Classification of Functioning, Disability and Health (https://www.who.int/classifications/icf/en/). This provides a framework where one can identify potential contributors to fatigue. For example, anatomic/physiological abnormalities, function, activity and participation in life activities may need to be assessed to thoroughly evaluate fatigue. Potential biomarkers or biomarker signatures for fatigue have emerged with a better understanding of the (1) Fatigue construct; (2) Distinction of central and peripheral fatigue; (3) Potential mechanisms underlying peripheral and central fatigue; and (4) Significant improvement in use of PROs for measuring function and patient experience.

Potential biomarkers/biosignatures for fatigue include: (1) Physical performance: measures such as 6-minute walk times for ambulatory tolerance, up-and-go test for physical mobility, measures of exercise tolerance including gas exchange and strength and local muscle endurance testing; (2) Cognitive performance: measures offer an objective measure of memory, recall, executive functioning and visuospatial processing; (3) Mood/behavioral: measures for depressive symptoms, anxiety, pain and insomnia; and (4) Brain imaging: imaging studies have provided some new insights into brain metabolic activity, but there is no consensus about its meaning with respect to function. Some suggest that functional magnetic resonance imaging is useful in measuring cognitive fatigue[6,40]. These data provide direct support for the Chaudhuri and Behan model of "central" fatigue that suggests these are non-motor functions of the basal ganglia. Some claim there are no associations between fatigue and attention, cognitive performance and brain structure[66]. Others have shown correlations between brain volume[67] and brain health[68]. Despite these differences, imaging is very likely to serve as a biomarker for brain health and possible cognitive function and fatigue in the future[6].

Evidence exists for the role of pro-inflammatory cytokines in CLD. TNFα, IL-1β and IL-6 are elevated during the viremic phase of CHC and decrease after achieving SVR. This observation is temporally related to improved fatigue symptoms[27]. The literature on IL-1 is noteworthy, despite lack of data specifically for NAFLD/NASH and CHC. There are data for type 2 diabetes and because people with NAFLD are often diabetic, the findings may have significant relevance. Cavelti-Weder *et al*[69] assessed the efficacy of a monoclonal anti-IL-1β antibody compared to placebo in 30 type 2 diabetes patients. Fatigue was reported by 53% of patients and significantly correlated to diabetes duration but not to age. After treatment for 1 mo, fatigue decreased in the groups treated with moderate- and high-dose anti-IL-1β but not in the placebo group.

It is likely that a combination of these measures will need to be configured in order to identify endpoints for clinical trials of fatigue and may serve as treatment targets to better manage the symptom.

FATIGUE SPECIFIC TREATMENTS

Non-pharmacological approaches

A significant amount of literature has been written about the treatment of fatigue in MECFS and cancer related fatigue[70-72]. These reviews discuss a variety of non-pharmacological approaches to fatigue management including weight loss, exercise, dietary supplements, acupuncture, insomnia treatment and cognitive and behavioral interventions. These have helped guide treatment for fatigue in CLD.

With respect to CLD however, there are far fewer disease specific interventions that have been tested and shown to be promising. Starting with an approach to this problem is the TrACE model discussed by Swain[3]. This useful approach includes treating the treatable causes of fatigue (*i.e.*, anemia, other comorbidities), ameliorating the modifiable symptoms (*i.e.*, reduce symptom burden of sleepiness, depressive symptoms), coping and empathizing.

There is very little doubt on the effectiveness of exercise and diet/weight loss alone or in combination for treatment of CLD related fatigue[73-77]; and experts have indicated that this type of intervention is worth the effort[78]. Exercise and dietary interventions

appear to be effective by mobilizing fat from the liver, increasing insulin sensitivity, improving endothelial function, reducing oxidative stress and decreasing inflammation[54].

Several mechanisms have been postulated. One is that training increases peroxisome proliferator-activated receptor gamma coactivator 1-alpha expression, improves mitochondrial function and leads to reduced hepatic steatosis and inflammation[79]. An excellent review of mechanisms of action of exercise in NAFLD is available[79]. Further, exercise and to some degree increased activity improve all-cause and cardiovascular mortality[80-83]. There is ongoing research to determine the comparative effectiveness of aerobic training *versus* anaerobic training (*e.g.*, resistance training) in NAFLD/NASH. As of now, both are recommended[84].

The mechanisms by which exercise works is beginning to emerge and includes direct effects on metabolic regulation and increased cardiovascular resilience. Recently, the effects of exercise on the tryptophan clearance by activation of kynurenine pathway of tryptophan metabolism (Figure 1), which has been shown to mitigate fatigue[85] were reported. Tryptophan is the substrate for kynurenine (kynurenine pathway) as well as serotonin (serotonin pathway). Kynurenine and serotonin can cross the blood brain barrier and influence mood, cognition and fatigue[86]. Thus, peripheral tissues have a large impact on metabolism of kynurenine and serotonin and their availability to the CNS. Exercise stimulates not only the catabolism of tryptophan but also the clearance of kynurenine as kynurenic acid thereby reducing availability of kynurenine for transport across the blood brain barrier[87]. There is also a general improvement in insomnia, hypertension and mood.

In our experience, people who are sedentary, overweight, working, managing families and often feeling overwhelmed find it hard to commit to an active lifestyle and/or a specific exercise regimen. Self-efficacy and illness understanding are major determinants of lifestyle-modification among NAFLD patients. This information can assist clinicians in improving compliance with lifestyle changes among these patients[88].

Frith *et al*[89] reported that patients with NAFLD have significant fear of failing to meet expectations and lack confidence to proceed with an exercise program, which are factors that are modifiable. A recent study suggested that patients with NAFLD, supported by a Web-based approach, can increase the VO_{2peak} to a similar extent as in-person interventions[90]. They noted that patients with low body fat and low VO_{2peak} benefited the most.

The published literature on predictors for or factors promoting adherence to long-term exercise does not lead to a consensus of how to achieve this. A very good review[91] identified many factors and cited conflicting findings including: poorer health (trending towards increased adherence), depression (trending toward decreased adherence) and life stresses (trending toward decreased adherence). One fairly consistent factor influencing adherence included enabling patients to self-select their exercise programs and have flexibility in the types, duration and locations in which they are implemented[91]. Most of the published literature comes from the cardiovascular, cancer and geriatric populations.

Pharmacological agents

Much of the literature on the pharmacological treatment of fatigue in NAFLD is preclinical and is based on metabolism of tryptophan[92]. In the clinical setting, altered serotonergic neurotransmission has been reported in hepatitis C patients with fatigue, and treatment with serotonin receptor antagonists have been linked with improvements in fatigue as documented in patients with hepatitis C that were treated with ondansetron, a 5-HT3 receptor antagonist[93]. Additionally, s-adenosylmethionine (a methyl donor) is thought to work through the dopamine pathway and has been shown to mitigate symptoms of depression. Clinically, the level of evidence of effectiveness is low, although some therapeutic benefits have been reported in terms of fatigue reduction in people with intrahepatic cholestasis[3,94].

CONCLUSION

Fatigue is prevalent and persistent in people with NAFLD/NASH. Fatigue is a multi-domain construct whose deconstruction into central and peripheral fatigue enables us to better evaluate the condition and identify potential causes and/or correlates. Liver is central to the pathogenesis of peripheral and central fatigue, which in our view is dependent upon energy regulation and crosstalk between the gut, liver, muscle and brain. Measurement of fatigue has improved such that performance (objective) and PROs can effectively be used to identify potential causal factors, treatments and

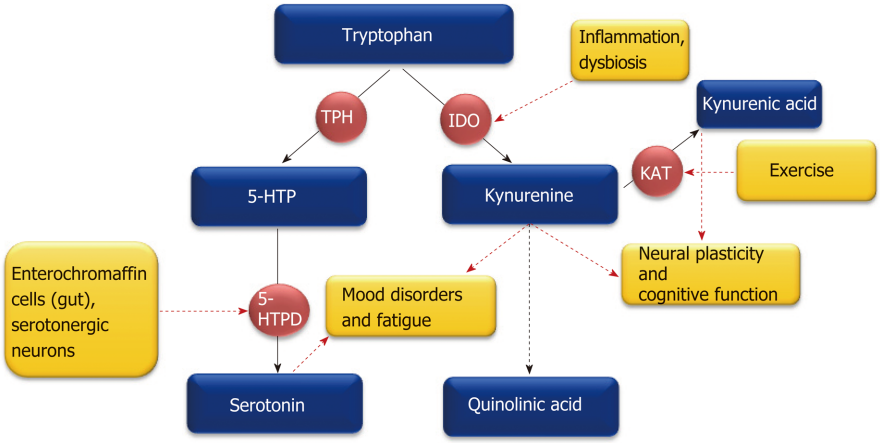

Figure 1 Tryptophan metabolism and the physiological role of its metabolites.

endpoints for treatment. Although further work is needed to provide even more specificity to the fatigue construct and its measurement. Biosignatures for fatigue are being tested and validated that reflect metabolic and inflammatory pathways of relevance. Non-pharmacological treatments have been explored and shown to be effective in NAFLD, NASH, and CHC. These include weight loss and aerobic and resistance exercise. Pharmacological agents to date have not been shown to have a significant, reliable effect in reducing fatigue.

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OPINION REVIEW

Acute kidney injury spectrum in patients with chronic liver disease: Where do we stand?

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Abstract

Acute kidney injury (AKI) is a common complication of liver cirrhosis and is of the utmost clinical and prognostic relevance. Patients with cirrhosis, especially decompensated cirrhosis, are more prone to develop AKI than those without cirrhosis. The hepatorenal syndrome type of AKI (HRS–AKI), a spectrum of disorders in prerenal chronic liver disease, and acute tubular necrosis (ATN) are the two most common causes of AKI in patients with chronic liver disease and cirrhosis. Differentiating these conditions is essential due to the differences in treatment. Prerenal AKI, a more benign disorder, responds well to plasma volume expansion, while ATN requires more specific renal support and is associated with substantial mortality. HRS–AKI is a facet of these two conditions, which are characterized by a dysregulation of the immune response. Recently, there has been progress in better defining this clinical entity, and studies have begun to address optimal care. The present review synopsizes the current diagnostic criteria, pathophysiology, and treatment modalities of HRS–AKI and as well as AKI in other chronic liver diseases (non-HRS–AKI) so that early recognition of HRS–AKI and the appropriate management can be established.

Key words: Acute kidney injury; Acute-on-chronic liver failure; Chronic liver disease; Hepatorenal syndrome; Plasma perfusion and bilirubin adsorption and double plasma molecular absorption system; Fractionated plasma separation and adsorption; Molecular adsorbent recycling system; Single-pass albumin dialysis

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Core tip: Acute kidney injury following advanced liver disease is a very common syndrome in clinical practice. Recent evidence from both basic research on pathophysiology and clinical studies has revealed a complex association between the liver and kidney through the vascular microenvironment and related immune mediators. These connections may play roles in promising new treatments of acute kidney injury on top of chronic liver disease. Furthermore, non-cell-based liver support systems have yielded promising preliminary data on the attenuation of the mortality rate of these conditions of dual organ failure.

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INTRODUCTION

Acute kidney injury (AKI) superimposed on chronic liver disease and cirrhosis is common and consists of varying phenotypes. Prerenal renal dysfunction caused by severe hypoalbuminemia is the most common clinical syndrome in patients with advanced liver disease. Although prerenal azotemia seems to be the first phase of AKI, it is difficult to differentiate from hepatorenal syndrome (HRS) and acute tubular necrosis (ATN). Once the onset of AKI occurs in chronic liver disease, a consequence of its complications is an increased morbidity and mortality rate. Accordingly, the characteristics of renal dysfunctions in both noncirrhotic and chronic liver diseases, such as prerenal HRS-ATN, require not only earlier recognition but also precise diagnosis with optimal management. Recently, there have been great advances, including in classification, nomenclature, and pathophysiology, in identifying the connection between chronic liver disease and acute renal dysfunction in patients with cirrhosis. Indeed, acute-on-chronic liver failure (ACLF) was first recognized in the early 2000s as a new classification that represents the distinct characteristics of chronic liver failure (or decompensated cirrhosis) with rapid deterioration leading to hepatic and extrahepatic multiorgan failure[1,2]. Since then, many efforts in natural history and pathophysiology have been made[3]. Substantial advancements have been made not only in the field of hepatology but also in the understanding of the significance of renal dysfunction in chronic liver disease, as suggested by the international guideline that all acute renal dysfunction in patients with cirrhosis requires the same clinician attention as AKI[4].

Since the first description by Hecker and Sherlock in the 1960s, renal dysfunction in patients with ascites and advanced cirrhosis has typically been called HRS[2], which refers to a syndrome of decreased renal function mainly resulting from the systemic hemodynamic effects of advanced portal hypertension. However, advanced chronic liver disease can impact renal function with a wide range of complications, including bile acid nephropathy, coagulopathy-induced bleeding from ischemic ATN, related glomerular diseases (*e.g.*, immunoglobulin, a nephropathy, hepatitis B-related glomerulonephritis, hepatitis C-related glomerulonephritis, cryoglobulinemia, membranoproliferative glomerulonephritis), and other comorbid diseases such as inherited cystic diseases. Herein, we review the updated information, including the etiology, pathophysiology, and therapeutic aspects, of renal dysfunction in advanced chronic liver disease.

NOMENCLATURE AND CLASSIFICATION OF ADVANCED LIVER DISEASES

The clinical spectrum of advanced liver disease is currently recognized as follows:

Chronic liver disease

Chronic liver disease is a progressive process of destruction and regeneration of liver parenchyma resulting in fibrosis and cirrhosis over a period of 24 wk (Figure 1) caused by inflammation, infection, abnormal metabolism, or malignancy. The

functional classification of chronic liver disease can be divided into compensated and decompensated liver disease.

Acute-on-chronic liver failure

ACLF is liver failure with one or more extrahepatic organ failures, leading to an increased 28-d mortality rate within 3 mo of disease onset[5]. However, there are currently at least 4 different definitions for ACLF in clinical practice: (1) The Asian Pacific Association for the Study of Liver (APASL); (2) The American Association for the Study of Liver Diseases (AASLD); (3) The European Association for the Study of the Liver (EASL) or AASLD-EASL; and (4) The World Gastroenterology Organization (WGO) definition (Table 1).

The first ACLF definition, given by the APASL in 2009, was "acute hepatic insult manifesting as jaundice, and coagulopathy complicated within 4 wk by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease"[6]. Then, in 2014, the revised ACLF definition included the presentation of a high mortality rate within 28 d of disease onset (short-term mortality)[7]. Later, the AASLD-EASL workgroup defined ACLF as "acute deterioration of preexisting chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 mo due to multisystem organ failure", based on the data from large prospective multicenter studies[8,9]. After that, the WGO workgroup announced an improved ACLF definition: "a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolonged international normalized ratio) and one or more extrahepatic organ failure that is associated with increased mortality within a period of 28 d and up to 3 mo from onset"[5]. Interestingly, while the timeframe between the onset of acute liver injury and liver failure development (4 wk) is clear in the APASL definition, time intervals are not mentioned in the AASLD-EASL or the WGO definition.

In addition, there are some differences in ACLF definition regarding the underlying liver conditions of the patients. Patients with cirrhosis and non-cirrhosis (*i.e.*, pre-cirrhotic) are included in the APASL and WGO but not in the AASLD-EASL definition. Patients with hepatic decompensation (previously or currently) are not included in the APASL definition, while they are included in the AASLD-EASL definition (which does not include noncirrhotic chronic liver disease). In parallel, the WGO definition includes both cirrhosis (compensated and decompensated) and noncirrhotic chronic liver disease.

Because ACLF can develop from: (1) Noncirrhotic liver disease (*e.g.*, hepatitis B, alcohol-related chronic liver disease, and nonalcoholic fatty liver disease (NAFLD); (2) Compensated cirrhosis with precipitating factors; and (3) Decompensated cirrhosis, the WGO suggested that all patients with chronic liver disease (no cirrhosis, compensated cirrhosis, or decompensated cirrhosis) should be included in the ACLF definition and divided into types A (noncirrhotic chronic kidney disease), B (compensated cirrhosis), and C (decompensated cirrhosis)[5] (Figure 1).

THE PARADIGM SHIFTS IN THE DEFINITION AND PATHOPHYSIOLOGY OF RENAL DYSFUNCTION IN LIVER DISEASE

The diagnostic criteria of AKI in patients with cirrhosis: an updated definition

Historically, AKI in patients with cirrhosis was often defined as HRS type 1 and type 2. HRS type 1 referred to AKI in cirrhosis with a relatively rapid progressive deterioration of renal function with serum creatinine (SCr) higher than 2.5 mg/dL for more than 2 wk, and HRS type 2 referred to AKI with slowly progressing renal function deterioration in cirrhosis with refractory ascites (SCr level of 1.5-2.5 mg/dL)[10]. Because SCr is a less sensitive biomarker of AKI, with several pathophysiological limitations due to sarcopenia caused by hepatic injury (discussed later), the International Club of Ascites (ICA) recently proposed a new diagnostic criterion for HRS in 2015[4]. Accordingly, the SCr > 2.5 mg/dL criterion was removed along with recommending HRS as another kind of AKI, called HRS–AKI. In addition, the 2-wk threshold for the diagnosis of HRS and its subtypes was removed. The ultimate changes to the diagnostic criteria from HRS to HRS-AKI are now in the context of "cirrhotic patients who develop AKI by detecting a change in absolute SCr level of ≥ 0.3 mg/dL or by an increase in SCr ≥ 50% from baseline within 48 h with a lack of volume expansion response without evidence of shock, recent exposure to nephrotoxic agents or preexisting structural renal disease"[4] (Table 2).

In 2007, the Acute Kidney Injury Network (AKIN) proposed the guidelines for

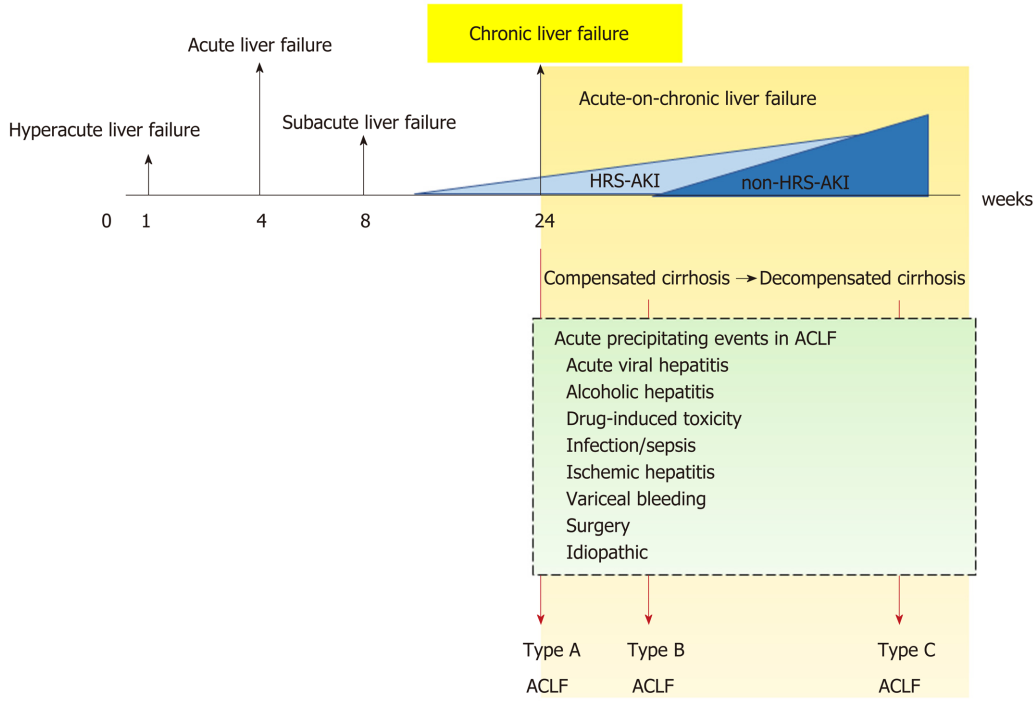

Figure 1 Definition of liver disease terminology according to timing and characteristics. ACLF: Acute-on-chronic liver failure; AKI: Acute kidney injury; HRS: Hepatorenal syndrome.

AKI-defining criteria[11], which were integrated into the ICA and the Acute Dialysis Quality Initiative (ADQI) in 2011[12] (Table 3), because several validation studies on the AKIN criteria show the independent mortality association depending on the stage of renal injury[13-16]. The most recently proposed guideline from Huelin *et al*[17] suggests that stage 1 AKI should be divided into 2 phases, stage 1A (SCr < 1.5 mg/dL) and stage 1B (SCr > 1.5 mg/dL), because stage 1 AKI with SCr > 1.5 mg/dL shows a similar mortality rate as stage 2 AKI. However, further validation study is needed due to the unclear differences in baseline characteristics between stage 1A and stage 1B AKI, where the more severe liver dysfunction is shown in the latter group.

Hepatorenal syndrome–acute kidney injury: A changing of pathophysiologic definitions

The new definitions of advanced liver disease and AKI improve the understanding of the underlying pathophysiologic mechanisms in the liver and kidneys. HRS is currently not the only form of AKI in chronic liver disease. Indeed, a vast majority of AKI in chronic liver disease is not characterized as HRS, particularly in ACLF (Table 4).

Splanchnic vasodilatation

The progression of advanced chronic liver disease into liver cirrhosis (liver architecture disruption) results from splanchnic vasodilatation in response to increased intrahepatic resistance (portal hypertension) caused by several mediators, including nitric oxides, prostacyclin, carbon monoxide, epoxyeicosatrienoic acids, glucagon, endogenous cannabinoids, and adrenomedullin[18-24]. In advanced cirrhosis, the loss of liver compensation that slows disease progression in the liver is due to progressive splanchnic vasodilatation (loss of the counteract vasoconstriction), leading to a decrease in the effective circulatory volume, reduced renal blood flow and AKI. This phenomenon simulates the renin-angiotensin-aldosterone system (RAAS) and vasopressin, which in turn cause more severe renal vasoconstriction and worsening renal hypoperfusion[25]. Evidence of their functional nature was illustrated by measuring copeptin, a 39-amino-acid glycopeptide released from the neurohypophysis, and arginine vasopressin (AVP). The higher copeptin level is, the greater the risk of AKI and the worse the outcomes of decompensated cirrhosis[26]. In addition, the deterioration of renal perfusion is caused by the alteration of renal blood flow autoregulation[27,28]. Together, the current treatment concepts of HRS-AKI are reversing the physiological responses by improving the hemodynamic vascular bed using volume expansion (such as with albumin) together with splanchnic vaso-

Table 1 Comparison of the definitions of acute-on-chronic liver failure from the Asian Pacific Association for the Study of Liver, American Association for the Study of Liver Diseases-European Association for the Study of the Liver, and World Gastroenterology Organization

Criteria	APSAL	AASLD-EASL	WGO
Preexisting or underlying chronic liver disease	Noncirrhotic chronic liver disease, compensated cirrhosis	Cirrhotic chronic liver disease, cirrhosis with prior decompensation	Noncirrhotic chronic liver disease, compensated cirrhosis, decompensated cirrhosis
Precipitating causes	Alcohol, drugs, hepatotropic viruses, surgery, trauma	Alcohol, drugs, hepatotropic viruses, surgery, trauma, variceal bleeding, infection/sepsis	Alcohol, drugs, hepatotropic viruses, surgery, trauma, variceal bleeding, infection/sepsis
Duration between acute liver injury and ACLF	4 wk	NA	NA
Organ failure	Hepatic failure	Extrahepatic organ failure	Hepatic failure, extrahepatic organ failure

APSAL: Asian Pacific Association for the Study of Liver; AASLD-EASL: American Association for the Study of Liver Diseases-European Association for the Study of the Liver; WGO: World Gastroenterology Organization; NA: Not available.

constrictors.

Role of inflammation

Systemic inflammation is one of the mechanisms responsible for decompensated cirrhosis because increased inflammatory cytokines are demonstrated in HRS-AKI (the late stage of cirrhosis). Advanced liver disease with spontaneous bacterial peritonitis (SBP) and renal insufficiency is characterized by high tumor necrosis factor (TNF)-α and interleukin (IL)-6 compared with advanced liver disease with normal renal function[29]. Furthermore, patients with acute decompensated cirrhosis and difficult-to-treat HRS-AKI (persistent AKI) demonstrate higher interferon-inducible protein-10 and vascular cell adhesion molecule-1 compared to patients with treatment-responsive HRS-AKI[30]. In addition, the growing evidence afforded by systems biology analysis has demonstrated a similar nature of inflammation in HRS-AKI in comparison with AKI in chronic non-hepatic conditions, such as lupus nephritis[30].

Adrenal insufficiency

Relative adrenal insufficiency is found in over 25%-30% of decompensated cirrhosis patients. Of note, adrenal insufficiency contributes to cardiomyopathy in cirrhosis patients via the downregulation of β-adrenergic receptors as well as the alteration of catecholamines' effects on the systemic vascular tone[31]. Furthermore, the presence of adrenal insufficiency in patients with stable decompensated cirrhosis is associated with poorer clinical characteristics, such as circulatory dysfunction, previous history of SBP, and worse survival rate[32].

Cardiac dysfunction

The impacts of advanced chronic liver disease on cardiac function and the systemic circulatory system are well known. Cirrhotic cardiomyopathy is a diminished cardiac contractile function with electrophysiological abnormalities in response to stress stimuli without preexisting cardiac disease[33]. The emerging data reflect a liver-heart-kidney interaction. Cirrhotic cardiomyopathy arises from sustained portal hypertension, which increases the risk of bacterial translocation and portosystemic shunt. Bacterial translocation stimulates the production of systemic inflammatory cytokines and eventually causes endothelial dysfunction[34], while an increased portosystemic shunt decreases systemic vascular resistance by increasing nitric oxide, adenosine, bradykinin, and endocannabinoids[35]. In addition, portal hypertension and splanchnic dilation activate the sympathetic nervous system and several neurohormones, including AVP, renin, and angiotensin, which affect heart function by increasing afterload and left ventricular end-diastolic pressure[36]. Decreased cardiac output and increased right atrial pressure cause renal tissue hypoxia and venous congestion, respectively, leading to kidney injury and lower glomerular filtration rate[37]. Accordingly, cardiac dysfunction in advanced chronic liver disease deteriorates renal function in HRS through a liver–heart–kidney connection, which is possibly related to a new model of therapeutic approaches to HRS[38].

Pathophysiology involved in AKI in other chronic liver diseases (non-HRS-AKI): An update of evidences

Table 2 The International Club of Ascites diagnostic criteria for hepatorenal syndrome

International Club of Ascites diagnostic criteria for hepatorenal syndrome
Diagnosis of cirrhosis and ascites
Diagnosis of acute kidney injury (AKI) according to ICA-AKI criteria (Table 3)
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion administration with albumin at 1 g/kg of body weight
Absence of shock
No current or recent use of nephrotoxic agents
No signs of structural kidney injuries, defined as the following:
Absence of proteinuria (> 500 mg/day or equivalent)
Absence of microscopic hematuria (> 50 red blood cells per high-power field)
Normal findings on renal ultrasonography

AKI: Acute kidney injury; ICA: Ascites diagnostic criteria.

Role of inflammation, apoptosis, and cell death: Hepatic inflammation is a novel major component for the initiation and progression of liver injury[39]. In chronic liver disease, hepatic inflammation is activated by several risk factors (*i.e.*, systemic infection, gastrointestinal bleeding, alcohol, viral infection, *etc.*) resulting in (Figure 1): (1) Hepatocyte damage that delivering several damage-associated molecular patterns (DAMPs) from liver cells; and (2) Gut immunity impairment that enhancing the translocation of pathogen-associated molecular pattern (PAMPs) from gut organisms[40]. Subsequently, both DAMPs and PAMPs enhance the more severe liver damage (ALF, ACLF, and liver cirrhosis). Several liver associated DAMPs including IL-1, IL-33, high-mobility group box-1, and bile acid[41] are recognized by several receptors [*e.g.*, toll-like receptors (TLR)-4, TLR-9 and the receptor for advanced glycation end-products] on Kupffer cells (liver macrophages)[42] resulting in the more enhanced hepatic damages (Figure 2).

In addition, the imbalance of inflammatory response in ACLF (a local inflammatory response) contributes to the systemic inflammatory response syndrome (SIRS) in different severity and subsequently turns into the compensatory anti-inflammatory response syndrome (CARS)[43]. While SIRS relates to the excessive liver inflammation and extrahepatic organ dysfunction, CARS is a counter regulatory mechanism against the inappropriate hyper-inflammatory process. Overwhelming of activated monocyte function may contribute to AKI, compatible with those in septic AKI[44]. In addition, Because macrophage polarization is related to pro- versus anti- inflammation, SIRS and CARS in ACLF might be associated with M1 and M2 macrophage polarization, respectively, of Kupffer cells in liver[45]. Moreover, bone marrow-derived macrophage that was recruited into liver by the inflammatory-induced CCL2 and CCR5 chemokine expression might also be important in liver injury[45]. Macrophage polarization and macrophage origin may be beneficial to the understanding in the inflammatory phase of liver injury (*i.e.*, initiation, propagation and resolution)[46]. The inhibition of Kupffer cells, the prevention of monocyte recruitment into liver, and the promotion of proper macrophage polarization might be the novel strategies for liver injury attenuation[47].

Systemic oxidative stress and several inflammatory cytokines (human non-mercaptalbumin 2, IL-6, and IL-8) are also higher in patients with ACLF compared to non-ACLF conditions[48]. Similarly, the severity of ACLF is associated with apoptosis as determined by the apoptosis index [plasma caspase-cleaved keratin 18 (cK18; an apoptosis biomarker)/keratin 18 (K18; an indicator of total cell death)][49], implying the influence of systemic inflammation and apoptosis in ACLF. Indeed, persistent infection (inflammatory activation) is an important risk factor in cirrhotic patients on the basis of the score of chronic liver failure-organ failure. Therefore, AKI superimposed in ACLF is associated with a 20% increase in mortality depending on AKI severity (more severe with SCr > 1.5 mg/dL)[9].

Role of bile acid: The limited responsiveness of terlipressin plus albumin treatment in HRS type 1 with high serum bilirubin (≥ 10 mg/dL) suggests the influence of bile acid in chronic liver disease[50]. Indeed, the markedly elevated serum bilirubin in chronic liver disease induces bile cast nephropathy, a common renal pathology of AKI with severe liver dysfunction diagnosed from the presentation of intratubular bile casts by Hall histochemical staining, which are associated with irreversible AKI in chronic liver disease[51-53]. In the less severe form of renal injury, bile acid accumulation in cirrhosis induces proximal tubulopathy mimicking Fanconi syndrome (low uric acid,

Table 3 The proposed classification system of renal dysfunction in patients with cirrhosis proposed by the Acute Dialysis Quality Initiative and the International Club of Ascites work group[12]

Diagnosis	Definition
Acute kidney injury (AKI)	Rise in serum creatinine (SCr) of ≥ 50% from baseline or a rise in SCr by ≥ 0.3 mg/dL (26.5 μmol/L) in < 48 h. Hepatorenal syndrome (HRS) type 1 is a specific form of AKI
	Stage 1: Increase in serum creatinine (SCr) ≥ 0.3 mg/dL (26.5 μmol/L) or an increase in SCr 1.5-fold to 2-fold from baseline
	Stage 2: Increase in SCr > 2-fold to 3-fold from baseline
	Stage 3: Increase in SCr > 3-fold from baseline or an increase in SCr ≥ 4.0 mg/dL (353.6 μmol/L) with an acute increase ≥ 0.3 mg/dL (26.5 μmol/L) or initiation of renal replacement therapy
Chronic kidney disease (CKD)	Glomerular filtration rate (GFR) of < 60 mL/min for > 3 mo, calculated using the MDRD6 formula. HRS type 2 is a specific form of CKD
Acute-on-chronic kidney disease	Rise in SCr of ≥ 50% from baseline or a rise of SCr by ≥ 0.3 mg/dL (26.5 μmol/L) in < 48 h in a patient with cirrhosis whose GFR is < 60 mL/min for > 3 mo, calculated using the MDRD6 formula

MDRD: Modification in diet of renal disease; GFR: Glomerular filtration rate; CKD: Chronic kidney disease; AKI: Acute kidney injury; SCr: Serum creatinine.

low phosphate but high bile acid in serum) without bile cast nephropathy[51-53]. Although serum bilirubin is an independent predictor of the therapeutic response of HRS, the precise role of bile cast nephropathy is still unclear.

Worsening portal hypertension: Markedly increased intrahepatic resistance is common in progressive ACLF patients and usually results in increased portal hypertension[54]. This, in turn, may potentiate hepatorenal reflex disturbance, causing progressive AKI[27].

Worsening cardiac output: ACLF worsens cardiac functions through arterial vasodilation in the splanchnic area and peripheral circulation, which can be demonstrated in all stages of liver injury, from the early compensated stage to progressive liver decompensation to the late stage of HRS. The low cardiac output due to excessive vascular dilatation is counteracted by: (1) Several vasoconstriction mediators (including the RAAS, vasopressin, and the sympathetic nervous system); and (2) Vigorous salt and water balancing from renal homeostasis[55]. Once cardiac function fails to compensate for arterial vasodilation, as determined by the low cardiac output and reduced systolic function, the more severe liver injury condition (late HRS) will develop due to the decreased effective circulating volume[56].

TREATMENT

General management

As discussed above, the points on the continuum of AKI disease in liver cirrhosis, *i.e.*, prerenal azotemia-HRS-ATN (prerenal-HRS-ATN), are difficult to differentiate clearly. AKI management in a certain setting should focus on early recognition with an understanding of the individual patient's clinical course (Figure 3). The disturbance of hemodynamics in cirrhosis patients is the principal cause of AKI that is precipitated by infection, abrupt onset of severe hyperbilirubinemia, gastrointestinal bleeding, over-diuresis, or nephrotoxic agents. All of these factors must be immediately identified and corrected in patients with advanced cirrhosis to prevent subsequent renal complications. An intravascular volume status assessment is an initial step for any AKI etiologies. Volume status assessment is challenging, particularly in cirrhosis, because the patients usually also have hyperdynamic circulation between a total-body hypervolemic state and a low effective circulatory volume status. Unfortunately, there is no effective monitoring tool for these patients. Central venous pressure monitoring not only has a poor correlation with the intravascular volume due to confounding effects from ascites but also is too invasive for the coagulopathy that is commonly found in chronic liver disease. Echocardiography for intravascular volume assessment depends solely on the determination of inferior vena cava size and variability, which relies mostly on operator expertise[57].

Although there is no advantage in mortality attenuation or AKI incidence when

Table 4 Comparison between the main mechanisms of the pathophysiology of hepatorenal syndrome–acute kidney injury and non-hepatorenal syndrome-acute kidney injury

Hepatorenal syndrome	Non-hepatorenal syndrome
Splanchnic vasodilatation	Acute-on-chronic liver failure
Inflammation	Inflammation
Adrenal insufficiency	Bacterial translocation
Cardiac dysfunction	Bile acid
	Worsening portal hypertension
	Worsening cardiac output

comparing albumin and crystalloids[58], albumin is usually the recommended volume expander in chronic liver disease due to albumin's pleiotropic effects (anti-inflammatory and antioxidant properties)[59,60]. Hydroxyethyl starch is contraindicated due to its associations with increased AKI and mortality rates[61]. In addition, intravenous albumin administration at 1-1.5 and 1 g/kg on days 1 and 3, respectively, with antibiotics attenuates the mortality of SBP and the AKI incidence[62]. In parallel, SBP prophylaxis with oral quinolones (norfloxacin 400 mg twice a day for 7 d) is recommended in the high-risk group (low protein in ascites fluid and previous history of SBP)[63], while intravenous ceftriaxone (1 g/d for 7 d) is more proper than oral quinolones in patients with active gastrointestinal bleeding[64]. Further, patients with high serum bilirubin (> 20 mg/dL) (with an abrupt onset or long duration) may develop nephropathy due to jaundice or bile cast induction[52,65], and selective bilirubin removal might be beneficial[66].

Intravascular volume depletion due to excessive diuretic treatment (diuretic-induced AKI) is common. Furthermore, electrolyte disturbance, such as hyperkalemia from aldosterone antagonists or other potassium-sparing diuretics, may necessitate urgent renal replacement therapy, particularly in those with renal impairment. Hypokalemia, a precipitating factor of hepatic encephalopathy, is a frequent diuretic complication. Accordingly, diuretic administration should be reserved for patients with a hypervolemic state or marked ascites and should be avoided in those vulnerable to intravascular volume depletion. All nephrotoxic agents, such as radiological contrasts, need to be prescribed with caution. Sepsis is also a common condition that is found with decompensated cirrhosis[67]. Organ failures such as AKI and acute respiratory distress syndrome may be a result of a high production of sepsis-induced proinflammatory cytokine production[67]. Cirrhosis patients with AKI should undergo a full septic workup and be treated with empirical antibiotics. Measuring the appropriate markers for early sepsis might be beneficial, as mentioned in the setting of resuscitation guided by serum lactate[68,69]. However, this approach remains controversial in advanced liver disease because of: (1) The poor lactic acid metabolism in liver diseases; and (2) The weak association between hyperlactatemia and tissue hypoperfusion[70].

Managements of HRS

If renal function does not improve after adequate volume expansion, HRS-AKI and non-HRS-AKI must be in line with the differential diagnosis and be further assessed with simultaneous treatment. The goal of HRS–AKI treatment is to optimize the cardiac output and mean arterial blood pressure (MAP). Although there was no significant difference in outcomes between targeting the higher MAPs (80-85 mmHg) compared with the lower MAPs (65-75 mmHg) in septic AKI[71], the most recent study revealed that AKI incidence was lowest among those whose postresuscitation MAP was closest to or higher than their preadmission MAP[72]. Perhaps an individualized target MAP acts as a key marker for HRS-AKI. To increase the MAP and cardiac output, intravenous albumin administration along with systemic vasoconstrictors has shown promising outcomes. A number of systemic vasoconstrictors are used to counter splanchnic vasodilation, including a vasopressin analog (terlipressin)[73,74], an α-adrenergic agonist (norepinephrine)[75,76], and a combination of α-adrenergic agonist (midodrine) and somatostatin analog (octreotide)[77]. The most recent meta-analysis demonstrates that: (1) The treatment of HRS type 1 with terlipressin plus albumin attenuates the short-term mortality; and (2) Terlipressin plus albumin or noradrenaline plus albumin is superior to triple therapy with midodrine, octreotide and albumin[78]. Regarding AKI outcome, terlipressin infusion gives an earlier and stronger response than noradrenaline, with a higher reversal rate of HRS (40% *vs* 17%) and a lower rate of renal support requirement (57% *vs* 80%)[79]. Interestingly, the

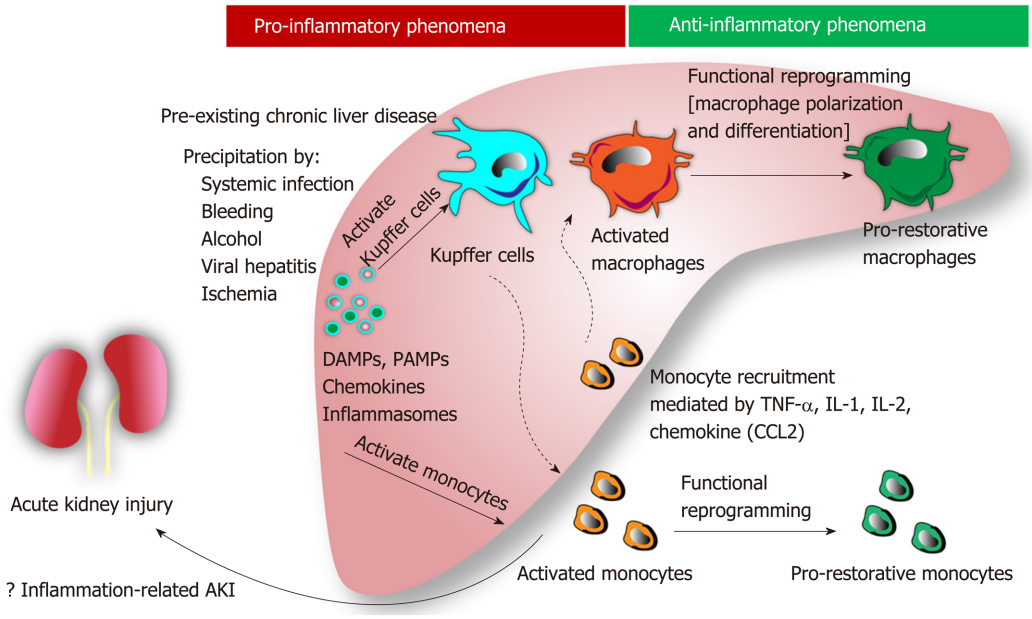

Figure 2 Role of monocytes and macrophages in the immunological aspects of acute-on-chronic liver failure and acute kidney injury. Several risk factors addition to pre-existing chronic liver disease initiate hepatic inflammation which release various types of damage-associated molecular patterns, pathogen-associated molecular pattern, chemokines and inflammasomes. These mediators affect to the inflammatory cascade through monocyte and Kupffer cell activation which subsequently turn on either liver or systemic immunity. While, in the liver, Kupffer cells signal to bone marrow-derived monocytes for recruiting them to the liver, systemic (peripheral) monocytes also become activated monocytes which expanding the pro-inflammatory responses or systemic inflammatory response syndrome (SIRS). Overwhelming of pro-inflammatory cascade is supposed to be the background of acute kidney injury (AKI), similarly septic AKI (inflammation-related AKI). However, the functional reprogramming of both activated macrophages and activated monocytes could attenuate SIRS by differentiating to pro-restorative phenotypes that favors liver tissue resolution and healing. DAMP: Damage-associated molecular pattern; IL: Interleukin; PAMPs: Pathogens-associated molecular patterns; SIRS: Systemic inflammatory response syndrome; TNF-α: Tumor necrosis factor-alpha; AKI: Acute kidney injury.

effectiveness of albumin depends on the cumulative administration dose, as a 100 g increase in cumulative albumin (max dose of 600 g albumin) increases the survival rate with a hazard ratio of 1.15 and a 95% confidence interval of 1.02-1.31[80]. Because most HRS-AKI develops in an ACLF setting and is associated with inflammatory mediators, therapeutic strategies not only for hemodynamic restoration but also for the attenuation of systemic inflammation might represent a paradigm shift in the treatment, as demonstrated by the balancing of monocyte function[81]. Recently, simvastatin, a well-known lipid-lowering agent, has demonstrated beneficial effects in an ACLF rat model with advanced chronic liver disease through the improvement of hepatic hemodynamics, microvascular dysfunction, and endotoxemia[82].

Roles of extracorporeal support systems

Compared with noncomplicated HRS-AKI, non-HRS-AKI and HRS-AKI in advanced ACLF have more morbidity and mortality because of their poor response to terlipressin and albumin. ACLF with ≥ 2 organ failures (ACLF grade 2-3) is associated with a 60%-75% rate of 28-d mortality[9], and therapies such as plasmapheresis that potentially ameliorate the ACLF severity by modulating the immune system may be an option. Currently, both renal and liver support in clinical studies have failed to have any survival advantage[83,84]. Regarding the mode of hemodialysis, continuous renal replacement therapy (CRRT) does not improve mortality in comparison with intermittent hemodialysis; however, CRRT might be well tolerated in patients with unstable conditions, including fulminant hepatic failure, as it does not raise intracranial pressure[85]. Indeed, the ADQI group recommends renal support only in cases with acute reversible components. Otherwise, renal support is not recommended in AKI-superimposed chronic liver disease, which is similar to the recommendation of limited utilization of liver support in liver transplantation[85]. However, extracorporeal albumin dialysis may improve outcomes based on the clearance of excess bilirubin, bile acid, inflammatory cytokines, and endotoxins in systemic circulation[84]. The extracorporeal liver support is currently divided into 2 kinds of systems.

Cell-based liver support systems (bioartificial liver support systems): The data on bioartificial liver support systems benefit in patients with ACLF are still limited and from uncontrolled studies with limited numbers of patients.

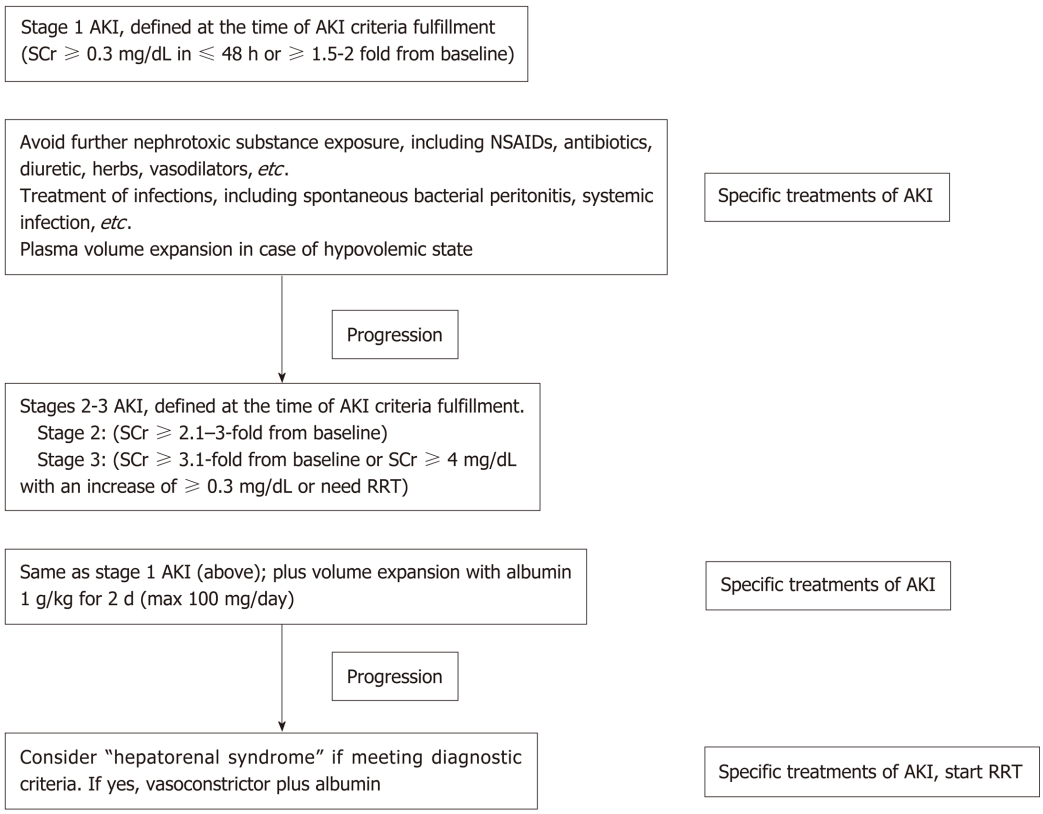

Figure 3 Summarized algorithm for the management of acute kidney injury according to the International Club of Ascites-acute kidney injury classification, which combines Kidney Disease Improving Global Outcomes criteria and conventional criteria in patients with cirrhosis and ascites.
NSAIDs: Nonsteroidal anti-inflammatory drugs; SCr: Serum creatinine; RRT: Renal replacement therapy; AKI: Acute kidney injury.

Non-cell-based liver support systems: There are two major modalities regarding to the non-cell-based liver support systems-plasma therapy and albumin dialysis. Plasma therapy comprises 4 subtypes of techniques: (1) Standard plasma exchange is a simple circuit (Figure 4) that enhances the elimination of inflammatory cytokines and endotoxins by using 1.2 L of plasma as fluid replacement. However, it has so far failed to show a confirmed survival advantage; (2) High-volume plasma exchange (HVP). Unlike standard plasma exchange, the HVP procedure uses a large amount of fresh-frozen plasma (approximately > 10 L of fresh-frozen plasma or 15%-20% of ideal body weight) as replacement fluid. The established technique was first used for immunologically driven disorders in the early 1990s[86]. HVP decreases the vasopressor dose requirement in resuscitation and improves hepatic encephalopathy symptoms by decreasing blood ammonia and urea[87]. A recent prospective, randomized study was conducted in 183 patients with acute liver failure, with approximately 2.4 treatments per patient and 9 h per treatment, and it demonstrated a slightly improved survival by an intention-to-treat analysis (59% *vs* 48%) and reduced circulating proinflammatory mediators [IL-6, TNF-α, DAMPs[88] and soluble B7 (CD80/CD89)[89]]. Unfortunately, there is no evidence on using HPV in ACLF so far. Further prospective studies are required to confirm these results in patients with acute liver failure and might be extended to patients with ACLF in the near future; (3) Plasma perfusion and bilirubin adsorption system and double plasma molecular absorption system, as shown in Figure 5. The fundamental mechanism in the plasma perfusion and bilirubin adsorption system is the separation of plasma that passes through an anion-exchange column (adsorbent), which has an adsorption effect on specific molecules (such as bilirubin, bile acid, and related similar molecular structures). Data from several studies showed a safe decrease in the plasma bilirubin concentration of approximately 18%-50% from baseline after one session[90,91]. The double plasma molecular absorption system is more sophisticated than plasma perfusion and bilirubin adsorption, combining both with an adsorbent for the reduction in inflammatory mediators, drugs or toxins (Figure 5). Although the rationale for using these systems seems to be that they will improve our understanding of ACLF pathophysiology, most studies on the double plasma molecular absorption system are in patients with hepatitis B-related liver failure[92-94].

In our experience, the double plasma molecular absorption system decreased bilirubin and ammonia 25%-30% from baseline after one treatment session in patients with ACLF and cancer (unpublished data). The reduction in hyperbilirubinemia in patients with sepsis-related ACLF was also demonstrated in our case series (unpublished data); (4) Fractionated plasma separation and adsorption (FPSA) (Prometheus®). FPSA, first introduced in 1999, is fractionated through an albumin-permeable filter with a cutoff of 250 kDa. Albumin and other plasma proteins cross the membrane and pass across 2 columns in a series-an anion-exchange column and a neutral resin adsorber. The cleansed albumin/plasma is returned to the standard blood pool circuit, where it is then treated by conventional high-flux hemodialysis (Figure 6). Clinical studies have evaluated the effect of FPSA in ACLF patients, with favorable outcomes, indicating that the use of FPSA is well tolerated and decreases the circulating levels of serum bilirubin, bile acids, and ammonia[95-100]. However, the improvement of neurological status and hemodynamics following FPSA treatment is controversial[96,98]. A prospective, randomized clinical trial (HELIOS study)[100] conducted in 145 ACLF patients demonstrated that FPSA decreased serum bilirubin with nondifferent 28-d survival rates (66% *vs* 63%). The secondary endpoint showed a significant improvement in survival in ACLF patients using the cutoff of Model for End-Stage Liver Disease (MELD) score > 30. It should be emphasized that there is no further confirmatory study or any study in an acute liver failure setting so far.

Albumin dialysis has been classified as molecular adsorbent recycling system (MARS) and single plasma albumin dialysis (SPAD). Technically, MARS consists of 3 main circuits of the blood delivery system, albumin flow, and routine hemodialysis system (Figure 7). In the MARS circuit, blood is dialyzed through an albumin-saturated high-flux dialyzer with 20% human albumin (600 mL) and is used as the dialysate for carrying the albumin-bound toxins into the dialysate, where the water-soluble and albumin-bound toxins will be removed from albumin through 2 sequential adsorbent columns containing activated charcoal and anion-exchange resin. Then, the toxin-free albumin will be circulated in the circuit. The high-molecular-weight toxins (> 50 kDa) are not removed by MARS due to the dialyzer pore size limitation. The RELIEF study is the largest randomized trial using MARS in ACLF, with 189 patients from 19 European centers, and it demonstrated that undergoing up to ten 6-h to 8-h sessions of MARS was associated with the improvement of hepatic encephalopathy (from grade 2-4 to grade 0-1; 63% *vs* 38%, respectively; $P = 0.07$) without a 28-d survival benefit[101]. Similarly, the FULMAR trial was a randomized controlled study using MARS in 102 patients with acute liver failure fulfilling transplant criteria and demonstrated no significant differences in 6-month survival between the MARS (85%) and standard medical treatment (76%) groups ($P = 0.28$)[102]. However, the major confounder in the study was the short transplant waiting time [median 16.2 h, mostly within 24 h (75%)], which might be too short to see the benefit of liver support. Interestingly, neither MARS nor FPSA showed significant decreases in inflammatory markers (IL-6, IL-8, IL-10, and TNF-α) after the treatment session in a small study[103].

In contrast to MARS, SPAD uses a standard CRRT system without any additional columns (Figure 8). After a SPAD cycle is run, water-soluble toxins (ammonia, creatinine, urea, uric acid) are removed almost completely. Blood is dialyzed against a standard dialysis solution with the addition of albumin to the dialysate. The most effective albumin concentration was 3%. A further increase in the albumin concentration to 4% did not lead to a significant increase in the detoxification[104]. However, SPAD increased the detoxification efficiency of albumin-bound substances from 350 mL/h to 700 mL/h (for bilirubin) or 1000 mL/h (for bile acids) of the dialysate flow in SPAD for the first time[104]. Unfortunately, SPAD has been evaluated in a case-control fashion mostly in drug overdose-related liver failure, with controversial outcomes[105-107].

Roles of liver transplantation

So far, liver transplantation is the only treatment modality for the reversal of either HRS-AKI or non-HRS-AKI in an ACLF setting. Recently, a large retrospective study of liver transplantation in patients with either HRS-AKI or non-HRS-AKI in ACLF demonstrated that 1-year and 5-year survival rates were 91% and 77%, respectively. However, those with a renal injury background of either diabetes or hypertension showed a lower survival rate (1-year and 5-year survival at 87% and 71%, respectively)[108]. Pretransplant AKI severity contributed as an important factor for renal function recovery at 4-6 wk posttransplantation. Thus, simultaneous liver-kidney transplantation should be considered in those with predicted renal recovery longer than 6 wk[85].

Roles of the novel monocytes and macrophage modulators

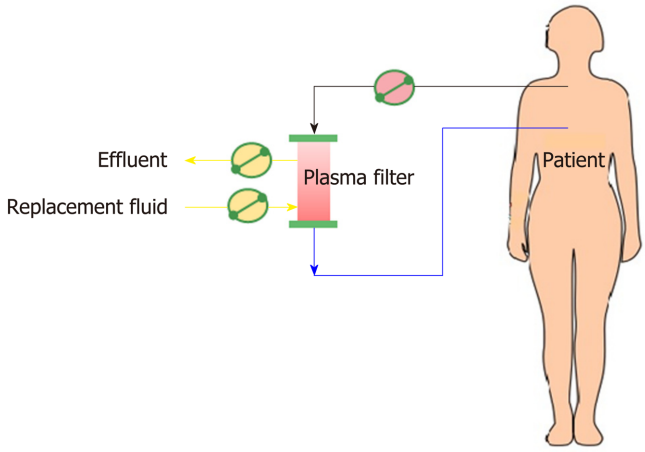

Figure 4 Plasma exchange circuit.

Regarding the high rate of mortality and limited treatment options for ACLF and AKI following ACLF; novel, robust therapies are needed.

Targeting liver macrophage: So far, unfortunately, none of proven macrophage-directed therapies has been recommended in ACLF although a number of immunomodulators including N-acetylcysteine, albumin and glucocorticoids are approved for other immune-related liver diseases[46]. The limitation of knowledge is probably due to the limitation in retrieving human liver tissue and the differentiation process for liver macrophage in human[46].

Targeting inhibition of Kupffer cell activation: Inhibition of progression of the early phase of SIRS in ACLF could be attenuate the signal induction for Kupffer cell activation especially targeting to inhibit released DAMPs. Recent study demonstrated potential beneficial of HMGB-1 blockade treatment in rat with ACLF model through alleviating inflammation in SIRS[109]. Likewise, the blocking responses against of histones (a DAMP) attenuated cytokine production and reduced liver injury severity[110]. In addition, the prevention and treatment of bacterial translocation by appropriate antibiotics is the most effective attenuation of initial innate immune activation leading to the subsequently Kupffer cell inhibition[111].

Targeting inhibition of monocyte recruitment into the liver: The recruitment of monocytes into liver is mediated mainly through chemokine system including; CCL2-CCR2 and CCL5-CCR5 for the recruitment of monocyte and lymphocyte, respectively[112]. As such, Cenicriviroc, an CCR2/CCR5 inhibitor, in a randomized, double-blind study in 289 patients with NAFLD and hepatic fibrosis demonstrated a reduction on fibrosis in treatment group (n = 145) compares with placebo (n = 144) (20% *vs* 10%) without the reduction of the primary endpoint (NAFLD activity score)[113] supporting the animal model data[112].

Targeting promotion of macrophage differentiation: An early promotion of macrophage differentiation from activated macrophages phenotype into a pro-restorative phenotype (such as by corticosteroids) might enhance the resolution of liver injury[111]. However, the data on macrophage differentiation treatment in ACLF is still too less. Corticosteroids might provides some advantages in the early phase of ACLF but possibly augment infectious complications in the late phase[114].

Roles of the novel granulocyte colony-stimulating factor therapy

ACLF is mainly mediated through immune dysfunction and is also susceptible to the serious infections. Accordingly, treatment by hematopoietic growth factor to induce immune cells seems reasonable to restore immune homeostasis through improving impaired phagocytosis[115] and mobilization of CD34+ progenitor cells into liver[116]. The first randomized placebo-controlled study in 2012 using granulocyte colony-stimulating factor (G-CSF) in patients with ACLF demonstrated an improved 60-d survival rate and a reduction in multiorgan injury on the basis of clinical scores, including those of the MELD and Sequential Organ Failure Assessment (66% *vs* 26%)[117]. Likewise, G-CSF improved the 90-d mortality rate (78% *vs* 30%) in a randomized trial on 46 patients with ACLF[118]. The largest study, on 55 patients with hepatitis B-related ACLF randomized to receive standard medical treatment or G-CSF

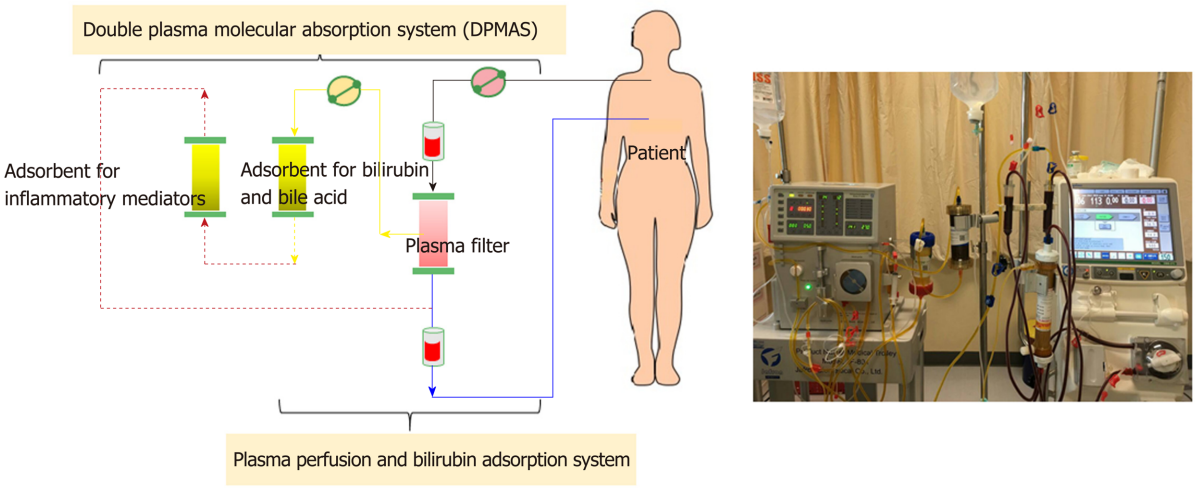

Figure 5 Plasma perfusion and bilirubin adsorption system and double plasma molecular absorption system circuit. DPMAS: Double plasma molecular absorption system.

in addition to standard medical treatment, again showed a significant benefit in the 90-d survival rate in the G-CSF-treated group (48% *vs* 28%)[119]. Interestingly, the most recent randomized study in 32 patients with hepatitis B virus-ACLF showed that 5 μg/kg/day of G-CSF for six consecutive days in addition to the standard treatment, improves survival, facilitates clinical recovery, prevents renal failure and protects from hyponatremia[120].

CONCLUSION

AKI following advanced liver cirrhosis is a critical condition. The early recognition and rapid diagnosis of AKI in these patients may improve therapeutic outcomes. However, the understanding of the pathogenesis and the quality of the diagnostic tools for the simultaneous injury of the kidney and liver are still limited. A distinct diagnostic criterion for differentiating the points on the prerenal-HRS-ATN spectrum needs robust validation as well as an accurate distinction between HRS-AKI and non-HRS-AKI in ACLF. Inflammation is increasingly recognized as an important driver of AKI, particularly in patients with infection and multiorgan failure. As AKI in chronic liver disease is persistent and rapidly becomes irreversible by medical treatment as the condition prolongs, novel therapies and new approaches for either liver or renal support are required.

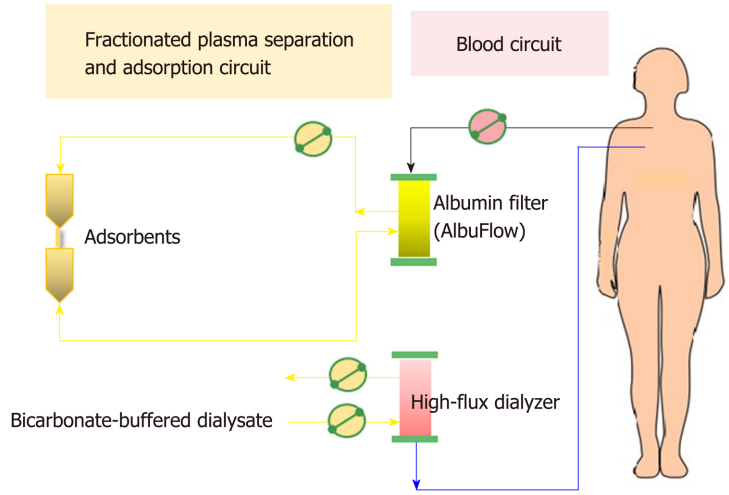

Figure 6 Fractionated plasma separation and adsorption (Prometheus®) circuit.

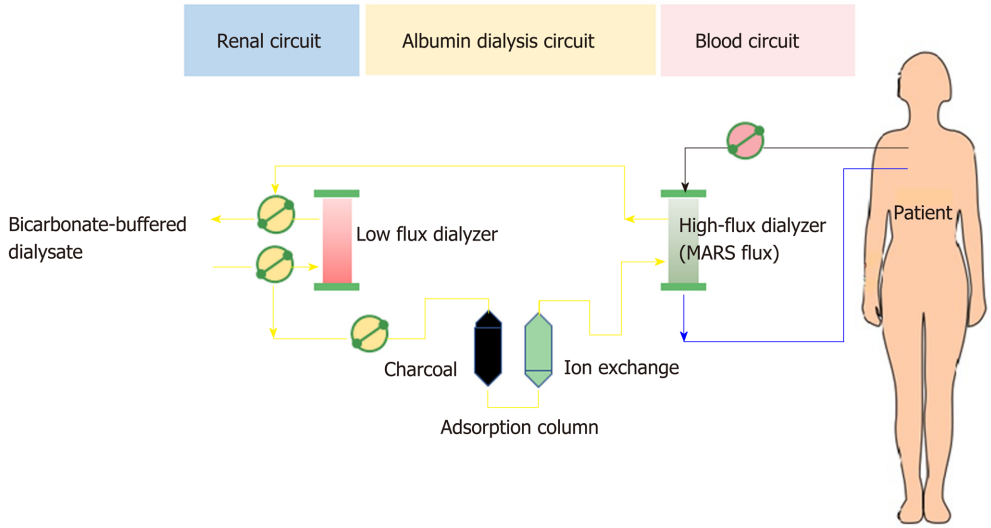

Figure 7 Molecular adsorbent recycling system circuit. MARS: Molecular adsorbent recycling system.

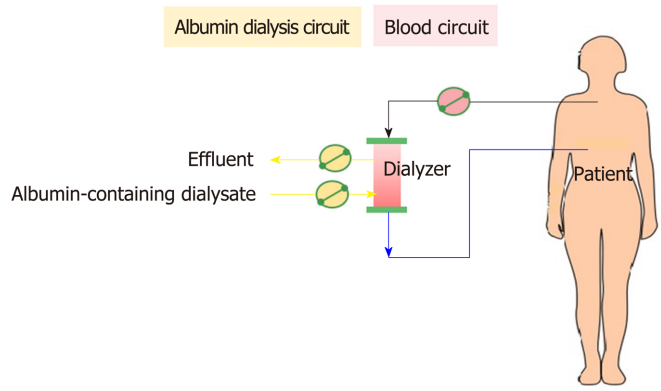

Figure 8 Single-pass albumin dialysis circuit.

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REVIEW

Neoadjuvant and adjuvant treatment strategies for hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most common liver malignancy worldwide and a major cause of cancer-related mortality for which liver resection is an important curative-intent treatment option. However, many patients present with advanced disease and with underlying chronic liver disease and/or cirrhosis, limiting the proportion of patients who are surgical candidates. In addition, the development of recurrent or *de novo* cancers following surgical resection is common. These issues have led investigators to evaluate the benefit of neoadjuvant and adjuvant treatment strategies aimed at improving resectability rates and decreasing recurrence rates. While high-level evidence to guide treatment decision making is lacking, recent advances in locoregional and systemic therapies, including antiviral treatment and immunotherapy, raise the

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prospect of novel approaches that may improve the outcomes of patients with HCC. In this review, we evaluate the evidence for various neoadjuvant and adjuvant therapies and discuss opportunities for future clinical and translational research.

Key words: Hepatocellular carcinoma; Neoadjuvant therapy; Adjuvant therapy; Neoplasm recurrence; Hepatectomy; Liver cirrhosis

Core tip: Liver resection is an important curative-intent treatment option for patients with hepatocellular carcinoma (HCC). However, advanced disease, underlying chronic liver disease and/or cirrhosis, limits the proportion of patients who are surgical candidates. Recurrent disease is unfortunately common even after undergoing resection. As such, the benefits of neoadjuvant and adjuvant treatment strategies aimed at improving resectability and decreasing recurrence rates are of great interest. While high-level evidence to guide treatment decision making is lacking, recent advances in locoregional and systemic therapies, including antiviral treatment and immunotherapy, raise the prospect of novel approaches that may improve the outcomes of patients with HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality worldwide, representing the third most common malignancy in men and seventh in women[1,2]. In the United States, there was an estimated 42220 new cases of HCC and an estimated 30200 HCC-related deaths in 2018[3]. Unfortunately, the incidence of HCC is rising and, unlike most other cancers, this increased incidence affects all major demographic groups and populations[4,5]. This increase is particularly higher in men, who have a four-fold increased risk of developing HCC[6,7]. The vast majority of HCC occurs in the setting of chronic liver disease (CLD) with or without cirrhosis most often secondary to chronic hepatitis B (HBV) and hepatitis C (HCV) infections, although there is also a rising incidence of non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) related cirrhosis[8-11]. Other major causes include alcoholic cirrhosis, as well as diabetes, hemochromatosis, Alpha 1-antitrypsin deficiency, Wilson's disease, hemophilia, and Aflatoxin[12-15]. Thus, patients with HCC have two simultaneous challenges: the malignancy itself and the underlying liver disease which can both complicate treatment and predispose to the development of recurrent or *de novo* cancers.

While numerous systemic and locoregional treatments exist for patients with HCC, curative-intent options mainly include liver transplantation (LT), surgical resection, and ablative therapies. Although LT is appealing in that it treats both the cancer and the underlying CLD, a major challenge is the deficiency of available organs in the United States and around the world. Furthermore, many patients with relatively preserved liver function (*e.g.*, chronic HBV) or those outside Milan criteria (*e.g.*, large solitary tumor or macrovascular invasion) are not eligible for LT. Ablation is a reasonable treatment option, but its outcomes are optimized in patients with small tumors[16]. Therefore, surgical resection remains an important primary treatment option for HCC which, in appropriately selected patients and when performed by experienced surgical teams, is associated with excellent results. Unfortunately, a minority of patients are surgical candidates due to either advanced disease or inadequate liver function to safely undergo hepatectomy. Furthermore, recurrence rates among those patients who are able to undergo surgical resection is relatively common[17].

The last few decades have led to significant advances in both the treatment of viral hepatitis as well as systemic and locoregional treatment options for HCC. Whether

these strategies can be used prior to or following surgical resection in order to increase the number of patients who are surgical candidates or to reduce the risk of tumor recurrence following resection remains poorly understood. Indeed, relatively little research has been conducted on the optimal multimodality therapy for patients with surgically resected HCC. In this review paper, we sought to evaluate the available literature on neoadjuvant and adjuvant treatment strategies for patients with resectable HCC.

NEOADJUVANT STRATEGIES FOR HCC

While neoadjuvant therapies are commonly used for patients with other solid-organ malignancies in order to downstage advanced disease, ensure appropriate patient selection, and assess tumor response to treatment prior to resection, the role of neoadjuvant therapies in the management of HCC is less well defined. Indeed, relatively little research exists to support the concept of neoadjuvant therapy, and current guidelines do not recommend this strategy for patients with otherwise potentially resectable cancers. On the other hand, the unique characteristics of HCC, including its relatively aggressive biology, frequent diagnosis at late stages, and the need to preserve normal liver function at the time of surgery given underlying CLD, suggest a neoadjuvant approach may be appropriate.

Transarterial chemoembolization

Transarterial chemoembolization (TACE) combines transarterial embolization (TAE) with chemotherapy infusion. Unlike normal liver tissue, which derives most of its blood supply from the portal venous system, HCCs derive most of their blood supply from the hepatic artery system. As such, embolization of the arterial system results in ischemia and tissue necrosis[18] while allowing for the concentrated delivery of chemotherapy agents. Embolization also prevents the chemotherapeutic agent from being washed out, allowing for a longer duration of action.

TACE was originally developed for management of advanced unresectable disease, but its role in the neoadjuvant treatment of potentially resectable disease has also been explored. One of the earliest experiences with neoadjuvant TACE was reported by Monden *et al*[19]. The investigators compared 71 patients treated preoperatively with TACE to 21 patients resected without TACE. Although they did not find any differences in survival, histopathologic review demonstrated that tumors from most of the patients who underwent TACE procedure were necrotized. In 2000, Zhang *et al*[20] conducted a retrospective review of 1457 patients who underwent hepatic resection for HCC at their hospital, including 120 patients treated preoperatively with TACE. Compared to those resected without TACE, patients who underwent preoperative TACE had significantly improved 5year diseasefree survival (DFS). In addition, patients who had more than two preoperative TACE treatments had longer recurrence-free survival (RFS) compared to patients who only had one session. However, a different institutional study from China comparing 183 neoadjuvant TACE to 405 resection-only cases found no difference in 1-, 3-, and 5-year overall survival (OS). Instead, repeated TACE use was associated with significantly higher hospital cost[21]. However, results from a meta-analysis by Qi *et al*[22] provided some insight into the discordant results. In their analysis of 32 randomized and non-randomized studies evaluating preoperative TACE to resection-only, they found that preoperative TACE did not improve DFS or OS. However, a subgroup analysis of the results suggested that the outcomes of neoadjuvant TACE followed by resection were influenced by the response to TACE. When patients had complete tumor necrosis following TACE, preoperative TACE had significantly better DFS and OS compared to resection alone. However, when patients had incomplete or no tumor necrosis, the OS did not differ between the two groups.

In addition to its prognostic impact, investigators have shown interest in the ability to downstage previously unresectable patients with neoadjuvant TACE[23-25]. Zhang *et al*[26] reviewed the results from 831 patients over 10 years treated with TACE. Of these, 82 patients were successfully downstaged, and 43 underwent salvage surgery. Compared to those who refused a salvage resection, those who underwent resection had a longer median OS (49 mo *vs* 31 mo, $P = 0.027$). However, there was no difference in survival based on the receipt of surgery among patients who experienced a complete response (50 mo *vs* 54 mo, $P = 0.699$) compared to patients with only a partial response (49 mo *vs* 24 mo, $P < 0.001$). These findings suggest a critical role for resection following downstaging with TACE in patients with a partial response.

Preoperative TACE has also been investigated in the management of recurrent but

resectable disease. Tao *et al*[27] showed that for patients with recurrent but resectable disease, preoperative TACE did not improve survival. On the other hand, it was associated with increased preoperative time and increased blood loss. For patients undergoing extended resections who require preoperative portal vein embolization (PVE) to stimulate compensatory hypertrophy of the future liver remnant[28], preoperative TACE has been investigated as a means of controlling tumor growth. Some speculate that, in the absence of TACE, PVE can result in increased ipsilateral hepatic artery flow, and as such, increased tumor growth. Indeed, some studies have demonstrated improved RFS and OS among patients undergoing TACE+PVE compared to PVE alone[29,30].

In conclusion, the role of TACE in neoadjuvant therapy continues to evolve. While some studies suggest an opportunity to downstage some patients to resection as well as improved long-term outcomes among patients who develop a radiographic response, these therapies currently apply to a minority of patients with HCC, and there is insufficient evidence to predict which patients will respond. Therefore, while TACE is commonly used as a bridging therapy prior to LT[31], its role in the neoadjuvant setting prior to resection remains unclear and is not routinely recommended.

Transarterial radioembolization

Transarterial radioembolization (TARE) is increasingly being performed as an alternative to TACE for patients with HCC. TARE uses ^{90}Yttrium (Y-90) loaded microspheres and delivers these radioactive microspheres via arterial cannulation of the feeding vessel[32]. While there is no overwhelming evidence to suggest superiority over TACE, TARE offers several advantages, including a lower side effect profile (*i.e.*, less post-embolization syndrome)[33]. In addition, for potentially resectable patients, TARE leads to hypertrophy of the contralateral future liver remnant (FLR) in addition to its cytotoxic effects on the tumor[34-36]. This characteristic of TARE has given rise to the concept of radiation lobectomy (RL), a technique which induces hypertrophy to equal or higher levels than PVE[34]. In 2013, Vouche *et al*[35] reported on 67 patients with HCC subjected to Y-90 radioembolization. 37% of the patients had a greater than 35% increase in the FLR, of whom 3 patients went on to have a successful right hepatectomy, and 6 were transplanted. In 2016, they reported on another group of 10 patients with HCC and insufficient or borderline FLR who underwent Y-90 RL prior to resection. Following RL, the median FLR increased from about 33% (pre-RL) to about 43% (post-RL). Additionally, they reported > 50% necrosis in greater than 92% of the resected tumors[37]. TARE has also been combined with PVE to successfully downstage patients for resection when additional FLR hypertrophy is required[38].

Another advantage of TARE is its application in patients with portal vein thrombosis. Patients with malignant lobar portal vein thrombosis are typically not considered candidates for TACE. Therefore, TARE offers an alternate and preferable approach in the neoadjuvant management of such patients. In a previously reported non-randomized trial comparing TARE to TACE, TARE resulted in a better response than TACE (61% *vs* 37% partial response) and resulted in more patients being downstaged from UNOS T3 to T2, which could be critical for patients awaiting transplantation[39]. So, while most guidelines do not recommend one modality over the other for downstaging[40-43], an expert consensus group recommend TARE over TACE as a bridging/downstaging therapy for patients with portal venous thrombosis[44]. Therefore, while further research is needed, including prospective clinical trials, neoadjuvant TARE with Y-90 may be appropriate for patients with advanced HCC who require downstaging for resection.

Systemic therapy

Until recently, there have been few effective systemic therapy options for patients with HCC. In 2007, the tyrosine kinase inhibitor (TKI) Sorafenib was approved for use in patients with Childs A cirrhosis and unresectable or metastatic HCC[45-47]. Sorafenib has activity against several tyrosine kinases including Raf, as well as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)[48,49]. Despite its poor side effect profile and OS improvement of < 3 mo, it quickly gained favor given the lack of other systemic therapy options available until 2017. While interest in Sorafenib as a bridging therapy to transplant was abundant[50,51], it was not felt to be an effective downstaging agent to facilitate surgical resection given the minimal response rate observed. Nevertheless, interest in the use of Sorafenib as a neoadjuvant chemotherapeutic agent remained[52,53] but its use has largely been limited by toxicity[54-57].

Over the past several years, there has been an explosion of newer agents approved for use or currently in clinical trials for advanced or metastatic HCC. For example, other TKIs and VEGF inhibitors including Lenvatinib[58], cabozantinib[59],

regorafenib[60], and ramucirumab[61] have all demonstrated efficacy against HCC. However, none have been investigated in the neoadjuvant setting. Some of the most exciting progress has been made in immunotherapy. Nivolumab[62,63], pembrolizumab[64], tremelimumab[65], atezolizumab[66] and chimeric antigen receptor (CAR) T cells[67] have all been investigated or are under investigation for management of advanced HCC. Investigations of these immunotherapeutic agents in the neoadjuvant setting are ongoing at this time[68-70].

Anti-viral therapy

Among patients with HBV or HCV related HCC, a primary contributor to late recurrence is the *de novo* formation of new tumors related to underlying chronic viral hepatitis[71,72]. Therefore, antiviral therapy prior to resection of HCC should be considered as part of the multidisciplinary treatment of these patients. Indeed, preoperative antiviral therapy has been associated with lower vascular invasion, decreased recurrence, decreased morbidity and faster recovery of liver function in HBV-related HCC[73,74]. On the other hand, antiviral therapy has been more commonly used in the adjuvant setting, which will be described later in this review.

ADJUVANT STRATEGIES FOR HCC

While neoadjuvant strategies are often employed to facilitate downstaging of unresectable patients to potentially resectable candidates, immediate surgical resection remains the recommended treatment for patients with resectable tumors and appropriate liver function. However, recurrence is relatively common even among patients who undergo surgical resection. The purpose of adjuvant therapy, therefore, is to help decrease the incidence of HCC recurrence among those who undergo surgical resection. In general, recurrences following resection of HCC occur in two patterns: early and late. Early recurrences are typically thought to be related to negative prognostic factors (*e.g.*, margin positivity, vascular invasion, *etc.*) associated with the primary tumor while late recurrences are more likely related to underlying CLD and the development of *de novo* tumors. Adjuvant strategies that address both of these factors may be most effective.

Antiviral therapy

It has been long known that antiviral therapy following resection of HBV or HCV related HCC may improve outcomes[75-77]. In a 2013 matched control study by Hsu *et al*[78], researchers compared patients treated with pegylated interferon (PEG-IFN) plus ribavirin to a matched anti-viral naïve cohort and found significantly lower rates of HCC recurrence at 5 years in patients treated with interferon (52.1% *vs* 63.9%, P = 0.001). Lee *et al*[79], also, reported on a prospective trial of PEG-IFN following surgical resection, which included 93 patients (31 treated and 62 controls). They reported significantly lower recurrence rates at 1 and 2 years treated with interferon (7% *vs* 24% and 14% *vs* 34% respectively, P=0.029). These findings were confirmed in a recent meta-analysis by Wu *et al*[80]. They reviewed 1 RCT and 4 cohort studies, totaling 1356 patients (345 PEG-IFN and 1011 control group) and reported a significant reduction in 3-year and 5-year recurrence rates with PEG-IFN treatment.

The development of direct-acting antiviral drugs (DAA) against HCV has increased the emphasis on adjuvant anti-viral therapy[81]. These interferon-free antivirals directly target the specific nonstructural proteins of the viral replication cycle, limiting replication and infectivity. The current classes include nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5A complex inhibitors, NS5B nucleotide polymerase inhibitors (NPIs), and NS5B non-nucleotide polymerase inhibitors (NNPIs). Combining two or more of these agents has been associated with up to 90% HCV clearance[82]. While adequate surgical resection is necessary for disease control and to improve long-term survival, postoperative control of the chronic viral infection, and maintenance of a sustained virologic response remain critical in preventing recurrence and in ensuring a favorable outcome[83]. While an initial report by Reig *et al*[84] initially suggested an increase in recurrence rates among patients treated with DAA drugs, this findings was refuted by a large multicenter by Singal *et al*[85]. In this large retrospective analysis of 783 patients, 304 (38.3%) of whom received DAA agents, there was no significant difference in overall or early HCC recurrence. Indeed, there might be evidence to the contrary. Using propensity-score matching, Cabibbo *et al*[86] compared 102 patients with BCLC stage O or A HCC treated with DAA agents following curative resection or ablation to 102 matched controls. The researchers reported a significantly higher OS in the DAA group compared to the non-DAA group (HR = 0.39 P = 0.03). In addition, patients in the DAA group who achieved a sustained virologic response had a better OS, lower HCC recurrence rate

and decreased incidence of hepatic decompensation. However, there was no difference in HCC recurrence between the DAA and non-DAA groups. As noted by Nault *et al*[87], despite these encouraging findings, more studies are needed to resolve this controversy.

The use of nucleoside analogs for adjuvant HBV treatment in HBV related HCC has also shown promise (Table 1). Indeed, multiple studies have demonstrated the efficacy of adjuvant antiviral therapy both for decreasing recurrence and for improving outcomes[72,88-91]. Huang *et al*[72] evaluated the role of nucleoside analogs on HCC recurrence in two separate RCTs. In 2015, the investigators randomized 200 patients with chronic HBV and no previous antiviral therapy, who had undergone an R0 resection of HCC to either postoperative antiviral therapy or no treatment. These authors reported a significant improvement in both OS and RFS. However, all patients in the study had high preoperative HBV-DNA levels (> 2000 IU/mL). More recently, they reported on a separate cohort, all with low (< 2000 IU/mL) preoperative viral levels. Following resection, patients were randomized to receive telbivudine daily or no treatment. The patients in the adjuvant antiviral treatment group had a significantly better 5-year OS (64% *vs* 44%) and RFS (52% *vs* 32%). Additionally, the treated patients had lower HBV reactivation rates[92]. Based on these studies, it may be appropriate to treat all patients with chronic HBV or HCV with antiviral therapy following resection, regardless of viral load. Current NCCN guidelines recommend consideration of such an approach[43,94].

Systemic therapy

Although systemic chemotherapy with is commonly used for patients with advanced and metastatic HCC, its use following curative resection is controversial. While early studies suggested that adjuvant systemic chemotherapy might be associated with decreased recurrence and prolonged RFS, other studies have found no benefit[95-97]. In contrast, some studies have shown that adjuvant chemotherapy may be associated with worse outcomes[96,98], which suggest that outcomes may be largely driven by the specific chemotherapeutic regimen and patient population. The STORM trial was a randomized phase 3, double-blind, placebo-controlled trial designed to evaluate the efficacy of sorafenib as adjuvant therapy in patients with resected HCC (although it included some patients with local ablation only). It included about 900 patients (450 in each arm) across 202 sites and in 28 countries who had undergone curative resection with evidence complete disease removal on radiography. After a median duration of about 12.5 months of treatment, there was no difference in RFS between the two groups. Instead, sorafenib treatment was associated with increased adverse effects, including four deaths[99].

The advent of immunotherapy and promising results of immunotherapeutic agents in advanced HCC has renewed interest in adjuvant systemic therapy following resection of HCC. One of the earliest uses of immunotherapy in the adjuvant setting was by Takayama *et al*[100]. From 1992-1995, the researchers randomized 150 patients to either lymphocyte infusions (termed adoptive immunotherapy) or no adjuvant treatment. Patients in the adoptive immunotherapy arm had a 41% decreased risk of recurrence and significantly longer RFS; however, OS was not different. Tumor-directed vaccines also showed moderate success as adjuvant therapy, decreasing tumor recurrence rates and increasing recurrence-free and OS[101,102]. In 2009, Hui *et al*[103] published on the results of adjuvant immunotherapy with cytokine-induced killer cells following HCC resection. While there was no difference in survival, patients in the immunotherapy group experienced a decrease in the rate of metastasis formation. However, in a 2015 study by Lee *et al*[104] using autologous cytokine induce killer T-cells and NK cells, the researchers reported increased RFS and OS in the immunotherapy group compared to no adjuvant therapy, though a minority of patients underwent surgery in the study.

The recent discovery of PD-1 and PD-L1 upregulation in tumor infiltrating lymphocytes in HCC and HCC-associated Kupffer cells[105-107], as well as promising results in patients with advanced HCC, has renewed interest in the use of these checkpoint inhibitors as adjuvant therapy following resection[62,65,108]. Unfortunately, there are no published randomized trials evaluating this approach and most of the current trials are evaluating the outcomes of patients with advanced disease[68-70,109]. However, the CheckMate 9DX is an ongoing trial evaluating the use of adjuvant Nivolumab in patients with HCC who are at high risk of recurrence after curative resection or ablation[110,111]. The findings of this trial are greatly anticipated.

Hepatic artery infusion pump

While hepatic arterial infusion (HAI) therapy is more commonly used in the management of colorectal liver metastases[112], its role in HCC remains limited[113]. Nevertheless, at least one study has evaluated the role of HAI as adjuvant therapy

Table 1 Selected studies on the use of adjuvant antiviral therapy

Ref.	Study type	Arms and Intervention	Number of patients	Main outcomes	Comments
Outcomes of adjuvant interferon-based therapy for HCV-related hepatocellular carcinoma.					
Ikeda *et al* (2000)[167]	RCT	36 mo of Interferon (IFN) with 2-yr follow-up	20 (8 per arm)	IFN treatment decreased tumor recurrence.	Included 4 patients treated with PEI.
Kubo *et al* (2001,[75] 2002,[77] 2005[76])	RCT	88 weeks of IFN versus no therapy. Median follow up of 1087 days.	30 (15 per arm)	IFN decreased the recurrence and survival after resection	All male patients with high viral loads.
Hsu *et al* (2013)[78]	Retrospective Cohort	PEG-IFN + Ribavirin for > 16 weeks versus no therapy.	1065 (213 treatment and 852 controls)	PEG-IFN + Ribavirin associated with decrease 1, 3 and 5yr recurrence rate of HCC and 1, 3 and 5yr mortality.	The NNT for one fewer recurrent HCC at 5 yr = 8. Risk attenuation higher in younger patients.
Lee *et al* (2013)[79]	Prospective Cohort	PEG-IFN for 12 mo versus no therapy. Median follow up of 24 mo.	93 (31 treatment and 62 controls)	PEG-IFN associated with decrease 1and 2 year recurrence and higher 1 and 2year survival.	All patients had MTA1 positive HCC and high viral levels.
Wu *et al* (2018)[80]	Meta-analysis	PEG-IFN versus no therapy	4 cohort studies, 1280 patients. 3 studies had 5-year survival data with 276 PEG-IFN and 911 control total.	PEG-IFN improved the 3- and 5-yr RFS and 5-yr OS.	Included data from Hsu *et al*, and Lee *et al*
Outcomes of nucleoside analog treatment for HBV related HCC					
Wu *et al* (2012)[90]	Retrospective Cohort	Nucleoside analog for at least 90 days *vs* no therapy	4569 (518 treated and 4051 controls)	Nucleoside analog treatment was associated with a lower risk of HCC recurrence.	Nucleoside analogues included lamivudine, entecavir, and telbivudine
Yang *et al* (2012)[91]	Prospective Cohort	Antiviral therapy *vs* no treatment.	330 patients (142 treated *vs* 188 untreated). All high viral loads.	Antiviral therapy was associated with RFS and OS. High associated with poor OS and RFS	High viral load (≥ 10000 copies/mL) and low viral load (< 10000 copies/mL). Antiviral included lamivudine, adefovir dipivoxil, or entecavir.
Yin *et al* (2013)[88]	Two-stage longitudinal clinical study (RCT and non-RCT)	Nucleoside analog (NA) *vs* no therapy.	617 in non-RCT (215 treatment and 402 controls) 163 in RCT (81 treatment and 82 controls)	NA treatment improved postop liver function, decreased HCC recurrence, and improved postoperative survival	Lamivudine, adefovir dipivoxil, or entecavir.
Chong *et al* (2015)[168]	Retrospective cohort	Antiviral therapy *vs* no therapy	404 (254 antiviral and 150 controls)	Antiviral therapy improves longterm survival post hepatectomy. No difference in early or late recurrence.	
Zhang *et al* (2015)[74]	Retrospective cohort	Entecavir antiviral therapy *vs* no therapy	112 (72 antiviral and 40 controls)	Antiviral treatment improves morbidity and improved postoperative liver function.	Patients with preop HBV DNA > 10^4 copies/mL received antiviral therapy as well.
Huang *et al* (2015)[72]	RCT	adefovir antiviral therapy *vs* no therapy	200 (100 antiviral and 100 controls)	adefovir antiviral therapy reduced late HCC recurrence and improved OS	Patients had high preoperative HBV DNA (> 2000 IU/mL)
Huang *et al* (2018)[92]	RCT	Telbivudine antiviral therapy *vs* no therapy	200 (100 antiviral and 100 controls)	Telbivudine HCC resulted in better 5-year OS and RFS, as well as a lower rate of HBV reactivation	Patient with low (< 2000 IU/mL) HBV DNA titer.

HCV: Hepatitis C virus; RCT: Randomized controlled trial; IFN: Interferon; PEI: Percutaneous ethanol injection; PEG-IFN: Pegylated interferon; HCC: Hepatocellular carcinoma; NNT: Number needed to treat; OS: Overall survival; RFS: Recurrence-free survival; NA: Nucleos(t)ide analog; HBV: Hepatitis B virus.

following HCC resection. In this retrospective study (42 patients in each group), the

investigators compared patients who received HAI chemotherapy to those who received no adjuvant treatment following curative resection for HCC and reported decreased intrahepatic recurrence, decreased RFS and OS at 5 years in patients who received HAI pump chemotherapy. The chemotherapeutic regimen: 5-fluorouracil (1000 mg/m^2), oxaliplatin (85 mg/m^2), and mitomycin-C (6 mg/m^2) was used in this trial, and started within 3 wk of surgery[114]. As noted above, this treatment option is rarely used in clinical practice for HCC management.

TACE

While TACE is primarily used in the neoadjuvant setting and for patients with unresectable disease, it has also been evaluated as an adjuvant regimen following resection, though with mixed results. Wang *et al* reported a phase III RCT of 280 high-risk patients with HBV-related HCC who were randomized to TACE or surveillance following curative hepatectomy. Patients in the TACE arm had significantly less recurrence and longer RFS and OS[115]. However, another trial involving low-risk patients was unable to reproduce these findings [116]. Multiple large single-institution studies have also found a benefit for TACE in patients with risk factors for recurrence[117-119]. Additionally, data from various meta-analyses and systematic reviews of the randomized studies in adjuvant TACE treatment suggest that this regimen may be of benefit in high-risk patients (tumor > 5 cm or vascular invasion). However, there does not appear to be any benefit in low-risk patients (see table below)[22,120-123]. While randomized controlled trials are rare, the findings from the current studies suggest adjuvant TACE treatment might be of benefit in resected patients at high risk for recurrence (Table 2).

Radiolabeled lipiodol

Lipiodol, derived from poppy seed, has been used as a radiotracer and contrast dye since the 1920s, including in the imaging of hepatic cancers[124]. In 1979, Nakakuma *et al*[125] reported on the ability of lipiodol to accumulate in HCC relative to normal liver. Injection of the molecule into the hepatic artery resulted in tumor necrosis, and therefore it was investigated as a treatment for HCC with promising results[126,127]. Further use of radiolabeled lipiodol has also been investigated in the adjuvant setting. In 2000, Partensky *et al*[128] conducted a phase 2 study evaluating the role of lipiodol in the adjuvant setting, confirming its safety and potential benefits. A prospective randomized trial by Lau *et al*[129,130] found that adjuvant radiolabeled lipiodol (^{131}I-Lipiodol) following resection of HCC was associated with improved DFS and OS. These findings have been replicated in other retrospective studies and meta-analyses[131-133]. Overall, the current data strongly favor the use of intra-arterial radiolabeled lipiodol as adjuvant therapy for HCC. However, this approach is not routinely used in clinical practice and requires further validation from large RCTs in order to be incorporated into practice.

Ablation

Tumor ablation is a form of local-regional directed therapy in patients with non-metastatic disease. Local ablation can include radiofrequency ablation (RFA)[134,135], percutaneous ethanol injection (PEI)[136-139], microwave ablation[140-142] or irreversible electroporation[143-145]. There is insufficient evidence supporting the use of one approach over the other[140,146], and as such the choice of local ablation therapy is primarily driven by institutional expertise. Ablation is typically used as either definitive therapy or as a bridging therapy to LT, enabling patients to either remain within the Milan criteria[16,147-149] or be downstaged to meet criteria[150,151]. As an adjuvant regimen, it can allow for the extension of the resection margin following tumor resection or debulking[152-155]. In some cases, it can be combined with resection, where the majority of the tumor is resected, and satellite nodules are ablated[156,157]. This combination has been associated with decreased recurrence and improved long-term survival.

Radiation therapy

While radiation therapy (RT) had traditionally been avoided in the liver due to the risk of radiation-induced liver disease and limited response, advances in technology and understanding of dose-volume effects has allowed for the use stereotactic body radiation (SBRT) in the management of HCC, primarily in patients with no other standard options but also as an adjunct to other therapeutic therapies[158-160]. While there is limited data on its use as a neoadjuvant or adjuvant therapy to surgical resection, it might be of benefit in patients where adequate margins are not attainable[161]. Some studies have suggested that adjuvant RT might be better than TACE with respect to RFS and OS[162]. However, a recent retrospective analysis of the SEER database showed preoperative radiation therapy had better outcomes (OS)

Table 2 Selected studies on the use of adjuvant transarterial chemotherapy

Ref.	Study type	Arms and intervention	Number of patients	Main outcomes	Comments
Peng *et al* (2009)[169]	Retrospective cohort	LR *vs* LR+TACE	53 control *vs* 51 treatment (TACE)	Improved 1-, 3- and 5-yr survival with TACE	HCC< 3 cm + portal vein thrombosis
Liu *et al* (2016)[118]	Retrospective cohort	LR *vs* LR+TACE	55 Control *vs* 62 Treatment	Overall: Improved 1-year OS with TACE, but no difference in 2- and 3-yr DFS rates.	For tumor size > 5 cm: improve 1-, 2- and 3-yr DFS. For tumor size ≤ 5 cm: no difference in 1-, 2- and 3-yr DFS
Li *et al* (2017)[117]	Retrospective cohort	LR *vs* LR+TACE	459 control *vs* 295 treatment	LR + TACE improved postoperative recurrence and long-term survival.	Patients with HCC beyond Milan Criteria.
Ye *et al* (2017)[170]	Retrospective cohort	LR *vs* LR+TACE	260 microvascular invasion (86 in LR +TACE) resection; 259 w/o microvascular invasion (72 in LR+TACE) arm	LR + TACE improved OS and DFS in patients with microvascular invasion but not in patients without microvascular invasion.	All patients had BCLC Stage A or B
Qi *et al* (2018)[171]	Retrospective cohort	LR *vs* LR+TACE	200 patients with microvascular invasion (91 LR +TACE *vs* 109 LR only)	Similar 1-, 2- and 3-yr DFS between groups. Subgroup with tumor size > 5 cm had better DFS and OS with LR+TACE.	All patients had microvascular invasion and were BCLC A or B stage.
Liao *et al* (2017)[123]	Meta-analysis	LR *vs* LR+TACE	8 RCTs and 12 retrospective studies, totaling 3191 patients (1193 treatment *vs* 1952 control).	Significantly higher RFS and OS benefit with postoperative adjuvant TACE compared to surgery alone	Good consistency in findings between RCTs and non-RCTs, however, chemotherapy regimens differed between centers/trials.

LR: Liver resection; LR+TACE: Liver resection plus adjuvant transarterial chemoembolization; HCC: Hepatocellular carcinoma; DFS: Disease-free survival; OS: Overall survival; BCLC: Barcelona Clinic Liver Cancer; RCT: Randomized controlled trial; RFS: Recurrence-free survival.

compared to adjuvant RT[163]. Overall, while there is great interest in the use of SBRT as a bridge to transplantation[164-166], its use as an adjunct to surgical resection remains underexplored.

CONCLUSION

HCC remains a challenging disease, with an increasing global incidence and high associated mortality. Resection remains an important curative-intent treatment that should be pursued for patients with resectable disease and appropriate liver function. Multimodality therapy is increasingly being explored in order to increase the number of patients who are surgical candidates as well as decrease the incidence of disease recurrence. Unfortunately, due to the paucity of conclusive literature on the subject, current NCCN guidelines do not recommend for or against the routine use of (neo)adjuvant strategies in HCC resection.

While more commonly used as a bridging therapy prior to LT[94], neoadjuvant transarterial therapies can successfully downstage some patients with advanced tumors to resection. There is insufficient evidence to directly compare preoperative TACE versus TARE though radioembolization with Y-90 has the advantage of stimulating contralateral hypertrophy of the FLR without the need for PVE. Long-term outcomes are improved among those patients who experience a response to neoadjuvant therapy. A major challenge in performing research on neoadjuvant treatments is defining the intent of therapy (*e.g.*, definitive, downstaging, or bridge to transplantation) *a priori*. Future research would benefit from well-designed prospective studies that clearly define goals of treatment and carefully measure short- and long-term outcomes. Following resection, based on a large phase III RCT, adjuvant Sorafenib is not recommended, but there is insufficient evidence to support the use of other adjuvant therapies. For those patients with HCC in the setting of viral hepatitis, aggressive treatment with antivirals, before or after resection, improves outcomes and should be pursued. The outcomes of these therapies reflect the different mechanisms of HCC recurrence following surgical resection: multicentric car-

cinogenesis *vs* intrahepatic metastasis. While antiviral therapies are effective in decreasing neocarcinogenesis, they have less impact on intrahepatic metastases. Cytotoxic therapies aim to decrease recurrence from intrahepatic metastases, but to date have demonstrated limited effectiveness.. The development of more effective targeted and immune-based therapies will hopefully lead to significant advances in recurrence rates.

In conclusion, the optimal multidisciplinary management of HCC continues to rapidly evolve. While surgical resection remains an important treatment option for patients with HCC, the addition of neoadjuvant and/or adjuvant treatment strategies may increase the proportion of patients who are surgical candidates and improve the long-term outcomes of those who undergo surgery. With exciting advances in locoregional and systemic therapies, including developments in immunotherapy, future research will be needed to identify the optimal components of multimodality therapy.

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REVIEW

Surgical techniques and postoperative management to prevent postoperative pancreatic fistula after pancreatic surgery

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Abstract

Postoperative pancreatic fistula (POPF) is one of the most severe complications after pancreatic surgeries. POPF develops as a consequence of pancreatic juice leakage from a surgically exfoliated surface and/or anastomotic stump, which sometimes cause intraperitoneal abscesses and subsequent lethal hemorrhage. In recent years, various surgical and perioperative attempts have been examined to reduce the incidence of POPF. We reviewed several well-designed studies addressing POPF-related factors, such as reconstruction methods, anastomotic techniques, stent usage, prophylactic intra-abdominal drainage, and somatostatin analogs, after pancreaticoduodenectomy and distal pancreatectomy, and we assessed the current status of POPF. In addition, we also discussed the current status of POPF in minimally invasive surgeries, laparoscopic surgeries, and robotic surgeries.

Key words: Postoperative pancreatic fistula; Pancreaticoduodenectomy; Pancreatojejunostomy; Pancreatogastrostomy; Distal pancreatectomy; Prophylactic drainage; Somatostatin analogs

Core tip: We reviewed recent reports concerning postoperative pancreatic fistula (POPF)-related factors, such as reconstruction methods, anastomotic techniques, stent usage, prophylactic intra-abdominal drainage, and somatostatin analogs, after pancreaticoduodenectomy and distal pancreatectomy, and we assessed the current status of POPF.

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INTRODUCTION

The incidence of pancreatic cancer has increased in both Asian and Western countries. Surgical resection is the cornerstone of treatment for this aggressive disease. With advances in surgical techniques and perioperative management, the operative mortality of pancreaticoduodenectomy (PD) in high-volume centers has decreased to less than 3%[1-3]. Postoperative pancreatic fistula (POPF), however, develops frequently, and previous prospective studies have reported an incidence of more than 10%[4-7]; therefore, POPF is the most frequent lethal complication after pancreatectomy, regardless of the type of procedure.

POPF is believed to be primarily caused by the leakage of pancreatic juice into the abdomen; it can lead to intraperitoneal abscesses and also occasional hemorrhage, which cause life-threatening conditions with mortality rates of up to 40%[4,6,7-11]. In clinical practice, various ingenuities have been attempted to prevent the development of POPF, and some randomized controlled trials (RCTs) have been conducted to compare different optional procedures.

In this review, we aimed to summarize the current status of POPF in pancreatic surgery and to present the recent findings of the reconstruction methods of PD, stump closure methods of distal pancreatectomy (DP) and evidence for the risk factors and preventive treatment for the development of POPF.

DEFINITION AND INCIDENCE

Pancreatic fistula was defined by the International Study Group on Pancreatic Fistula (ISGPF) in 2005[12] and was revised in 2016[4]. The ISGPF's definition divides pancreatic fistula into biochemical fistula and clinically significant POPF.

A grade A POPF is called a biochemical fistula and is defined as measurable fluid output on or after postoperative day 3, with an amylase content higher than three times the upper normal serum level; a grade A POPF has no clinical impact on the normal postoperative pathway. Clinically significant POPFs are classified as grades B and C. A grade B POPF requires one of the following conditions: an endoscopic or radiological intervention, a drain in situ for > 3 wk, clinical symptoms without organ failure, or clinically relevant change in POPF management. Whenever a major change in clinical management or deviation from the normal clinical pathway is required or organ failure occurs, the fistula shifts to a grade C POPF[4,6].

Following this definition, the incidence of clinically significant POPF has been reported to vary from approximately 1% to 36%[4,6,7,12-17]. There are different causes related to the development of POPF in the PD and distal pancreatectomy (DP)[18] procedures, and the incidence is generally recognized to be relatively higher in DP than in PD. Therefore, we discuss recent findings and evidence of POPF in PD and DP separately as described later in this review.

PANCREATICODUODENECTOMY

PD remains the only curative treatment option for malignant and some borderline/benign tumors of the pancreatic head and periampullary region even though the excessive invasive procedure is associated with high morbidity and mortality rates. One of the most important factors of morbidity and mortality following PD is the incidence of POPF. Many previous studies have reported several risk factors in PD, such as gender (male)[19], BMI > 25 kg/m^2[20], anastomotic method[6,21], external stent[22], fasting blood glucose level < 108.0 mg/dL[23], *etc*. However, the most reliable consensus risk factors for POPF after PD are small pancreatic duct (≤ 3 mm) and soft pancreas[6,21,23-28], which reflect the possibility that adequate anastomosis of the pancreatic duct and active exocrine function are deeply involved in the development of POPF. Therefore, various surgical techniques have been attempted to prevent

POPF.

Reconstruction methods

Identifying the best anastomosis technique for pancreatic surgery has remained controversial thus far. Of the several available techniques, pancreaticogastrostomy (PG) and pancreatojejunostomy (PJ) are the most commonly performed. Some RCTs[28-35] and meta-analyses[36-44] have compared PG and PJ. Topal *et al*[32] reported comparative results of the occurrences of POPFs (grade B or C) in an RCT with 329 patients. They stratified the randomization according to the pancreatic duct diameter, and the results clearly demonstrated that the occurrence of POPF was significantly lower after PG than after PJ (OR = 2.86; 95%CI: 1.38-6.17; P = 0.02). Conversely, a recent German multicenter RCT[35] demonstrated that there was no significant difference in the rate of grade B/C fistulas after PG *vs* PJ (20% *vs* 22%, respectively, P = 0.617). Each RCT has variable eligibility criteria for patients with diseases and suture methods for reconstruction; therefore, their conclusions should be interpreted with caution.

Several meta-analysis results on this issue have been reported and demonstrated the apparent superiority of PG in the risk for POPF despite the slight difference in the included studies[36-44]. However, PJ was found to have physiological advantages compared to PG although the follow-up periods were relatively short[34,45-48].

In recent retrospective studies, a significantly higher postoperative atrophic change of the pancreatic parenchyma and frequent severe steatorrhea were reported in the PG group during long-term follow-up periods[45-48]. Additionally, a higher frequency of impaired glucose tolerance after PG has been reported compared to PJ during the follow-up period. Considering the function of the remnant pancreas, the use of only short-term results is not sufficient for comparison[34,49].

Reconstruction after pancreatic surgery remains under debate, and it is impossible to confidently conclude which method is better after PD. Therefore, the reconstruction method should be determined based on the patient and tumor characteristics, such as pancreatic duct diameter, consistency of pancreas, and oncological prognosis (Table 1).

Anastomotic techniques

In recent years, several simple and facilitating surgical anastomotic techniques have been reported.

A transpancreatic U-suture technique was devised by Blumgart *et al*[50], and the ratio of clinically relevant PFs was reported to be only 6.9% in the original report. Other researchers have conducted confirmatory studies and reported that the occurrence rates of POPFs were less than 5%[51,52]. Furthermore, favorable short-term outcomes have been achieved by some modifications of the novel technique. Fujii *et al*[53] reported on the modified Blumgart's method. The differences between the original and modified method are described below. The original Blumgart's method used four to six transpancreatic jejunal seromuscular U-shaped sutures to approximate the pancreas and the jejunum[50], whereas the modified Blumgart's method used only one to three sutures. In the original method, the sutures were tied at the pancreatic wall, whereas the sutures were tied at the ventral wall of the jejunum in the modified method. The results showed that the ratio of clinically relevant POPFs was significantly lower after the modified Blumgart's method than after Kakita's method (2.5% *vs* 36%, respectively)[53]. However, other studies did not confirm the superiority of the Blumgart or modified Blumgart's methods in preventing POPFs compared to Kakita's method or conventional interrupted sutures[54,55].

The most beneficial feature of duct-to-mucosa PJ is the secure drainage of pancreatic juice into the intestinal lumen. The anastomotic procedure, however, is not always easy, particularly with narrow pancreatic ducts. An invagination method in which the cross-sectional surface was inserted into the intestinal lumen might be a substitutive option of duct-to-mucosa PJ as an easier reconstruction method.

Nearly a decade ago, two types of invagination methods were examined to reduce POPF after PD in large-scale RCTs[56-62] (Table 2). Peng *et al*[56] performed binding PJ, in which the stump of the jejunum was everted and the remnant of the pancreas and the everted jejunum were anastomosed in a circular fashion; finally, the everted jejunum was restored to wrap over the pancreatic stump. Conversely, Berger *et al*[57] performed invagination PJ in endo-to-side anastomosis. Both RCTs clearly revealed significantly decreases in POPF rates in invagination PJ compared to conventional duct-to-mucosa PJ; likewise, the tendency was more remarkable in soft pancreases compared to hard pancreases. Recently, however, several RCTs were unable to confirm the superiority in POPF rates with invagination PJ. Although RCTs are recognized to provide the most reliable results suggesting future evidence-based medicine, the results could be affected by many factors, including patient-related, tumor-related, and surgeon-

Table 1 Characteristics and intraoperative data of 7 randomized controlled trials included studies comparing pancreatogastrostomy *vs* pancreatojejunostomy

				Sample	Pancreatic parenchyma (soft/hard)		Technique	
First author	Country	Pubrication year	Setting	*n* (PG/PJ)	PG group	PJ group	PG group	PJ group
Fernandez-Cruz *et al*[30]	Spain	2008	Single center	108 (53/55)	24/29	25/30	Double layer with stent	Double layer with stent
Wellner *et al*[31]	Germany	2012	Single center	116 (59/57)	36/23	29/28	Invagination	Double layer with stent
Topal *et al*[32]	Belgium	2013	Multiple canters	329 (162/167)	N/A	N/A	Double or single layer	Double or single layer
Figueras *et al*[33]	Spain	2013	Multiple canters	123 (65/58)	34/31	33/58	Double or single layer	Double layer with stent
El Nakeeb *et al*[34]	Egypt	2014	Single center	90 (45/45)	26/19	22/23	Double layer	Double layer without stent
Grendar *et al*[35]	Canada	2015	Single center	98 (48/50)	25/23	18/32	Double layer	Double layer with or without stent
Keck *et al*[5]	Germany	2016	Multiple canters	320 (171/149)	95/66	83/62	Invagination	Duct-to-mucosa

PG: Pancreatogastrostomy; PJ: Pancreatojejunostomy; N/A: Not applicable.

related factors. In fact, for patient-related factors, Senda *et al*[57] indicated the possibility of reducing POPFs in invagination PJ for high risk patients with a soft pancreas although they revealed the non-superiority of invagination over duct-to-mucosa PJ with the risk of POPF as their primary endpoint. To overcome surgeon-related factors, Bai *et al*[59] conducted a similar RCT in which all procedures were performed by the same surgeon. They demonstrated that the overall POPF and morbidity rates were similar between invagination and duct-to-mucosa PJ; however, clinically relevant POPFs and severe complications were more frequent in the invagination PJ group.

Some meta-analyses were conducted concerning the superiority of invagination PJ on the rate of POPFs and demonstrated that invagination PJ did not reduce POPF rates and other adverse events compared to duct-to-mucosa PJ[63,64]; however, many of the analyzed studies were heterogeneous in several respects. The duct-to-mucosa PJ was performed by the conventional anastomotic technique, and therefore, invagination PJ does not appear significantly better than the current duct-to-mucosa PJ with respect to the incidence of POPF for low risk patients at least.

Stent or no-stent

Another concern is the necessity of stent placement for PJ anastomosis, whether a stent should be used, and whether the stent should be external or internal stent. Non-stent PJ anastomosis is the ideal and physiologically favorable procedure because stenting is sometimes associated with tube-related complications, digestive fluid loss, and subsequently impaired digestive and absorptive functions with external stents. Several previous studies, however, have reported that draining the pancreatic juice from the pancreaticojejunal anastomosis with a stent placed in the main pancreatic duct is an effective method to promote the healing of the anastomotic site by preventing pancreatic trypsin from corroding the anastomotic site during the early period after surgery, thereby reducing the rate of POPFs after PD[65,66].

Several RCTs have been conducted to examine the short-term outcomes of patients with external or internal stents compared to those without stents after PJ[65-69]. However, there were no differences in the incidence of POPFs or other morbidities between the stent (external or internal) and the no-stent groups. One meta-analysis reported that an external stent for PJ decreased the rates of POPFs[70]; however, another recent comprehensive systematic review with a meta-analysis reported that there was no significant difference in the rates of POPFs, in-hospital mortality, re-operation, delayed gastric emptying, wound infection, and intra-abdominal abscesses between the stent and no-stent groups. They only found that the postoperative overall morbidity was lower and the total hospital stay was shorter in the external stent group compared to the no-stent group[71].

Table 2 Characteristics and intraoperative data of 7 randomized controlled trials included studies comparing invagination *vs* duct-to-mucosa

		Pubricat-ion	Sample		Pancreatic parenchyma (soft/hard)		stents		Use of smatostatin analogs		
First author	Country	year	D to M	Inv	D to M	Inv	D to M	Inv	D to M	Inv	Result
Peng *et al*[56]	China	2007	111	106	39/72	37/69	NA	No	No	No	Invagination significantly reduced POPF
Berger *et al*[57]	United States	2008	97	100	50/47	51/49	Intraoperative temporary	No	No	No	Invagination significantly reduced POPF
Senda *et al*[58]	Japan	2018	61	59	31/30	30/29	Yes	Yes	NA	NA	NS
Bai *et al*[59]	China	2016	64	68	36/28	44/24	47 used	52 used	2 used	12 used	D to M significantly reduced POPF
El Nakeeb *et al*[60]	Egypt	2018	53	54	25/28	27/27	Intraoperative temporary	Intraoperative temporary	NA	NA	NS
Singh *et al*[61]	India	2017	97	96	42/55	48/48	15 used	26 used	38 used	31 used	NS
Maggiori *et al*[62]	France	2010	25	22	11/14	10/12	NA	NA	11 used	10 used	NS

D to M: Duct to mucosa; Inv: Invagination; NA: Not available; NS: Not significant.

Other studies have reported comparable results in POPFs between external and internal stents for PJ anastomosis. Compared to an internal stent, an external stent has the advantage of more complete diversion of pancreatic juice from the PJ anastomosis and the prevention of activation of pancreatic enzymes by bile juice[66]. However, there are shortcomings of more surgical procedures, liquid loss, and the risk of local peritonitis after removal of the stent tube[72]. Moreover, an external stent may develop tube-related complications, kinks, and obstructions[73]. Wang *et al*[74] reported that the length of pancreas juice in the stent tube was the predicting factor for clinical POPF. Internal drainage with a stent is considered one of the optimal methods to avoid exposing pancreatic juice to the PJ anastomosis without digestive fluid loss and impaired digestive and absorptive function[72,73,75]. However, the real-time drainage status of pancreatic juice cannot be monitored, and the stent rarely migrates into the bile duct with internal stents. Several RCTs have reported that internal stents tend to reduce the POPF ratio compared to external stents; however, no difference was observed in the incidence of POPF between the two stent methods[76-78]. This is also reported in past RCTs that internal stents did not reduce the POPF ratio compared to non-stents[79,80].

Almost all of the previous studies were conducted in single centers. Therefore, additional multicenter RCTs comparing the efficacy of external pancreatic duct stenting versus internal pancreatic duct stenting versus non-stenting must be performed, particularly for cases with a soft pancreas.

The use of surgical tissue adhesives

Several studies evaluated the effect of topical application of fibrin glue applied to the pancreatic anastomosis[81-85]. When a pancreatic tissue tearing occurred, it was expected to be covered by the fibrin sealant. Although there was also a report that evaluated the effect[81], most reports concluded that fibrin sealants might have no effect on POPF in patients undergoing pancreaticoduodenectomy[82-85].

Also, omental wrapping was expected to reduce the incidence of the POPF and intra-abdominal hemorrhage[86,87]. Although there have been reports of reduced intra-abdominal complications, this method did not significantly reduce POPF[86-89].

DISTAL PANCREATECTOMY

The primary indications for DP include both benign and malignant tumors of the pancreatic body and tail. Although the mortality associated with DP has decreased in recent decades because of improvements in operative techniques and perioperative managements, morbidity remains high. The most ominous complication is POPF, which may cause life-threatening conditions. The incidence of clinical POPF (Grade B or C) after DP ranged from 5% to 40%[20,21,90-96]; this rate is higher than that after PD. However, POPFs that occur after DP are usually clinically less severe compared to those that occur after PD[97,98]. Various surgical techniques that involve transecting the pancreatic parenchyma have been attempted to reduce the incidence of POPF after DP. In recent years, these techniques include hand-sewn closure and stapler closure.

Numerous risk factors for POPF after DP have been previously reported, particularly pancreatic thickness[21,91-93,98], age[90,93], and BMI[90,94,96,99]. In patients with a thick pancreas, the stapler method may crush the pancreas parenchyma, which leads to the breakage of small pancreatic ducts and causes the development of POPF[99]. BMI may influence the physiological condition of the pancreas because fibrosis or fatty changes may occur [92]. In any case, the most important factor to reduce the incidence of POPF is to close the stump of the remnant pancreas completely at the time of surgery.

Stump closure methods

Recently, the most commonly used techniques for stump closure are hand-sewn closure or stapler closure. Hand-sewn closure is a common technique that involves suturing the pancreatic stump in a fish-mouth fashion after ligating the main pancreatic duct. Conversely, the stapler method has become a widely used technique for pancreatic stump closure in recent years because of its convenience. Zhou *et al*[100] performed a meta-analysis comparing stapler versus hand-sewn closure of the pancreatic stump; they described that indicate the superiority of the stapler method (22.1% *vs* 31.2%) although it did not reach statistical significance. However, in a multicenter randomized DISPACT trial that was conducted among 21 centers in Europe in 450 randomized patients (of whom 296 were analyzed), the stapler closure method did not reduce the incidence of POPF compared to hand-sewn closure for DP (stapler closure, 32% *vs* hand-sewn closure, 28%)[101]. Although the occluded areas of the stapler develop local necrotizing pancreatitis and may cause POPF[99], the stapler method is used as the standard technique. However, this technique experiences difficulties when the cutting line of the pancreas is on the right side of the portal vein.

To reinforce the staple line, RCTs assessing the use of several different materials have been reported. Three RCTs and one meta-analysis attempted to demonstrate the effect of reinforcement with an absorbable fibrin sealant patch (TachoSil®) over the pancreatic stump[102-106]. This technique was unable to reduce POPFs compared to conventional methods of the stapler only. However, Montorsi *et al*. reported that the amylase level of the drainage fluid was significantly lower in the TachoSil® group on day 1[104]. This result suggests that TachoSil® may be useful in sealing the cutting line of the pancreas. However, many reports described that fibrin sealants might lead no difference in POPF[82].

The DISCOVER trial was conducted to investigate the technique of remnant pancreatic reinforcement by use of a teres ligament patch to prevent POPF. Although this clinical trial was unable to significantly reduce the rate of POPFs (P = 0.1468), the rates of clinically relevant POPFs with coverage and without coverage were 22.4% and 32.9%, respectively, resulting in a 10% reduction in clinical POPF[106].

A reinforced stapler (REINF) with bioabsorbable materials is used with the expectation of further effects. Kawai *et al*[107] clarified the safety of the REINF for pancreatic stump closure during DP. A 2013 meta-analysis including five retrospective and five prospective studies compared staplers without reinforcement (STPL) *vs* REINF. Although the incidence of POPF was 24% and 17%, respectively, and tended to be lower in REINF, the superiority of reinforcement was not proven[108]. Additionally, a recent RCT reported that REINF significantly reduced POPF to a clinically relevant degree compared to STPL (11.4%, and 28.3%, respectively)[109]. Conversely, Kondo *et al*. reported that REINF for pancreatic stump closure during DP does not reduce the incidence of clinically relevant PF compared to STPL. However, in patients with a pancreatic transection line thickness of less than 14 mm, a significant difference was shown in the incidence of clinically POPF (4.5% *vs* 21.0% in the reinforced stapler vs. bare stapler groups, respectively, P =0.01)[110]. Jensen *et al*[108] reported that polyglycolic acid mesh induces an inflammatory reaction immediately after insertion, and this may promote adhesion and prevent leakage of pancreatic juice from the cutting line of the remnant pancreas. As described above, although the efficacy of REINF has not been sufficiently proven, the incidence of POPF tends to

decrease compared to previous techniques.

Pancreatoenteral anastomosis

Three retrospective studies have demonstrated that pancreatoenteral anastomosis (PE) of the pancreatic stump significantly reduced POPFs compared to stump closure only[111-113]. In these reports, the main pancreatic duct was ligated in both groups, and the anastomosis of the PE was performed by the invagination method. Octreotide was administered in two of these studies[107,109], and in the other study, PJ and PG were both performed in the PE group and hand-sewn closure and stapler closure were both performed in the stump closure group[112]. Additionally, the rate of postoperative hemorrhage was high in all reports. However, the statistical power of these studies was limited because of the small sample size of patients.

Two recent RCTs have been reported. Kawai *et al*[114] compared PJ of the pancreatic stump with the stapler without reinforcement method. In this study, anastomosis was performed in a non-stented duct-to-mucosa fashion using a single layer of interrupted absorbable suture and the addition of a seromuscular-parenchymal anastomosis. However, the ratio of POPFs in PJ tends to be lower than that in stapler closure, but the difference is not significant. Furthermore, Uemura *et al*. investigated whether PG of the pancreatic stump reduced clinical POPFs compared to hand-sewn closure[115]. In this RCT, PG was performed as described below. Interrupted 5-0 absorbable monofilament sutures were placed between the gastric mucosa and the main pancreatic duct, and interrupted sutures were placed between the wall of the pancreatic parenchyma and the gastric seromuscular layer. Additionally, an internal stenting tube was inserted for internal drainage of the pancreatic juice into the stomach. Hand-sewn closure was performed so that the main pancreatic duct was ligated and the cutting line of the remnant pancreas was closed using the fish-mouth technique. The incidence of intra-abdominal fluid collection was significantly lower in the PG group than in the hand-sewn group. However, PG did not reduce the incidence of clinical POPF and other complications compared to hand-sewn closure. Thus, the efficacy of PE has not yet been demonstrated.

However, the above two RCTs have a problem: even if the main pancreatic duct is reconstructed, small branches remain always present and may be a source of pancreatic leakage. Additionally, PE may cause the activation of pancreatic enzymes by enterokinase. Furthermore, in recent years, there has been a tendency to perform this operation with a laparoscopic procedure. It seems that adaptation should be carefully selected.

LESS INVASIVE SURGERIES

Less invasive surgeries have recently become more popular worldwide in pancreatic resection. In laparoscopic DP, a linear stapler is commonly used for stump closure of the pancreas. Therefore, the incidence of POPF from the pancreatic stump is thought to be generally similar between laparoscopic and open DP. In fact, some retrospective well-designed studies using a propensity score-matching analysis and systematic review with non-randomized trials have suggested that there was no significant difference in clinically relevant POPF although an RCT has never been conducted to examine this issue[116-120]. More recently, a robotic approach has been attempted for DP and compared with the laparoscopic approach concerning perioperative outcomes. The study demonstrated that there was no significant difference in the rate of the occurrence of POPF although spleen-preserving DP was performed more frequently in the robot-assisted approach[119-121].

Palanivelu *et al*[117] reported the results of an RCT comparing the laparoscopic approach for PD with the open approach. In this study, 64 of 268 patients were randomized to each group and assessed for eligibility. The results suggested that laparoscopic PD offered significant benefits in terms of hospital stay although there was no significant difference in the overall complication rates including POPF. Other systematic reviews and meta-analyses also revealed that the incidence of POPF was not significantly different between minimally invasive PD (laparoscopic and robotic PD) and open PD[122,123].

Another study using multi-institutional data from the American College of Surgeons National Surgical Quality Improvement Program compared pancreas-specific outcomes of minimally invasive PD (MIS-PD), including open assistance and open PD (OPD), with a focus on clinically relevant POPF[124]. In this study, 16% of patients underwent MIS-PD, of whom 15% converted to unplanned conversion. The rates of POPF were slightly greater in MIS-PD compared to OPD (15.3% *vs* 13.0%, respectively, $P = 0.03$); however, MIS-PD was not an independent factor associated

with POPF in the adjusted multivariable analysis. Other studies compared the rates of postoperative 30-d overall complications between laparoscopic PD and robotic PD[125,126]. This type of approach was not correlated with the overall complication rates.

The advantage of MIS-PD over open PD concerning POPF remains unclear. However, MIS-PD has a shorter exposure time in the abdominal cavity, and a smaller surgical wound than open-PD. This may reduce the potential infection during surgery. As a result, there is a possibility of reducing the occurrences of septic POPF because surgery is performed under conditions where infection is less likely to occur. Some surgeons have recently developed more suitable techniques for laparoscopic or robotic PJ[127,128], and additional experiences and the development of new devices may improve perioperative outcomes.

PERIOPERATIVE MANAGEMENT

Intraperitoneal drainage

Drains are frequently placed at the time of pancreatic surgery. However, adaptation and drain insertion and the time of removal have not yet been clarified. Drains allow for the evacuation of blood, pancreatic juice, bile, and lymphatic fluid. However, drains may increase the chances of retrograde infection. Moreover, there is a possibility that the indication may differ depending on whether the operation to be performed is PD or DP.

One of the issues concerning intraperitoneal drainage is the need for prophylactic intraperitoneal drainage. There was no significant difference in the incidence of POPFs in a comparison between DP with and without a drain[129-132]. However, Van Buren *et al*[130] and Fisher *et al*[131] reported that the elimination of routine intraoperative drain placement was associated with a statistically significant decrease in the length of hospital stay. In these reports, the incidence of clinical POPF tended to decrease in DP without drainage[129-132].

Two RCTs on PD with different results have been reported. In one RCT, the PANDRA trial, 395 patients were analyzed, and comparisons were made between patients with routine prophylactic intraperitoneal drains or those without drains. In the group with drains inserted, the drains were removed on the second postoperative day or later, whenever the amylase and lipase values of the drain fluid were lower than three times the serum amylase activity and there was less than 150 ml of fluid. Otherwise, the drains were not removed until the criteria were fulfilled. This trial concluded that prophylactic drainage was not necessary because clinical POPF was significantly reduced in the patients without drainage although there was no significant difference in the overall morbidity[133]. Another RCT was interrupted prematurely because the PD without prophylactic intraperitoneal drainage had a higher mortality compared to PD with drainage, although the criteria for drain removal were similar[134]. A subsequent meta-analysis reported that patients without prophylactic drainage had a significantly higher mortality despite fewer overall major complications and readmissions[135]. Patients who had a low risk of POPF may have benefits from avoiding routine intraperitoneal drainage[135]. The need for drainage after pancreatic resection continues to be controversial, particularly following PD.

Another issue is the timing of drain removal. First, the criteria for early drain removal are not defined. Kawai *et al*[136] reported improved outcomes with early drain removal after pancreatoduodenectomy. In this prospective cohort study, early drain removal was defined as removal on POD4 and as late as or after POD8. Adachi *et al*[137] demonstrated the improvement of POPF after DP with early drain removal. The authors defined early drain removal as POD1 and late removal as POD5; there was a 0% incidence of CR-POPF in the early group compared to 16% in the late removal group. However, in this study, gabexate mesilate, octreotide, and antibiotics were administered to patients with a high drain amylase level. Bassi *et al*[138] randomized 114 patients who underwent either PD or DP with early removal on POD3 or late removal on or after POD4. They concluded that early drain removal was associated with a decreased rate of POPF. However, in this study, Penrose drains were used, and patients whose amylase value in the drain was greater than 5000 U/mL were excluded. Although the best time to remove the drain remains unclear, prolonged placement of a drain might be a major cause of POPF because retrograde intra-abdominal infection may occur[133,136,139].

Somatostatin analogs

Octreotide and octreotide analogs are well known to inhibit the effects of pancreatic exocrine secretion[140], and they have been used as prophylactic agents to prevent POPF after pancreatic surgery. Therefore, the efficacy of octreotide after pancreatic

surgery in the prevention of POPF was expected. Two RCTs reported the efficacy of a prophylactic somatostatin analog for the prevention of POPF following PD[141,142]; however, these RCTs were reported before the definition given by ISGPF in 2005. Conversely, a recent RCT and meta-analysis evaluating somatostatin analogs did not demonstrate the reduction in the incidence of POPF after pancreatic surgery[143-151]. In particular, Nakeeb *et al*[152] evaluated the effect of the postoperative use of octreotide on the postoperative outcomes of PD in patients with soft pancreas and nondilated pancreatic duct. In this study, pancreatogastrostomy was used for pancreatic reconstruction. The results showed that octreotide did not affect the incidence of POPF and other complications.

Recently, the efficacy of pasireotide, which displays a broader affinity to somatostatin receptor subtypes and acts than octreotide, was noted. Allen *et al*[153] investigated whether pasireotide can be used to prevent POPFs in both PD and DP. In this RCT, patients received subcutaneous pasireotide or a placebo twice daily beginning preoperatively on the morning of the operation and continuing for seven days. PJ was typically performed by a duct-to-mucosa anastomosis, and pancreatic transection during DP was performed either with the use of a stapler with or without reinforcement or with hand-sewn closure. The RCT on pasireotide demonstrated the significant reduction of POPF after PD and DP. Furthermore, this drug reduced the rate of POPFs in patients who had nondilated pancreatic duct (normal pancreas).

Although there have also been reports that the use of pasireotide after pancreatic surgery does not decrease clinical POPF[154,155], a therapeutic effect by pasireotide is expected. Unfortunately, a key problem of pasireotide is cost-effectiveness because it is expensive. However, some studies have reported that pasireotide appears to be a cost-saving treatment following PD[156-158]. Indeed, the efficacy of pasireotide in reducing the incidence of POPF or other complications remains unclear, and it may be cost-effective in patients with a high risk of POPF.

CONCLUSION

POPF is still regarded as the most relevant and severe complication of pancreatic surgery, and it might develop intra-abdominal infection, hemorrhage, shock, and consequently death in some cases. Furthermore, POPF leads to increased health care costs and prolonged hospital stay. Several attempts to reduce the incidence of POPF have been made in recent years several RCTs described about methods of the reconstruction and anastomotic techniques in PD, stump closure in DP and need for stents; however, standard methods with which to minimize the incidence of POPF have not yet been established for both PD and DP. The perioperative management of POPF also remains controversial including the best time to remove the drain and the need of somatostatin analogs. Therefore, innovative attempts and further further RCTs should be performed to standardize surgical techniques and perioperative management.

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MINIREVIEWS

Current approaches to the management of patients with cirrhotic ascites

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Abstract

This review describes current approaches to the management of patients with cirrhotic ascites in relation to the severity of its clinical manifestations. The PubMed database, the Google Scholar retrieval system, the Cochrane Database of Systematic Reviews, and the reference lists from related articles were used to search for relevant publications. Articles corresponding to the aim of the review were selected for 1991-2018 using the keywords: "liver cirrhosis," "portal hypertension," "ascites," "pathogenesis," "diagnostics," and "treatment." Uncomplicated and refractory ascites in patients with cirrhosis were the inclusion criteria. The literature analysis has shown that despite the achievements of modern hepatology, the presence of ascites is associated with poor prognosis and high mortality. The key to successful management of patients with ascites may be the stratification of the risk of an adverse outcome and personalized therapy. Pathogenetically based approach to the choice of pharmacotherapy and optimization of minimally invasive methods of treatment may improve the quality of life and increase the survival rate of this category of patients.

Key words: Liver cirrhosis; Ascites; Diuretics; Large volume paracentesis; Peritoneovenous shunting; Transjugular intrahepatic portosystemic shunting

Core tip: This review describes current approaches to the management of patients with cirrhotic ascites in relation to the severity of its clinical manifestations. The literature analysis has shown that despite the achievements of modern hepatology, the presence of ascites is associated with poor prognosis and high mortality. The key to successful management of patients with ascites may be the stratification of the risk of an adverse

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outcome and personalized therapy. Pathogenetically based approach to the choice of pharmacotherapy and optimization of minimally invasive methods of treatment may improve the quality of life and increase the survival rate of this category of patients.

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INTRODUCTION

Ascites, the abnormal fluid accumulation in the abdominal cavity, occurs in about 60% of patients with compensated liver cirrhosis within 10 years after establishing the diagnosis[1]. It is associated with poor prognosis and high mortality, which reaches 40% within a year and 50% within 2 years. In the case of refractory ascites, median survival does not exceed 6 mo, which is due to the development of severe complications including hyponatremia and progressive renal failure[2]. The most unfavorable predictors are hyponatremia, arterial hypotonia, high serum creatinine, low urine sodium level[3], spontaneous bacterial peritonitis[4], low total protein concentration in the ascitic fluid (≤ 2 g/dL)[5], and the number of red blood cells in the ascitic fluid of more than 10.000/mm^3 (hemorrhagic ascites)[6].

Also, the well-known scores, namely Child-Turcotte-Pugh (CTP), Model for End-Stage Liver Disease (MELD), and its modified version MELD-Na, as well as the recently developed Chronic Liver Failure Consortium - Acute-on-Chronic Liver Failure (CLIF-C ACLF) scale, help to suggest a poor outcome for patients with cirrhosis[7].

In a retrospective, observational study by Wang *et al*[8], nosocomial mortality positively correlated with ascitic volume in patients with ascites of more than 300 mL, regardless of the CTP and MELD scores.

CAUSES AND MECHANISMS OF ASCITES DEVELOPMENT IN CIRRHOSIS

At present, the leading theory of ascites formation is the hypothesis of peripheral arterial vasodilation, the reasons for which include systemic inflammatory response syndrome (SIRS) (Figure 1).

Peripheral arterial vasodilation hypothesis

Cirrhotic ascites is caused by pathophysiological disorders typical for portal hypertension (PH). Splanchnic and systemic arterial vasodilation, along with the activation of various neurohormonal pathways, cause kidney dysfunction with sodium and water retention and a decrease in glomerular filtration rate[9]. Further systemic hemodynamic disorders lead to the progression of ascites, dilutional hyponatremia, and hepatorenal syndrome development. Conventionally, there are five phases of this process at different possible intervals[10].

During the first, preascitic phase, splanchnic arterial vasodilation does not lead to a decrease in the effective arterial blood volume due to the presence of hyperdynamic circulation accompanied with an increase in plasma volume and cardiac output. Blood pressure, kidney function, renin activity, noradrenaline level, and antidiuretic hormone concentration in plasma stay normal[11].

During the second phase, the nature of hemodynamic abnormalities caused by PH does not fundamentally change. Renal perfusion, glomerular filtration rate, free water excretion, renin activity, noradrenaline level, and antidiuretic hormone concentration in plasma stay within physiological values. Despite elevated levels of endogenous natriuretic hormones, there is a moderate decrease in sodium excretion, which has no relation to the activity of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. The reason for such a decrease in sodium excretion remains unknown and may be due to the interaction of several factors/systems including aldosterone, angiotensin II, still undefined factors that affect calcium-sensing receptors and the bumetanide-sensitive Na-K-Cl cotransporter expression, without forgetting the potential roles of the sympathoadrenergic system and

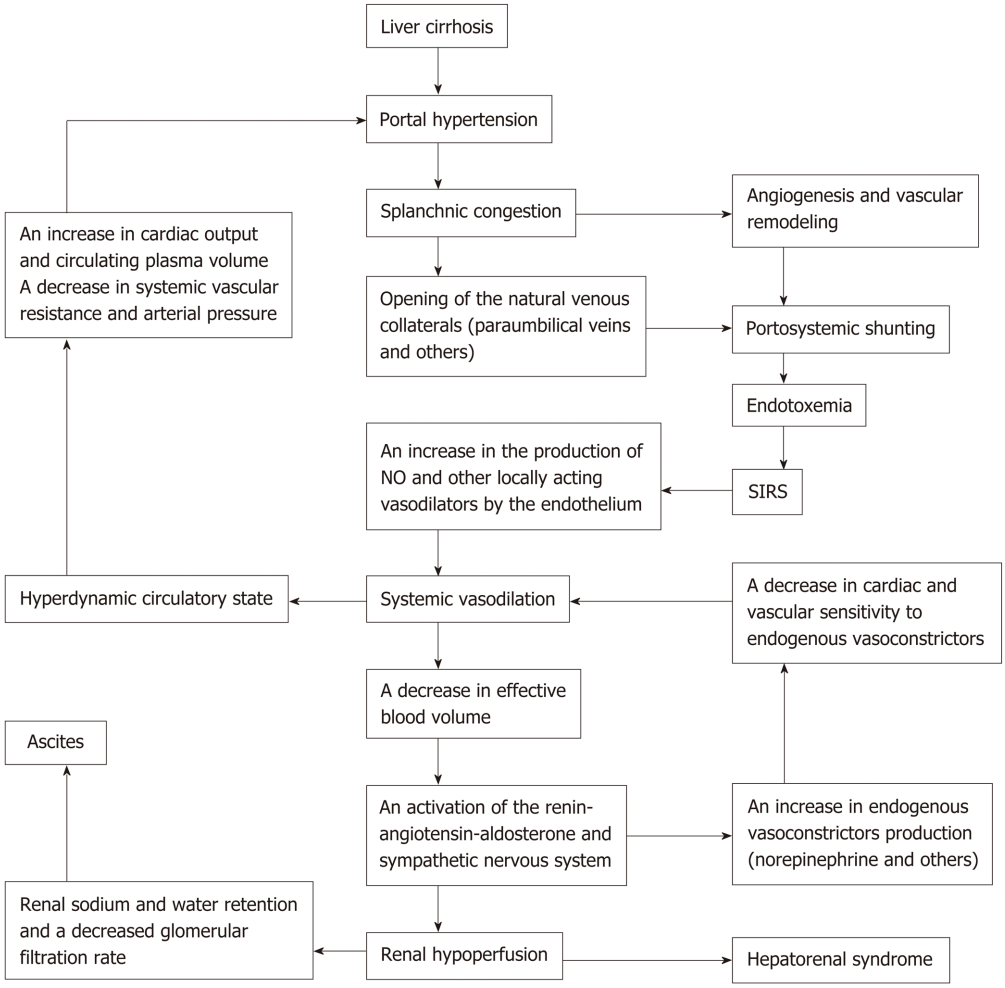

Figure 1 Potential mechanisms of ascites development in cirrhosis. SIRS: Systemic inflammatory response syndrome.

prostaglandins[12].

During the third phase, sodium retention is caused by the activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system as a result of progressive splanchnic arterial vasodilation. Despite an increase in plasma renin activity and plasma noradrenaline concentration, plasma volume remains unchanged. Cardiac output decreases, although it exceeds the average level. Blood pressure parameters during this period mostly depend on the activity of the RAAS and sympathetic nervous system. High peripheral vascular resistance leads to a reduction in cerebral and muscular blood flow. However, renal perfusion and glomerular filtration rate are not affected or are moderately reduced due to renal prostaglandins, which counter angiotensin and catecholamines. Besides, prostaglandins inhibit the effect of antidiuretic hormone and prevent the development of significant hyponatremia[13].

During the fourth phase, renin activity, noradrenaline level, and antidiuretic hormone level in plasma increase significantly, so renal perfusion and glomerular filtration rate reduce. The reduced ability of kidneys to excrete osmotically free water leads to dilutional hyponatremia[14].

During the fifth phase, patients with cirrhosis present with type 2 hepatorenal syndrome, which develops as a result of left ventricular systolic dysfunction accompanied by cardiac output decrease and severe systemic vasodilation. The extreme activity of the RAAS and sympathetic nervous system induces vasopressin production. Secondary hyperaldosteronism and tubular hypersensitivity to aldosterone increase sodium reabsorption in the distal parts of the nephron, whereas the sympathetic nervous system stimulates sodium reabsorption in proximal tubules and Henle's loop. Angiotensin II-induced spasm of predominantly efferent arterioles significantly reduces glomerular filtration rate leading to a further decrease in sodium excretion, even if blood pressure is stable[15].

Systemic inflammatory response syndrome

Recently, SIRS was noted to play an important role in the development of ascites and other complications of PH in cirrhosis, even in the absence of bacterial infection. The main mechanism of its development is the translocation of viable microorganisms, mainly gram-negative microflora, from the intestinal lumen to the mesenteric lymph nodes and other organs and tissues. Bacterial products or pathogen-related molecular structures interact with the corresponding receptors and promote the formation and release of pro-inflammatory cytokines. Subsequent inflammatory response increases the production of nitric oxide, aggravating the existing vasodilation[16]. In particular, it was shown that pro-inflammatory cytokines and chemo-attractant elements are increased in cirrhosis in comparison with healthy subjects and display higher values concomitantly with cirrhosis progression[17].

The reasons for bacterial translocation from the intestinal lumen in liver cirrhosis include a violation of local immunity, changes in the composition of bacterial flora due to decreased motility and the development of bacterial overgrowth syndrome, and increased permeability caused by mucosal damage due to oxidative stress[18]. A high level of endotoxemia may serve as an indirect confirmation of bacterial translocation in those patients with liver cirrhosis, who have acute bleeding from esophageal varices[19]. The role of bacterial translocation is also indirectly evidenced by the positive effect of drugs, which normalize the intestinal microflora and prevent bacterial translocation, on portal hypertension[20].

ASCITIC FLUID ANALYSIS

In order to determine the cause of ascites formation, diagnostic paracentesis with the ascitic fluid analysis is recommended for all patients with cirrhosis and first diagnosed ascites of the second or third stage in the case of ascites progression. Ascitic fluid analysis is also recommended for patients hospitalized because of other complications of cirrhosis, in particular, suspected spontaneous bacterial peritonitis[21]. Moreover, it is necessary for differential diagnosis between spontaneous bacterial peritonitis and peritonitis caused by acute surgical diseases of the abdominal cavity (Figure 2).

If ascites is due to PH, serum-ascites albumin gradient, which shows the difference in the levels of serum and albumin contained in the ascitic fluid, exceeds 1.1 g/dL[22]. This parameter inversely correlates with ascitic fluid viscosity, the increase of which indicates the threat of acute kidney injury development[23].

The concentration of total protein in the ascitic fluid of less than 1 g/dL and that of glucose exceeding 500 mg/L indicate an increased risk of spontaneous bacterial peritonitis, and the number of neutrophils in the ascitic fluid exceeding 250 cells/mm^3 (0.25 × 10^9/L) is the diagnostic criterion for it[24]. It should be noted that the prophylactic prescription of antibiotics may be helpful in patients with cirrhosis, who have low total protein concentration in the ascitic fluid (< 1.5 g/dL) and severely impaired liver (CTP class C, bilirubin level > 3 mg/dL) and renal (serum creatinine level > 1.2 mg/dL, urea nitrogen > 25 mg/dL, or sodium < 130 mEq/L) function. Antibiotics can significantly reduce the possibility of spontaneous bacterial peritonitis and hepatorenal syndrome and increase 1-year survival rate[25].

In patients with cardiac pathology, cardiac cirrhosis can be suspected if total protein concentration in ascitic fluid is less than 4.3 g/dL and if other predisposing factors for liver damage are excluded[26].

The signs of chylous ascites include cloudy, milky ascitic fluid containing a large number of lymphocytes (> 500/mL). The concentration of triglycerides in the chylous ascitic fluid exceeds 200 mg/dL (often > 1000 mg/dL), the total protein level is between 2.5 and 7.0 g/dL, the level of glucose exceeds 100 mg/dL, the lactate dehydrogenase activity is between 110 and 200 IU/L, the serum-ascites albumin gradient is less than 1.1 g/dL, and the cholesterol concentration gradient between ascitic fluid and serum is less than 1[27].

The high levels of C-reactive protein and insulin-like growth factor-1 in ascitic fluid make it possible to suspect malignant ascites[28], and a cholesterol level of more than 45 mg/100 mL in combination with cytology and carcinoembryonic antigen determination have diagnostic value[29]. Malignant ascites can also be assumed if there is a high level of C-reactive protein both in ascitic fluid and blood serum[30].

The values of adenosine deaminase activity and results of the Quantiferon test (QuantiFERON-TB Gold) can be used for the rapid diagnosis of tuberculous peritonitis with high sensitivity and specificity[31].

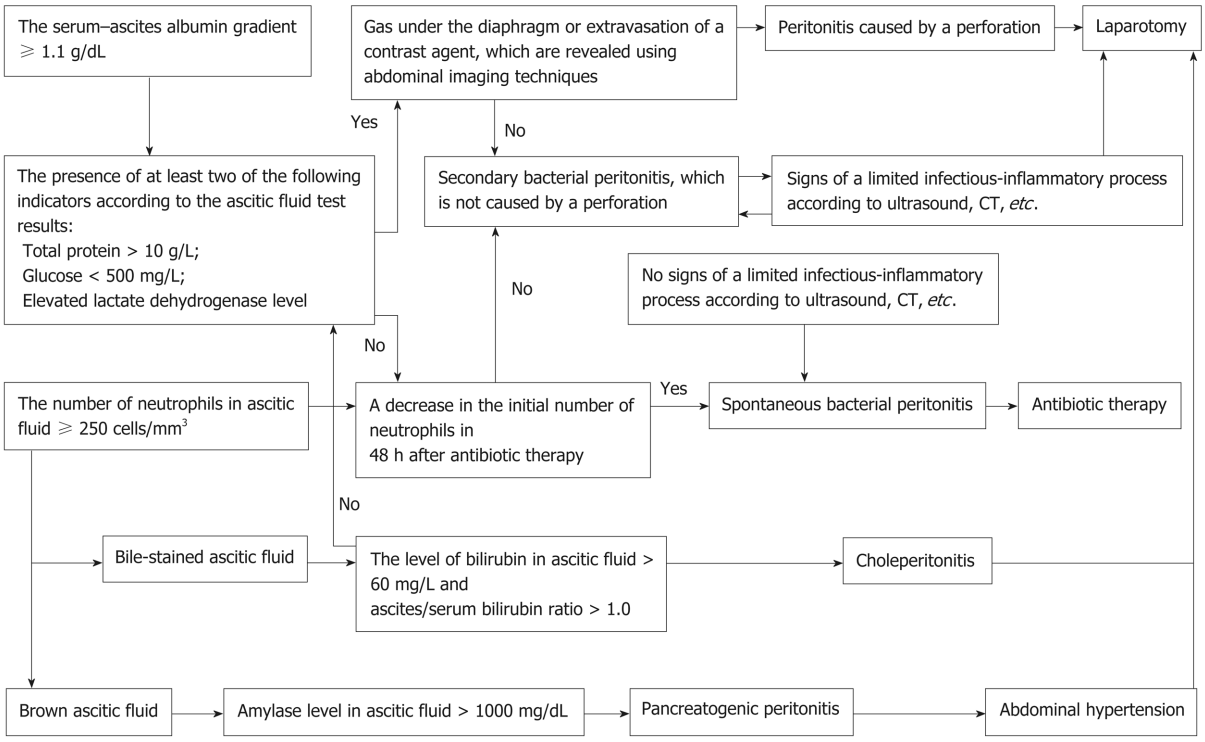

Figure 2 The algorithm for the differential diagnosis between ascites caused by portal hypertension, spontaneous bacterial peritonitis, and peritonitis caused by acute surgical diseases of the abdominal organs. CT: Computed tomography.

CLASSIFICATION OF CIRRHOTIC ASCITES

By the recommendations of the International Club of Ascites, ascites is classified into uncomplicated and refractory in patients with cirrhosis[32]. Ascites is considered uncomplicated if it is not accompanied by infection or hepatorenal syndrome. It is divided into three grades: Grade 1: mild ascites, which can be diagnosed only by ultrasound; Grade 2: moderate ascites, which is presented with a slight symmetrical stretching of the abdomen; and Grade 3: massive, tense ascites.

Refractory ascites is defined as ascites that does not recede to at least grade 1 with the use of diuretic treatment and dietary sodium restriction or the early recurrence of which after large volume paracentesis (LVP) cannot be satisfactorily prevented by medical therapy. It has two subtypes: *diuretic-resistant* and *diuretic-intractable*. In the first case, there is a resistance to optimal doses of diuretics. In the second case, the lack of effect is due to the insufficient dosage of diuretics conditioned by the threat of diuretic-induced complications[33].

TREATMENT OF ASCITES IN PATIENTS WITH CIRRHOSIS

Management of uncomplicated ascites

According to the clinical guidelines of the European Association for the Study of the Liver (EASL), the management of uncomplicated ascites depends on the severity of its clinical manifestations[34].

Patients with cirrhosis and *grade 1* ascites do not need diuretics and a low sodium diet. Patients with *grade 2* ascites can be treated in an outpatient center. Since sodium excretion is low (although not significantly) in most of them, therapy aims at reducing sodium consumption and stimulating its excretion by using diuretics and maintaining a usual drinking regimen. Sodium intake should be reduced to 80-120 mmol/d, which corresponds to 4.6-6.9 g of salt per day. Greater restrictions are undesirable, as the deterioration of food taste can lead to anorexia. Ideally, sodium balance in patients with cirrhosis and ascites should be changed on an individual basis by a hepatologist and nutritionist[35]. Due to the lack of reliable evidence for the negative effect of vertical posture on the activation of sodium retention systems and renal perfusion, bed rest prescription is unnecessary. Moreover, it is not recommended because already existing muscular atrophy may progress[36].

Sodium retention associated with ascites in patients with cirrhosis occurs mainly

due to reabsorption increase in renal tubules. Moreover, the mechanism of sodium reabsorption in proximal tubules is not fully established, whereas sodium reabsorption in distal tubules is mainly associated with hyperaldosteronism. Considering this, diuretic agents of choice for ascites treatment are aldosterone antagonists (spironolactone, canrenone, potassium canrenoate, *etc*.), which not only inhibit the retention of sodium and water but also suppress the potassium-excretory effect of sodium and reduce the synthesis of permeases in the aldosterone-dependent part of the collecting tubules and distal tubules. Also, loop diuretics are used. For example, furosemide can inhibit sodium reabsorption throughout the ascending limb of Henle's loop. However, due to lower efficacy and a greater number of complications in comparison with aldosterone antagonists, loop diuretics are not recommended as monotherapy[37].

The optimal variants are the sequential administration of aldosterone antagonists and loop diuretics at the initial stage of ascites treatment and the combination of these drugs if recurrence occurs. In the first case, treatment begins with the administration of spironolactone at 100-200 mg/d, then, in the absence of an effect, furosemide is added at 20-40 mg/d within two weeks. In the following, their daily dosage can be increased to 400 and 160 mg respectively. The second method suggests the combined use of diuretic agents from the very beginning, with a gradual increase in the dose of spironolactone up to 400 mg/d and furosemide up to 160 mg/d[38,39]. For the prevention of hypovolemia and eventually occurring acute kidney injury and hyponatremia, it is necessary to control daily diuresis and body weight during treatment. The decrease of body weight should not exceed 500 g/d in patients without peripheral edema and 1000 g/d in patients with it[40].

The combination of rational diuretic therapy and a low sodium diet makes it possible to achieve success in 90% of patients with cirrhosis and with uncomplicated grade 2 ascites. The effect is considered sufficient even if a small amount of fluid stays in the abdominal cavity, but there should be no peripheral edema. After achieving a positive result, diuretic agents should be reduced to a minimum, down to a complete withdrawal[41].

Side effects associated with diuretics may occur during the first weeks of treatment and are usually caused by impaired water-electrolyte balance. They mainly include dehydration, hypovolemic hyposmolar hyponatremia, and hypo- or hyperkalemia. Besides, possible complications include hepatic encephalopathy, gynecomastia, muscle cramps, and acute kidney injury.

The unreasonable intake of aldosterone antagonists may contribute to hypovolemic hyposmolar hyponatremia, although it mostly occurs because of the unreasonable use of thiazides in patients with cirrhosis and ascites, especially in the elderly. Agents of this group inhibit the reabsorption of sodium and chloride in distal convoluted tubules, act in the cortical thick ascending limb of Henle's loop and block the processes of urine osmotic dilution. Hypovolemic hyposmolar hyponatremia is characterized by a serum sodium level of less than 130 mmol/L, low plasma osmolarity, and a simultaneous decrease of extracellular fluid volume. Its main clinical presentations are a weakness, apathy, irritability, dizziness, arterial (including postural) hypotension, nausea, vomiting[42]. The development of severe hyponatremia (serum sodium level < 125 mmol/L), the worsening of hepatic encephalopathy, the presence of muscle cramps, and the signs of acute kidney injury require the withdrawal of the drugs causing them.

Hypokalemia is possible during the administration of loop diuretics, while hyperkalemia may be caused by aldosterone antagonists. Respectively, these drugs should be withdrawn when the level of serum potassium is less than 3 mmol/L or more than 6 mmol/L.

In spite of the fact that the nature of hepatic encephalopathy during treatment with diuretic agents is not fully understood, it is suggested to be caused by hyponatremia, which leads to brain cell swelling in the case of a rapid decrease in the level of serum sodium. In the case of a chronic process, hyponatremia may cause osmotic myelinolysis[43].

The long-term use of spironolactone in men is often accompanied by gynecomastia. However, spironolactone may be replaced with potassium canrenoate or amiloride only if breast pain appears[44].

Diuretic-induced hypovolemia may cause muscle cramps that are eliminated by decreasing the dose of diuretics or their complete withdrawal. In small uncontrolled studies, vitamin E, albumin, zinc, taurine, eperisone hydrochloride, and branched-chain amino acids have shown some efficacy[45]. In a randomized controlled trial (RCT) by Elfert *et al*[46], baclofen (centrally acting muscle relaxant) was successfully applied at 10 mg/d with a weekly increase up to 30 mg/d.

In addition to an intravascular volume decrease caused by the unreasonable use of diuretics, acute kidney injury may develop if they are combined with nonsteroidal

anti-inflammatory drugs[47], ACE inhibitors[48], angiotensin II receptor antagonists[49], α1-adrenergic blockers[50], aminoglycosides[51], dipyridamole[52], and contrast agents[53].

In patients with cirrhosis and massive, tense ascites (*grade 3*), the method of choice is LVP allowing simultaneous removal of more than 5-6 L of the ascitic fluid. It is then followed by the administration of diuretic agents and a low sodium diet[54]. Recent studies have shown the reduction in short-term mortality and an increase of hospitalization period in patients who underwent LVP[55], as well as the high probability of their repeated hospitalization within 30 d[56].

LVP is a relatively safe procedure. Even elevated creatinine level, hepatic encephalopathy, hypotension, and severe jaundice are not absolute contraindications for it[57]. However, LVP should be performed only by experienced specialists[58], preferably with a 15 or 16-gauge needle and under ultrasound control in order to prevent damage to venous collaterals and other vital structures[59].

The frequency of severe intra-abdominal bleedings during LVP does not exceed 1%[60]. Therefore, the use of fresh frozen plasma or platelet concentrate can be recommended only in certain clinical cases and not as standard therapy[61]. For example, they could be used in the case of severely impaired liver function assessed using the CTP and MELD scores[62] and in patients with severe thrombocytopenia[63]. In this regard, it may be useful to do a bedside hemostatic test for determining the activated clotting time, as well as to perform thromboelastometry/ thromboelastography (thromboelastography-guided transfusion strategy)[64]. Bacterial infection (sepsis) is an important risk factor for hemorrhagic complications in patients with cirrhosis[65]. However, in a recent retrospective single-center case-controlled study, it was shown that acute kidney injury is the most significant predictor for such complications after LVP[66].

The possible leaking of ascitic fluid from a puncture site is prevented by careful observance of all recommendations for the procedure[67].

The most dangerous consequence of LVP is paracentesis-induced circulatory dysfunction (PICD) which is an important independent indicator of an adverse outcome. Predisposing factors for PICD are not fully established, however, the rate of ascitic fluid removal does not play any significant role[68]. It is known that PICD occurs in the background of preexisting systemic arterial vasodilation and is accompanied by significant but ineffective RAAS activation. It is characterized by severe hemodynamic disturbances which are accompanied by increased cardiac output, decreased central venous pressure, and peripheral vascular resistance reduction[69]. Meta-analysis of seventeen RCTs including 1225 patients with cirrhosis who underwent LVP showed that PICD is associated with frequent recurrences of ascites, dilutional hyponatremia, hepatorenal syndrome development, and high mortality[70]. PICD is diagnosed considering renin concentration in blood plasma, which increases by 50% from baseline values or exceeds 4 ng/mL per hour in 5-6 d after LVP[71]. Albumin infusions in the amount of 8 g per 1 L of removed ascitic fluid may prevent this complication. The positive effect of albumin infusions is associated not only with an increase in oncotic pressure in the intravascular space but also with anti-inflammatory and antioxidant properties of albumin[72]. As an alternative to albumin infusions, Japanese authors have proposed cell-free and concentrated ascites reinfusion therapy (CART), which is aimed for maintaining serum albumin levels by filtrating and concentrating the removed ascitic fluid, followed by intravenous reinfusion of the collected proteins. In a retrospective observational study, Kozaki *et al*[73] performed 24 procedures in 11 patients with decompensated cirrhosis and showed the effectiveness and safety of CART. Even though CART reduces the need for albumin, there are problems with the high cost of equipment for it. To conduct one CART procedure, the estimated expense was ¥90500 (¥62400 for material costs and ¥28100 for technical costs).

Treatment of refractory ascites

Refractory ascites develops due to severe hemodynamic disturbances which are characteristic for decompensated cirrhosis. It should be noted that refractory ascites may be misdiagnosed and successfully corrected by eliminating its cause in the following clinical situations[57]: in patients receiving only loop diuretics, or in the case of prescribing aldosterone antagonists without taking into account the severity of hyperaldosteronism; during diuretic therapy, when increased diuresis is accompanied by the negative water balance of more than 900 mL/d and a rapid decrease in body weight that lead to hypovolemia with the development of prerenal azotemia; due to competing but potentially reversible complications that increase arterial vasodilation, and therefore worsen the discrepancy between intravascular volume and vascular capacity (dehydration caused by vomiting or diarrhea, gastrointestinal bleedings, bacterial infections); and in patients not keeping a low sodium diet.

Due to the poor prognosis, all patients with cirrhosis and refractory ascites should be considered as candidates for liver transplantation. Unfortunately, it is not possible

for many of them due to the presence of contraindications or problems related to the lack of donors[74]. In normal clinical practice, the first-line therapeutic intervention is LVP repeated every 2-3 wk in combination with albumin infusions. Moreover, diuretics are prescribed only when the concentration of sodium in urine is more than 30 mmol/d[75]. For increasing the effectiveness of therapy, it is possible to add clonidine (α2-presynaptic receptor agonist), which provides an early diuretic response with fewer complications and decreases the need for diuretics[76]. The positive effect of this drug is associated with the ability to reduce plasma norepinephrine concentration, followed by increased glomerular filtration rate, decreased sodium reabsorption in the proximal tubule, and increased sodium delivery to the distal tubule[77]. To obtain optimal results, clonidine is administered at 0.075-0.15 mg/d under the control of blood pressure, which should not be less than 135 mmHg[37].

Midodrine, an α1-adrenoreceptor agonist, can positively affect systemic and renal hemodynamics and increase sodium excretion by reducing plasma renin activity in patients with cirrhosis and refractory ascites without azotemia[78]. Its effectiveness was evaluated in the recent systematic review and meta-analysis of ten RCTs, six of which considered midodrine at 15 mg/d as a new drug for treating refractory ascites in patients with cirrhosis, and four regarded it as an alternative to albumin infusions during LVP. The results showed that midodrine is therapeutically effective and does not have a statistically significant effect on survival in comparison with placebo. Although midodrine cannot be considered as an alternative to albumin infusions during LVP, both treatment methods were equally successful in preventing PICD[79]. In an RCT by Hanafy *et al*[80], midodrine (15 mg/d) and rifaximin (1.1 g/d), which were added to diuretic agents, increased diuresis, improved systemic and renal hemodynamics, and subsequently improved short-term survival.

Despite the positive results of the aforementioned studies, the addition of clonidine or midodrine to the diuretic treatment in refractory ascites is not recommended according to current guidelines.

Terlipressin, a synthetic analog of vasopressin with longer biological activity and better safety profile, is the drug of choice for the treatment of acute bleeding from esophageal varices[81] and type 1 hepatorenal syndrome in patients with cirrhosis[82]. Terlipressin causes the contraction of arteries, in particular, arterioles of abdominal organs by stimulating specific V1 receptors on the arterial muscle cells. Reduced splanchnic vasodilation decreases portal pressure and therefore has a positive effect on hyperdynamic circulation, which in turn increases effective blood volume and renal perfusion pressure[83]. Intravenous bolus administration of 2 mg of terlipressin was found to increase glomerular filtration rate and sodium excretion in urine, and reduce renin activity and noradrenaline level in plasma of patients with cirrhosis and refractory or uncomplicated ascites[84].

Although octreotide, a synthetic analog of somatostatin that is also used to treat acute bleeding from esophageal varices, alone does not improve renal function in cirrhotic patients with ascites, its combination with diuretic treatment increases glomerular filtration rate and sodium and water excretion, mainly through the suppression of an activated renin-aldosterone axis[85].

If euvolemic or hypervolemic (dilutional) hyponatremia develops (serum sodium level < 125 mmol/L), patients with cirrhosis and refractory ascites should stop the intake of diuretic agents and limit fluid intake to 1 L/d. Hyponatremia correction is possible using tolvaptan, a selective oral vasopressin V_2-receptor antagonist. Tolvaptan inhibits the action of antidiuretic hormone, increasing free water excretion and thereby contributing to an increase in serum sodium level without significantly affecting sodium and potassium excretion[86]. However, considering that the results of phase III multicenter clinical studies are not received yet, it is recommended to use tolvaptan only when the need for treatment outweighs the risk of its use. Therapy should be carried out in a hospital, and serum sodium level should be monitored for the first 8-12 h, and then daily. Tolvaptan is administered once a day, starting with 15 mg. If necessary, this dose may be increased up to 60 mg. There is no need to correct the dosage depending on age, sex, heart, liver, or kidney function (if creatinine clearance ≥ 10 mL/min). During treatment, water restriction is not required[87].

Currently, the question remains whether it is possible to use nonselective β-adrenergic blockers in patients with decompensated cirrhosis and ascites, although they are the drugs of choice for the prevention of bleeding from esophageal varices[88]. A recent systematic review and meta-analysis of three RCTs and eight observational studies of propranolol, carvedilol, nadolol, and metoprolol, involving a total of 3145 patients with decompensated cirrhosis and ascites, revealed no reason to abandon β-adrenergic blockers[89]. However, careful monitoring of blood pressure, kidney function, and infectious screening should be conducted in order to identify cases requiring the reduction of non-selective β-blockers dose or their complete withdrawal[90].

A large number of publications have shown that refractory ascites can be successfully treated by transjugular intrahepatic portosystemic shunting (TIPS)[91]. Portal pressure reduction caused by TIPS improves the function of the cardiovascular system that contributes to increased renal blood flow and increased glomerular filtration rate[92]. At the same time, current clinical guidelines consider TIPS as a second line measure and recommend using it only in the case of frequently required LVP or its inefficiency. The reason for it is the development of TIPS-related hepatic encephalopathy and high mortality in patients with decompensated cirrhosis[93].

Nevertheless, the accumulation of experience and the development of new technologies, in particular, self-expanding polytetrafluoroethylene-covered stents, reduce the number of typical TIPS-related complications[94]. The smaller amount of complications leads to an increase in 1-year survival in patients who undergo TIPS without liver transplantation in comparison with those who receive repeated LVP in combination with albumin infusions[95]. Moreover, stents with a diameter of 10 mm control ascites better than stents with a diameter of 8 mm and do not increase the frequency of hepatic encephalopathy[96].

Also, the careful selection of candidates for TIPS among patients with cirrhosis and refractory ascites improves the results of the operation. The adverse outcome after TIPS is found in CTP class C patients[97] with the following: (1) MELD score > 25 points and a portosystemic gradient < 8 mmHg[98]; (2) INR value > 2[99]; (3) Total serum bilirubin level > 3 mg/dL and platelet count < 75 × 10^9/L[100]; (4) Serum creatinine level > 1.9 mg/dL[101]; (5) Glomerular filtration rate < 90 mL/min and platelet count < 125 × 10^9/L[102]; (6) Recurrent hepatic encephalopathy, which equals or exceeds the 2nd stage[103]; and (7) Diastolic dysfunction (E/A ratio ≤ 1)[104].

Besides, an important TIPS-related mortality risk factor is experience with its use. Mortality is lower in those hospitals, where at least 20 procedures are done per year[105].

Additionally, early stent placement turns out to be more cost-effective in those patients with cirrhosis and refractory ascites who need LVP more often than every 10 wk (> 5 LVPs per year) and are candidates for TIPS[106].

If a patient has contraindications to TIPS, implantation of a permanent Pleurx® tunneled peritoneal catheter may serve as an alternative. It is commonly used in the treatment of recurrent ascites caused by malignant neoplasms and allows to drain a small amount of ascitic fluid (< 2 L per day) in small portions even at home[107]. The first experience of using this method in a small cohort of patients with cirrhosis and refractory ascites showed its sufficient effectiveness in decreasing the need for diuretics, LVP, and albumin infusion. The procedure made it possible to avoid hyponatremia and the deterioration of renal function[108]. According to the data, 38% of patients developed spontaneous bacterial peritonitis, which was successfully treated with antibiotics[109]. CT-guided paracentesis with a pigtail catheter is a clinically effective, cheap, and safe alternative to conventional bedside paracentesis[110]. In an observational study performed by Riedel *et al*[111], the safety of Pleurx® catheter implantation almost did not differ from the standard LVP. Despite positive preliminary results, it is too early to talk about the feasibility of using these catheters in patients with cirrhosis and refractory ascites, and prospective RCTs are needed for conclusions.

In 1998, Rozenblit *et al*[112] proposed the first mechanical device designed to actively move ascitic fluid from the abdominal cavity to the bladder. However, it did not find widespread clinical use because of technical problems. A few years later, this idea was implemented by developing an automatic low-flow pump (Alfapump® system, Sequana Medical AG, Zurich, Switzerland). It consists of a subcutaneously implanted battery-operated pump connected to a catheter placed in the abdominal cavity. The pump aspirates ascitic fluid and transfers it through the second subcutaneous catheter to the bladder. The alfapump® system is equipped with internal sensors to monitor the pressure in the abdominal cavity and the bladder. They stop the pump when there is no ascites or when the bladder is full. The device is fully automated and programmed by the attending physician depending on the needs of the patient. The alfapump® system moves ascites to the bladder in small portions (usually 5-10 mL) every 5-10 min, from 0.5 to 2.5 L of ascitic fluid per day without the necessary administration of albumin. For patients' convenience, the pump is usually set to work only when they are awake[113].

In a multicenter non-randomized trial, Bellot *et al*[114] evaluated the efficacy of the alfapump® system in 40 patients with cirrhosis and refractory ascites. The patients were treated in 9 hospitals, and the observational period was up to 6 months. It was noted that 40% of patients had no need for LVP after alfapump® system implantation, and 70% needed LVP less than once a month. Nevertheless, there was a high percentage of complications, which mainly involved the migration and blockage of urinary or peritoneal catheters (22.5% and 12.5%, respectively).

In a prospective observational study involving 10 European referral centers, the alfapump® system was applied for at least 12 months, and the results were evaluated in 56 patients with cirrhosis and refractory ascites. The patients had an average MELD score of 13 and CTP score of 8.9 [36 patients had CTP class B (64.3%), 15 patients had CTP class C (24.8%), and CTP class was unknown in 5 patients]. The average duration of ascites before implantation of the device was 11.0 mo. As a result, 3 patients completed the 24-mo observational period, 3 patients continued observation, 9 patients underwent liver transplantation, 17 patients were excluded from the study because of serious side effects, and 23 patients died. The most frequent technical complication was the blockade of the peritoneal catheter. During the observation, 23 reinterventions related to the pump were required (17 patients), and in 12 cases the pump was changed (11 patients). The alfapump® system was removed in 48% of patients (in 17 cases because of serious side effects, in 9 cases during liver transplantation, and in 1 case because of recovery from refractory ascites). The average frequency of LVP decreased from 2.17 to 0.17 per month[115].

An RCT by Bureau *et al*[116] showed an advantage of the alfapump® system as compared to LVP, which consisted of reducing and for the most part eliminating the need for paracentesis. The quality of life and nutritional status were also improved. Despite the higher implantation cost of the alfapump® system (£22230), there was a trend towards stabilized post-intervention costs, whereas the cost of repeated LVP steadily increased. The total number of infectious complications between groups was similar and the overall outcome was the same. However, there were significantly more cases of acute kidney injury among those who had the alfapump® system. Such a negative effect on the renal function is possibly associated with a decrease in the glomerular filtration rate and a noticeable activation of the endogenous vasoconstrictor systems, as well as in PICD[117].

Although the alfapump® system can reduce the need for paracentesis, it remains unclear whether this method has a significant advantage over LVP in improving the survival rate of patients with cirrhosis and refractory ascites. At present, it cannot be considered a standard of medical care, but theoretically, it may serve as a "bridge" to liver transplantation in patients who have contraindications to TIPS.

Peritoneovenous shunting (PVS) allows protein-rich ascitic fluid to flow from the abdominal cavity to the venous system in the positive pressure gradient, which leads to an increase in circulating plasma volume and stimulation of diuresis and natriuresis. M. de Routte, who for the first time described PVS in 1907, used a large saphenous vein for its implementation. The unidirectional movement of ascitic fluid was achieved by the ostial valve functioning. The shunt functioned for a short period because it was frequently obstructed by a thrombus or the greater omentum. Therefore, the operation was rarely used in the future. In 1962, A.N. Smith, when performing PVS, took advantage of the Holter drainage system with a slit-like valve at the distal end, previously proposed for the treatment of hydrocephalus[118]. Among the numerous modifications described subsequently, the LeVeen and Denver shunts were the most common. The initially used surgical technique was later replaced by the laparoscopic approach, which, in addition to its low invasiveness, makes it possible to histologically verify the diagnosis and determine the following therapy. At present, the development of interventional technologies and devices allows the procedure to be performed percutaneously, which is faster, cheaper, and does not require general anesthesia[119].

PVS has been reported to improve glomerular filtration rate in patients with cirrhosis and refractory ascites, and especially in those having moderate and severe renal insufficiency[120]. Ascites control was achieved faster than after TIPS. However, long-term results were worse[121]. An RCT by Ginès *et al*[122] showed an advantage of PVS over LVP with albumin infusion in reducing the incidence of ascites recurrence and the need for diuretics. However, the high frequency of shunt obstruction had a negative impact on survival, which was about the same in both groups studied.

Despite its technical simplicity, PVS can be accompanied by severe and sometimes fatal complications including infection and shunt thrombosis, disseminated intravascular coagulation of blood, air embolism, and other pathological conditions[123]. In this connection, according to the EASL guidelines, this method plays a minor role in the treatment of refractory ascites in patients with cirrhosis[34].

Numerous literature data indicate that shunt surgery is dangerous in patients with cirrhosis and refractory ascites because it has a high risk of adverse outcome. However, Orloff *et al*[124] published unique clinical and metabolic results after portocaval side-to-side shunt surgery in this category of patients. Within the group of 34 patients (CTP class A - 0, B - 23, C - 11), two died in the immediate postoperative period (the causes of death were hepatoma in one case and heart failure in the other). Long-term survival rates after 5, 10, and 15 years were 75, 74, and 73%, respectively. Due to effective diuresis and natriuresis, ascites formation was stopped in all patients

without the need for diuretics. The liver function was improved in 81% of cases, and recurrent encephalopathy was found in 6% of patients.

CONCLUSION

Patients with cirrhosis complicated by ascites constitute a sufficiently large population and are treated by doctors of different specialties. The analysis of the literature has shown that despite the achievements of modern hepatology, the presence of ascites is associated with poor prognosis and high mortality. The key to successful treatment of ascites may be the stratification of the risk of an adverse outcome and personalized therapy. Pathogenetically based approach to the choice of pharmacotherapy and optimization of minimally invasive methods of treatment may improve the quality of life and increase the survival rate of this category of patients.

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MINIREVIEWS

Pyrrolizidine alkaloids-induced hepatic sinusoidal obstruction syndrome: Pathogenesis, clinical manifestations, diagnosis, treatment, and outcomes

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Abstract

Hepatic sinusoidal obstruction syndrome (HSOS) can be caused by the intake of pyrrolizidine alkaloids (PAs). To date, PAs-induced HSOS has not been extensively studied. In view of the difference in etiology of HSOS between the West and China, clinical profiles, imaging findings, treatment, and outcomes of HSOS associated with hematopoietic stem cell transplantation or oxaliplatin might be hardly extrapolated to PAs-induced HSOS. Reactive metabolites derived from PAs form pyrrole-protein adducts that result in toxic destruction of hepatic sinusoidal endothelial cells. PAs-induced HSOS typically manifests as painful hepatomegaly, ascites, and jaundice. Laboratory tests revealed abnormal liver function tests were observed in most of the patients with PAs-induced HSOS. In addition, contrast computed tomography and magnetic resonance imaging scan show that patients with PAs-induced HSOS have distinct imaging features, which reveal that radiological imaging provides an effective noninvasive method for the diagnosis of PAs-induced HSOS. Liver biopsy and histological examination showed that PAs-induced HSOS displayed distinct features in acute and chronic stages. Therapeutic strategies for PAs-induced HSOS include rigorous fluid management, anticoagulant therapy, glucocorticoids, transjugular intrahepatic portosystemic shunt, liver transplantation, *etc*. The aim of this review is to describe the pathogenesis, clinical profiles, diagnostic criteria, treatment, and outcomes of PAs-induced HSOS.

Key words: Hepatic sinusoidal obstruction syndrome; Pyrrolizidine alkaloids; Hepatic sinusoidal endothelial cells; Pyrrole-protein adducts; Diagnostic criteria; Symptomatic

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Core tip: Hepatic sinusoidal obstruction syndrome (HSOS), also named hepatic veno-occlusive disease, is a hepatic vascular disease presenting with abdominal distension, painful hepatomegaly, jaundice, and weight gain. The intake of pyrrolizidine alkaloids (PAs) is one of the major etiologies of HSOS in China. Unfortunately, PAs-induced HSOS has not been extensively studied up to now. Here, we describe the pathogenesis, clinical profiles, diagnosis, treatment, and outcomes of patients with PAs-induced HSOS.

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INTRODUCTION

Hepatic sinusoidal obstruction syndrome (HSOS), previously known as hepatic veno-occlusive disease (HVOD), is an obliterative venulitis of the terminal hepatic venules[1-5]. HSOS is typically manifested as a classical triad of weight gain, painful hepatomegaly, and jaundice. The etiologies of HSOS include cytoreductive therapy prior to hematopoietic stem cell transplantation (HSCT)[2,6-8]; oxaliplatin-containing adjuvant chemotherapy[9-15]; intake of pyrrolizidine alkaloids (PAs)-containing plants[16-21]; use of tacrolimus in liver transplantation[22]; autosomal recessive condition of veno-occlusive disease with immunodeficiency, *etc*. In developed countries, HSOS usually occurs in patients who have received cytoreductive therapy prior to HSCT or oxaliplatin-containing chemotherapy for colorectal carcinoma[8,23-25]. In China, the primary cause of HSOS is the ingestion of PAs-containing herbals or dietary supplements[16,20,26]. Most clinical studies have focused on HSCT-related HSOS and oxaliplatin-induced HSOS in recent decades. Given the difference in etiologies of HSOS between western countries and China, clinical profiles, imaging findings, treatment, and outcome of HSOS associated with HSCT or oxaliplatin might be hardly extrapolated to PAs-induced HSOS.

The purposes of this review were: (1) To elucidate the pathogenesis of PAs-induced HSOS; (2) To describe clinical manifestations; (3) To describe imaging features; (4) To define the criteria for diagnosis; and (5) To evaluate treatment and outcome.

PATHOGENESIS

HSOS is characterized by toxic injury to small hepatic vessels, particularly the sinusoidal endothelium in zone 3 of the liver acinus[27]. Damaged sinusoids lead to sloughing and downstream occlusion of terminal hepatic venules[27]. A core pathogenic event of HSOS is toxic destruction of hepatic sinusoidal endothelial cells (HSECs)[1]. Injured HSECs and central venous endothelial cells can be replaced by progenitor cells derived from bone marrow, and toxicity of the drugs and the plants to bone marrow progenitors impairs the replacement of the injured endothelial cells[28,29]. All these indicated toxic injury to sinusoidal/central venous endothelial cells and bone marrow progenitors contributes to the pathogenesis of HSOS.

PAs-containing plants are widely distributed in the world. More than 300 PAs have been identified in over 6000 plants[5]. Although the precise mechanism of PAs-induced HSOS remains unknown, it is well accepted that the initial event in PAs-induced HSOS is toxic destruction of HSECs in zone 3 of the liver acinus by toxic metabolites of PAs[16,17]. Firstly, water-soluble PAs salts are readily absorbed from the gastro-intestinal tract and then transported to the liver through the portal venous system when individuals ingest herbal remedies or herbal teas containing PAs. Then, in liver, PAs are metabolized through cytochrome-P450-mediated activation to produce dehydropyrrolizidine alkaloids (DHPAs) and dehydroretronecine (DHR). DHPAs

and DHR further interact with glutathione (GSH) or proteins to generate pyrrole-glutathione conjugates[30] or pyrrole-protein adducts (PPAs)[31], respectively. PPAs are believed to be the primary cause of PAs-induced HSOS[32,33]. GSH conjugation of DHPAs and DHR is a main detoxification mechanism in metabolism-mediated PAs intoxication[18,34]. HSECs have a low basal GSH level, thus HSEC is susceptible to the reactive metabolites with severe GSH depletion and PPAs formation[34]. PPAs covalently bind to the F-actin cytoskeleton of the HSECs, which results in depolymerization of F-actin. Depolymerization of F-actin triggers the release of matrix metalloproteinase (MMP)-9. The combination of F-actin depolymerization, which allows HSECs to round up, and degradation of the subcellular extracellular matrix by MMP-9, which loosens HSECs tethering to the space of Disse, creates gaps within and between HSECs[35]. Then, erythrocytes, leukocytes, and cellular debris penetrate the gaps in the endothelium into the space of Disse, and the sinusoidal lining consisting of HSECs, Kupffer cells, and hepatic stellate cells is dissected. Emboli of dead sinusoidal lining cells obstruct the sinusoidal flow. With progressively narrowing venous lumen and reduced sinusoidal venous outflow, post-sinusoidal portal hypertension occurred[23]. In addition, the occlusion of the small centrilobular veins leads to hepatic congestion and subsequent hemorrhagic parenchymal necrosis. This pathophysiological process gives rise to the presence of the clinical syndrome of HSOS, including weight gain, ascites, painful hepatomegaly, and jaundice[23] (Figure 1).

CLINICAL MANIFESTATION AND LABORATORY TESTS

The clinical presentation of HSOS includes jaundice, right upper quadrant pain, tender hepatomegaly, ascites, and weight gain. In western countries, HSOS occurs most commonly in cytoreductive therapy prior to HSCT or oxaliplatin-containing chemotherapy. For HSCT-related HSOS, the patients present with a wide spectrum of severity. Severe HSOS is typically associated with multiorgan failure. For oxaliplatin-induced HSOS, clinical manifestations of the patients appear to be mild or absent[9,13,36]. This indicates that clinical presentation of HSOS correlates with the etiology of HSOS. To determine the clinical presentation of the patients with PAs-induced HSOS, clinical profiles of patients with PAs-induced HSOS have been analyzed. The clinical presentation of the patients is summarized in Table 1. The most common clinical features were ascites (98%-100%), hepatomegaly (65.1%-92%), jaundice (39.8%-57.8%), and abdominal distention (98.3%-99.1%); whereas, a small proportion of PAs-induced HSOS patients had weight gain (16%-18%), edema (37.3%-39.5%), and right upper quadrant pain (19.7%-36.4%). In addition, splenomegaly (27%-34%) and gastroesophageal varices (18.3%-36.8%) were observed in a small proportion of patients with PAs-induced HSOS[17,26,37-39].

In addition, laboratory tests have been analyzed in patients with PAs-induced HSOS. The results of laboratory tests are summarized in Table 1. Routine blood tests showed that levels of erythrocytes, leukocytes, and platelets were within the normal range in most patients with PAs-induced HSOS. Abnormal liver function was observed in most PAs-induced HSOS patients. Elevation of serum bilirubin, alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transpeptidase was observed in patients with PAs-induced HSOS; moreover, albumin level was abnormal (Table 1). Ascites is the most common clinical presentation of PAs-induced HSOS, and laboratory investigation showed that patients had a serum ascites albumin gradient > 11 g/L, which indicated portal hypertensive ascites[16,39]. A wide spectrum of disease severity was observed in patients with PAs-induced HSOS. Mild HSOS is considered when it meets diagnostic criteria and has a self-limiting course. Patients with severe HSOS developed multiorgan failure and had a high risk of mortality.

IMAGING FEATURES

The use of imaging techniques to evaluate liver lesions has been confirmed in clinical practice. Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) have been widely used in diagnosing liver diseases. Recently, several researchers have investigated the imaging characteristics of PAs-induced HSOS and determined the diagnostic value of radiological imaging. Imaging techniques provide valuable imaging signs as well as an effective method for diagnosing PAs-induced HSOS.

Liver ultrasonography is a cost-effective method in the diagnosis of liver diseases. A recent study demonstrated that ultrasonography is useful for diagnosis of PAs-induced HSOS. Doppler ultrasound examination of patients with PAs-induced HSOS

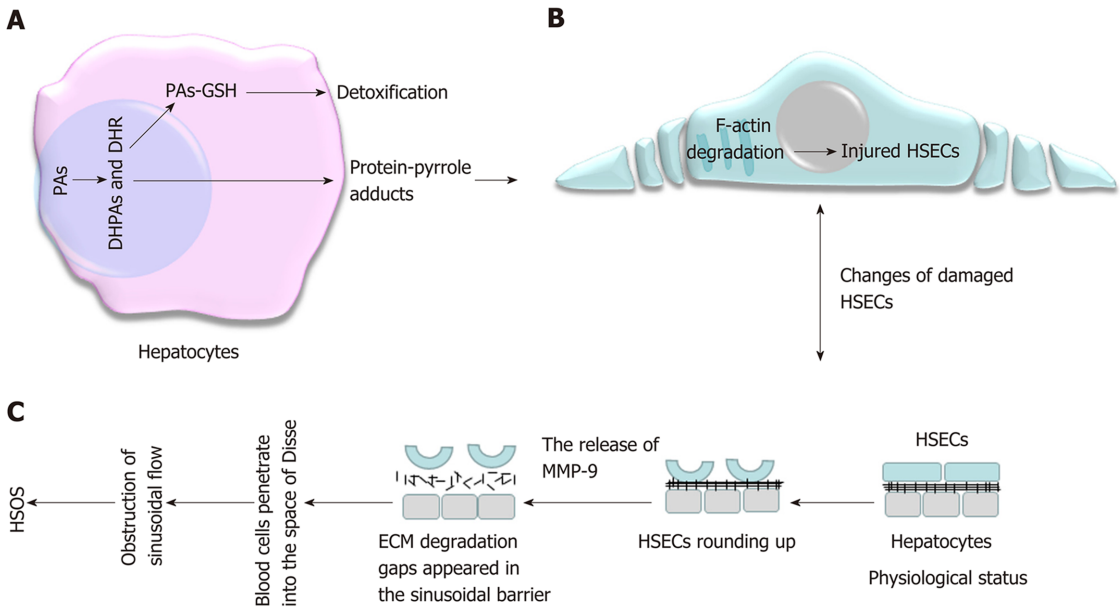

Figure 1 Pathogenesis of pyrrolizidine alkaloids-induced hepatic sinusoidal obstruction syndrome. A: Oral PAs are transported into the liver, metabolites bind with glutathione, resulting in detoxification, or combine with protein to generate PPAs; B: In HSECs, PPAs cause depolymerization of F-actin and release of MMP-9, which damages HSECs; C: Injured HSECs round up, MMP-9 triggers degradation of extracellular matrix, then gaps between HSECs appear, blood cells penetrate the gaps into the space of Disse, and sinusoidal lining cells obstruct the sinusoidal flow, resulting in postsinusoidal portal hypertension. PAs: Pyrrolizidine alkaloids; GSH: Glutathione; PPAs: Protein-pyrrole adducts; HSECs: Hepatic sinusoidal endothelial cells; MMP-9: Matrix metalloproteinase-9; ECM: Extracellular matrix; DHPAs: Dehydropyrrolizidine alkaloids; DHR: Dehydroretronecine; HSOS: Hepatic sinusoidal obstruction syndrome.

includes hepatomegaly, decreased portal vein flow velocity, and hepatic vein stenosis[17]. In addition, typical ultrasonic features include heterogeneous enhancement of the arterial phase, slow portal vein filling, and an extended transit time between the hepatic artery and vein[16,40].

Several studies have described radiological features of PAs-induced HSOS. Early studies described the imaging features of PAs-induced HSOS based on small samples. They found that ascites, patchy liver enhancement, narrowing of the right hepatic vein, hepatomegaly, and gallbladder wall thickening are common features of CT (Figure 2)[19,41]. Recently, our group[39] and Zhuge *et al*[17] confirmed the above findings in large sample sizes. Beside this, heterogeneous hypoattenuation, pleural effusion, obscure or invisible hepatic veins, and stenosis of the hepatic segmental inferior vena cava were observed in most patients (Figure 2). Splenomegaly and portosystemic collateral circulation were observed in a small proportion of patients with PAs-induced HSOS[16,17,39]. Importantly, we found that patchy liver enhancement and heterogeneous hypoattenuation were valuable signs of PAs-induced HSOS[39]. Quantitative analysis of CT images revealed that the ratio of hepatic lesion volume to liver volume in patients with PAs-induced HSOS is associated with clinical course and outcome[42].

MRI is a good choice of imaging technique because it yields different information and does not have the hazards of X-rays compared with CT. Recent studies demonstrated MRI is useful in detecting oxaliplatin-induced HSOS in patients with metastatic colon cancer[11,15,36,43]. Our previous work demonstrated that the common signs of PAs-induced HSOS include ascites, heterogeneous hypointensity, narrowing of the inferior vena cava, periportal edema, gallbladder wall thickening, hepatomegaly, abnormal hepatic vein (narrowing or invisibility of right hepatic vein), and pleural effusion (Figure 3). We have also found inhomogeneous enhancement around the hepatic veins ("claw" type enhancement) in the portal venous phase that results from differential blood perfusion in the peripheral and central region of the liver parenchyma as well as hypointensity in susceptibility-weighted imaging (SWI) and T2*-weighted imaging (T2*WI)[44] (Figure 3). Hemosiderin derived from extravasated erythrocytes in the space of Disse is detected by T2*WI and SWI, which results in the imaging sign of hypointensity. We have also investigated the imaging features of PAs-induced HSOS on gadoxetic acid-enhanced MRI[45]. Heterogeneous hypointensity of liver parenchyma in hepatobiliary phase (HBP) is an imaging sign of PAs-induced HSOS (Figure 3). The severity of heterogeneous hypointensity scored by volume fraction in HBP of gadoxetic acid-enhanced MRI is positively correlated with prothrombin time and international normalized ratio, and the severity of

Table 1 Demographic information, clinical manifestation, and laboratory tests of pyrrolizidine alkaloids-induced hepatic sinusoidal obstruction syndrome

Reference	Wang *et al*[37]	Zhuge *et al*[17]	Song *et al*[38]	Wang *et al*[26]
Number	n = 117	n = 108	n = 116	n = 84
Sex (male/female)	78/39	66/42	78/38	45/39
Age (yr)	63 (52.5-69)[1]	61 (55-69)[1]	56.92 ± 12.39[2]	52.97 ± 15.28[2]
Clinical manifestation				
Ascites	99.1% (116/117)	98% (50/51)	100% (79/79)	100% (83/83)
Hepatomegaly	70% (82/117)	92% (47/51)	75.95% (60/79)	65.1% (54/83)
Abdominal distention	98.3% (115/117)	99.1% (107/108)	98.3% (113/115)	
Jaundice		39.8% (43/108)	52.9% (54/102)	57.8% (48/83)
Right upper quadrant pain	19.7% (23/117)		36.4% (40/110)	
Edema	39.3% (46/117)		39.5% (43/109)	37.3% (31/83)
Weight gain	18% (21/117)		15.5% (16/103)	
Splenomegaly	34.2% (40/117)	27% (14/51)	25.35% (18/71)[39]	
Gastroesophageal varices			18.31%(13/71)[39]	36.8%(7/19)
Laboratory tests				
Variable	Median (25^{th}-75^{th} percentiles)	Median (25^{th}-75^{th} percentiles)	mean ± SD	mean ± SD
ALT (U/L)	49 (25.0-152.5)	52.6 (26.8-125)	134.50 ± 154.89	216.83 ± 235.78
AST (U/L)	75 (39.0-158.5)	69.6 (42.4-115)	146.31 ± 156.30	221.15 ± 221.70
ALP (U/L)	122 (86.8-191.3)	130 (105-178)	170 ± 106.89	183.48 ± 59.96
γ-GT (U/L)	100.7 (61.8-164.8)	120 (72.4-170)	160.52 ± 114.56	155.70 ± 99.45
TB (μmol/L)	33.3 (19.7-47.0)	39.7 (28.3-62.4)	65.07 ± 78.83	52.96 ± 45.95
ALB (g/L)	30.6 (27.7-33.6)	32.1 (29.8-34.7)	30.71 ± 5.50	32.02 ± 4.51
PT (sec)	14.8 (12.7-17.0)	15.1 (14.2-16.7)	17.43 ± 2.64	18.08 ± 4.12
WBC (10^9/L)	6.1 (5.0-8.7)	6.1 (4.8-7.3)	6.90 ± 2.81	
RBC (10^{12}/L)	4.4 (3.9-4.9)		5 ± 4.33	
PLT (10^9/L)	113 (78-153)	95 (74-134)	114.06 ± 63.48	

[1]Continuous variables were expressed as medians (25^{th}-75^{th} percentiles);
[2]Continuous data were expressed as mean ± standard deviations. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; γ-GT: γ-Glutamyl transpeptidase; TB: Total bilirubin; ALB: Albumin; PT: Prothrombin time; WBC: White blood cell; RBC: Red blood cell; PLT: Platelet.

hypointensity in HBP is a mortality risk factor. In summary, these studies have demonstrated that heterogeneous hypoattenuation/hypointensity and irregular enhancement are valuable imaging features of CT and MRI.

PATHOLOGY

Liver biopsy and histological examination are gold standards for diagnosis of HSOS. PAs-induced HSOS exhibits acute and subacute/chronic features. In the early stage, the first recognizable histological change is widening of the subendothelial zone between the basement membrane and the adventitia of central veins and sublobular veins[46,47]. In acute disease, swelling, damage, and shedding of HSECs are observed in acinar zone 3 (Figure 4). Significant dilation and congestion of hepatic sinusoids with centrilobular hepatocellular necrosis, dissection of erythrocytes into the space of Disse, thickening of the walls of small intrahepatic veins with narrowing and occlusion of the lumen are frequently observed[16,38]. In the later stage, deposition of extracellular matrix in subendothelial spaces and sinusoids and extensive collagenization of sinusoids and venules were characteristic histological features[38]. In addition, our studies also found complete loss of pericentral hepatocytes as well as sinusoidal dilatation in subacute or chronic stages (Figure 4)[38]. However, percutaneous liver biopsy is difficult to perform in patients with PAs-induced HSOS due to extensive ascites, coagulation disorders, and thrombocytopenia. Furthermore, the uneven distribution of HSOS decreases histopathological credibility. Transjugular liver biopsies have been performed in PAs-induced HSOS patients with extensive ascites, coagulation disorders, and thrombocytopenia. More importantly, transjugular

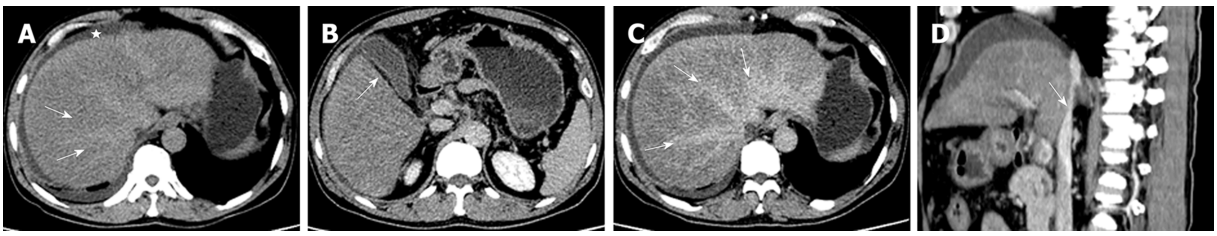

Figure 2 A 53-year-old man with pyrrolizidine alkaloids-induced hepatic sinusoidal obstruction syndrome who received contrast-enhanced computed tomography. A: Image of plain phase. The imaging signs included hepatomegaly, ascites (white star), heterogeneous hypodensity (white arrow); B and C: Image of equilibrium phase. Gallbladder wall thickening (white arrow, B), patchy liver enhancement, "claw-shaped" enhancement surrounding hepatic veins (white arrow, C), obscuring of hepatic main veins; D: Sagittal images. Stenosis of hepatic segmental inferior vena cava (white arrow) was indicated.

liver biopsy with hepatic venous pressure gradient (HVPG) provides valuable information. HVPG > 10 mmHg has > 90% specificity and > 85% positive predictive value for the diagnosis of HSOS following HSCT[48]. In a retrospective study, seven patients with PAs-induced HSOS underwent HVPG measurement, and they all had a significant increase in HVPG (mean value 23.50 ± 3.02 mmHg)[17]. However, this technique has not been widely used in many hospitals because it requires a dedicated setting and is expensive.

CRITERIA FOR DIAGNOSIS OF PAs-INDUCED HSOS

In clinical practice, the combination of history, clinical manifestation, laboratory data, imaging, biomarkers, and pathological findings has established diagnosis of diseases. Diagnosis of HSOS relies on history, clinical symptoms, laboratory examination, imaging, biomarkers, and liver histopathology. To date, most of the studies on diagnostic criteria of HSOS have focused on HSCT-related HSOS. The diagnosis of HSCT-related HSOS is largely based on history and the classical triad of weight gain, painful hepatomegaly, and jaundice. Symptoms of HSCT-related HSOS occur within 10 d after HSCT. Established clinical criteria, including modified Seattle[49] and Baltimore[50] criteria, require that patients must be within 21 d after HSCT to establish the diagnosis (Table 2). Cytoreductive therapy prior to HSCT is essential for diagnosis of HSOS. However, late onset HSOS/HVOD beyond day 21 has been reported. The researchers thus recommended including late onset HSOS/HVOD (beyond day 21) in HSCT-related HSOS[6].

Since clinical manifestations of the PAs-induced HSOS and HSCT-related HSOS are similar, some of the diagnostic criteria for PAs-induced HSOS have been developed according to those for HSCT-related HSOS (Table 2). History of PAs exposure is essential to establish the diagnosis. However, PAs exposure is always obscure, due to variability of the plant components, storage conditions for the plant products, mislabeling or misidentification of the plant, and outright contamination[5]. Fortunately, a serum biomarker derived from toxic PAs metabolites has been identified in patients with PAs-induced HSOS. PPAs are used as biomarkers of toxic PAs exposure. PPAs measured by ultra-performance liquid chromatography–tandem mass spectrometry are highly sensitive and specific for diagnosis of PAs-induced HSOS. Thus, the measurement of PPAs should be used together with the conventional HSOS clinical criteria for definitive diagnosis of PAs-induced HSOS. Given this, a history of PAs exposure, biomarkers, and clinical symptoms provide important evidence for the diagnosis of PAs-induced HSOS. Thus, the diagnostic criteria proposed by Gao *et al*[51] were as follows: (1) Meeting the criteria for drug-induced liver injury, Roussel Uclaf Causality Assessment Method score > 3; (2) Meeting the modified Seattle criteria for HSOS; and (3) A history of PAs exposure and detection of PPAs. These criteria (Table 2) have been used in some studies[37,45]. However, blood PPA concentrations decrease after 40 d exposure to PAs. Moreover, blood PPA concentration is related to the severity of HSOS, and PAs metabolites bind with multiple serum proteins that affect blood PPA concentration. All these confined the diagnostic value of PPA determination. More importantly, this assay is not performed in most hospitals.

Recently, some studies have described the imaging signs of PAs-induced HSOS and demonstrated the diagnostic value of the imaging techniques[39,42,44,45]. Histopathological findings provide confirmative evidence of PAs-induced HSOS. Thus, imaging techniques and liver biopsy were incorporated into the Nanjing Criteria[16] (proposed by the Chinese Society of Gastroenterology Committee of Hepatobiliary

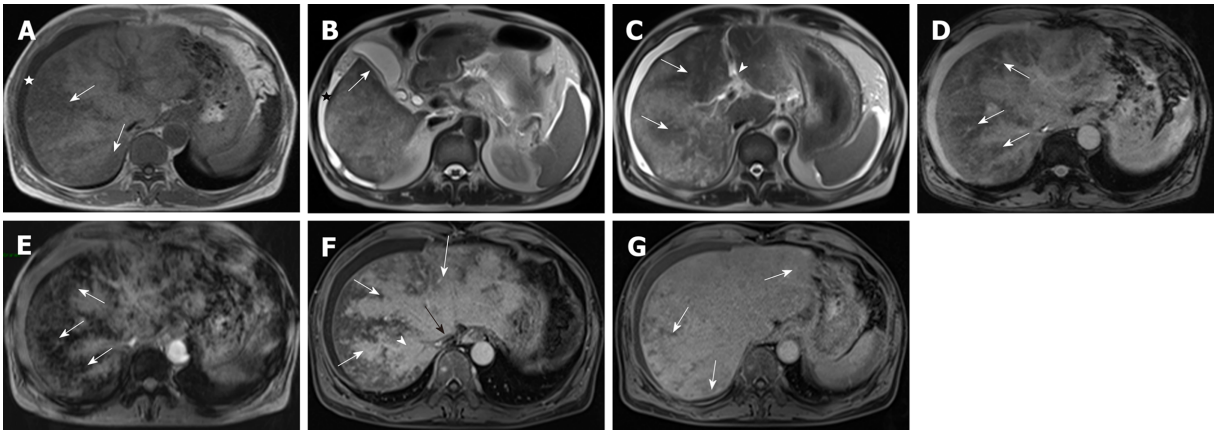

Figure 3 A 53-year-old man with pyrrolizidine alkaloids-induced hepatic sinusoidal obstruction syndrome (same patient) received gadoxetic acid-enhanced magnetic resonance imaging scan. A: T1-weighted imaging. Ascites (white star), heterogeneous hypointensity (white arrow) were shown; B and C: T2-weighted imaging. Imaging findings included ascites (black star, B), gallbladder wall thickening (white arrow, B), periportal edema (arrowhead, C), heterogeneous hypointensity (white arrow, C); D and E: T2*WI (D) and SWI (E). Heterogeneous hypointensity (white arrow) was observed, and distribution of hypointensity in SWI and T2*WI was similar; F: Image of portal venous phase. Patchy liver enhancement, "claw-shaped" enhancement surrounding hepatic veins (white arrow), stenosis of right hepatic vein (arrowhead) and inferior vena cava (black arrow); G: Image of hepatobiliary phase. Heterogeneous hypointensity (white arrow) was shown. SWI: Susceptibility-weighted imaging; T2*WI: T2*-weighted imaging.

Disease). However, prospective data on performance of Nanjing Criteria have not been provided until now, and further studies should be performed to evaluate their diagnostic performance in large sample sizes. Another important issue is the classification of staging and severity. Unfortunately, the natural course and severity of PAs-induced HSOS are still unknown, and relevant data are not available.

TREATMENT

Current management of PAs-induced HSOS is a challenge for hepatologists. Unfortunately, no definitive treatment for PAs intoxication is available. The therapeutic strategies for PAs-induced HSOS consists of termination of PAs exposure, symptomatic treatment, anticoagulant therapy, transjugular intrahepatic portosystemic shunt (TIPS), liver transplantation, *etc*. Importantly, different strategies should be performed in patients with PAs-induced HSOS according to disease severity and stage. In mild cases as spontaneous recovery occurs, symptomatic treatment is needed[52]. In severe cases, symptomatic treatment, anticoagulant therapy, TIPS, or liver transplantation should be performed.

Symptomatic treatment is important for PAs-induced HSOS and includes discontinued exposure to PAs, liver protection, and management of ascites. The latter consists of restriction of water and sodium supply, use of diuretics, albumin infusion, serial paracentesis, and TIPS. Oral furosemide and spirolactone are preferentially used for diuretic therapy. Albumin infusion is beneficial in patients with hypoalbuminemia. Serial paracentesis is recommended in patients who have poor response to diuretics. TIPS may be considered to control refractory ascites. Hemodialysis and mechanical airway protection may be required in HSOS patients with multiorgan failure.

Recent studies have demonstrated the beneficial effect of anticoagulant therapy in prevention of HSCT-related HSOS; however, a systematic review and meta-analysis showed negative results[53]. Recently, some studies have been performed to determine the effect of anticoagulant therapy on PAs-induced HSOS. In a retrospective study reported by Nanjing Drum Tower hospital, anticoagulant therapy (low molecular weight heparin combined with warfarin) significantly improved response rate of patients with PAs-induced HSOS compared with the non-anticoagulant group (60% *vs* 27%)[17]. A retrospective study from the first Affiliated Hospital of Zhengzhou University confirmed these results[37]. In addition, some of the studies demonstrated the effectiveness of anticoagulant therapy in Chinese journals[54-56]. Thus, Chinese guidelines recommend that anticoagulant therapy should be started as soon as possible in patients with acute/subacute HSOS after ruling out contraindications. Low molecular weight heparin is the anticoagulant of choice, either combined with or followed by oral administration of warfarin. The recommended dose of low molecular weight heparin is 100 IU/kg, every 12 h, subcutaneous injection. Warfarin is the

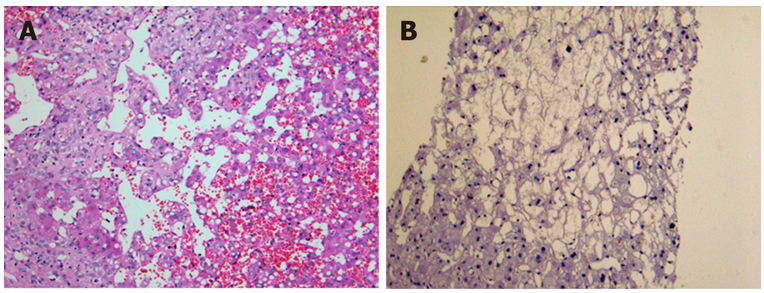

Figure 4 Pathology of pyrrolizidine alkaloids-induced hepatic sinusoidal obstruction syndrome. A: Acute stage (200 ×). Dilation and congestion of hepatic sinusoidals, the penetration of erythrocytes into the space of Disse; B: Subacute stage (200 ×). Complete loss of pericentral hepatocytes, sinusoidal dilatation.

preferred oral anticoagulant for long-term therapy, and the recommended international normalized ratio is 2.0-3.0, which may satisfy both the anticoagulant effect and safety. To date, prospective multicenter studies have not been performed to determine the effectiveness of anticoagulant therapy, thus large randomized control trials (RCTs) should be performed in future.

Defibrotide is the only approved drug for severe HSCT-related HSOS and HSCT-related HSOS with renal or pulmonary dysfunction in western countries[57]. Since defibrotide is not approved in China, its effectiveness remains unknown in patients with PAs-induced HSOS. Steroids have also been used in HSOS patients, and beneficial effects of early high-dose steroid therapy have been shown in severe pediatric HSCT-related HSOS[58], but adverse events such as infection should be considered. Although sporadic reports show the effectiveness of steroids in both PAs-induced HSOS patients and mouse models[59-61], the effectiveness of steroids for PAs-induced HSOS remains inconclusive and further RCTs should be performed.

TIPS may be considered when PAs-induced HSOS patients have refractory ascites or severe portal-venous hypertension. In a retrospective study, TIPS improved the prognosis of 29 patients who did not respond to symptomatic treatment plus anticoagulation[17]. While another retrospective study showed that TIPS failed to improve survival[37]. The efficacy of TIPS should be evaluated based on RCTs in the future. Liver transplantation can be considered in severe cases of PAs-induced HSOS with liver failure, and in theory, this should improve survival. Other treatments such as ursodeoxycholic acid, antithrombin III, and recombinant human thrombomodulin have been tried in HSCT-related HSOS, but the evidence in PAs-induced HSOS is lacking.

OUTCOME

The mortality rate of PAs-induced HSOS is reported to vary from 16% to 40%[17,26,37,45,51], and a common cause of death is liver failure[26,37]. A systematic review showed that increased total bilirubin and aspartate transaminase are indicators of poor survival in patients with PAs-induced HSOS[26]. A retrospective study of 117 cases demonstrated that hepatic encephalopathy, serum bilirubin, and albumin levels were major prognostic factors for *Gynura segetum*-induced HVOD[37]. In addition, Gao *et al*[51] demonstrated that PPA concentration was related to the severity and clinical outcome of PAs-induced HSOS.

CONCLUSION

The intake of PAs is one of the major etiological causes of HSOS in China. Here, we described the pathogenesis, clinical profiles, diagnostic criteria, treatment, and outcomes of patients with PAs-induced HSOS. Although progress has been made in PAs-induced HSOS, several issues remain to be resolved. A suitable animal model of PAs-induced HSOS should be established through repeated administration of PAs, which resembles the pathological status of PAs-induced HSOS in humans; the Nanjing criteria should be validated in prospective studies; disease severity grading should be developed; large-scale RCTs should be performed to determine the safety and efficacy of therapeutic strategies for PAs-induced HSOS; and prognostic factors should be accurately identified.

Table 2 Diagnostic criteria for hepatic sinusoidal obstruction syndrome

HSCT-related HSOS			PAs-induced HSOS		
Classical HSOS		Late onset HSOS (> 21 d after HSCT)	Criteria proposed by Gao *et al*[51]	Nanjing criteria[16]	
Modified Seattle criteria[49]	Baltimore criteria[50]	New EBMT criteria[6]			
Presence of 2 of the following criteria within 20 d after HSCT:	Presence of bilirubin ≥ 34.2 μmol/L within 21 d after HSCT and at least 2 of the following criteria:	Baltimore criteria beyond 21 d OR Histologically proven HSOS OR Presence of at least 2 of the following criteria: Bilirubin ≥ 2 mg/dL (34.2 μmol/L)	1 Meeting the modified Seattle criteria 2 Meeting the criteria for DILI 3 A history of taking PAs-containing herbs; detection of PPAs	A definite history of taking herbs containing PAs	
				Pathological evidence	Presence of the following three criteria 1 Abdominal distention and/or pain in the hepatic region, hepatomegaly, and ascites; 2 Increased serum total bilirubin or other abnormal liver function; 3 Typical contrast-enhanced CT or MRI findings
1 Bilirubin ≥ 34.2 μmol/L; 2 Hepatomegaly or right upper quadrant pain; 3 Weight gain > 2%	1 Hepatomegaly; 2 Ascites; 3 Weight gain > 5%	1 Hepatomegaly 2 Ascites 3 Weight gain > 5% AND hemodynamical or/and ultrasound evidence of HSOS	Other liver diseases were excluded		

HSCT: Hematopoietic stem cell transplantation; HSOS: Hepatic sinusoidal obstruction syndrome; HVOD: Hepatic veno-occlusive disease; PAs: Pyrrolizidine alkaloids; DILI: Drug-induced liver injury; PPAs: Pyrrole-protein adducts; CT: Computed tomography; MRI: Magnetic resonance imaging.

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ORIGINAL ARTICLE

Basic Study

Novel technique for endoscopic *en bloc* resection (EMR+) - Evaluation in a porcine model

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Author contributions: Meier B and Caca K have performed the *ex vivo* and *in vivo* experiments; Meier B has analyzed the data; Meier B, Andreas W and Christoph K have prepared the manuscript; and Caca K has approved the final version.

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Abstract

BACKGROUND

Endoscopic *en bloc* resection of larger polyps is relevant because risk of advanced neoplasia or malignancy correlates with tumor size. Recurrence rates after piecemeal endoscopic mucosal resection (EMR) are high and endoscopic submucosal dissection (ESD) is associated with higher complication rates in the western world.

AIM

To develop a modified endoscopic *en bloc* resection technique using an external additional working channel and novel agent for submucosal injection.

METHODS

EMR+ was considered as modified grasp and snare technique. For simultaneous use of a grasping and cutting device a novel additional working channel was used (AWC®, Ovesco Endoscopy, Tübingen, Germany). AWC® is installed on the outer surface of the endoscope, covered with a plastic sleeve and designed for single use. For submucosal injection a new agent consisting of poloxamers was used (LiftUp®, Ovesco Endoscopy, Tübingen, Germany). The agent is liquid at room temperature and forms a stable and permanent gel cushion after injection. Safety of LiftUp® has been shown in a pre-clinical study in domestic pigs. LiftUp® is commercially not yet available but approval is expected in early 2019. EMR+ was first developed *ex vivo* (explanted pig stomach) and subsequently evaluated *in vivo* (stomach, porcine model, 3 domestic pigs). Main outcome measurements were: Procedure time, macroscopic *en bloc* resection and adverse events.

RESULTS

Concept of EMR+ was first developed *ex vivo* (explanted pig stomach). *Ex vivo*, 22 resections were performed after technique was established. Median procedure time (measured from begin of injection to extraction of resection specimen) was 7 min (range 5-11, SD 1.68) and median size of resection specimens was 30 mm × 26

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mm × 11 mm *ex vivo*. Subsequently 13 resections were performed *in vivo* (stomach, porcine model, 3 domestic pigs). *In vivo*, median procedure time (measured from begin of injection to extraction of resection specimen) was 5 min (range 3-12, SD 2.72) and median size of resection specimens was 35 mm × 35 mm × 11 mm. *In vivo*, resection was macroscopic complete in 92.3%, major adverse events were not observed. In one case (7.7%) minor periprocedural bleeding was observed and managed by coagulation.

CONCLUSION
EMR+ appeared to be effective and safe and was easy and fast to perform in the porcine model. EMR+ needs to be further evaluated clinically in comparative trials.

Key words: Endoscopic resesection; *En bloc*; Additional working channel; Submucosal injection; LiftUp

Core tip: We report on a novel modified grasp and snare technique (EMR+) forendoscopic *en bloc* resection. The technique was developed *ex vivo* (explanted pig stomach) and evaluated *in vivo* in a porcine model (stomach, 3 domestic pigs). EMR+ includes a novel additional working channel (AWC®) and a new agent (consisting of poloxamers) for submucosal injection (LiftUp®, approval expected in early 2019). EMR+ appeared to be effective and safe in the stomach and allowed for *en bloc* resection for lesions up to 40 mm. EMR+ needs to be further evaluated clinically in comparative trials.

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INTRODUCTION

Endoscopic resection (ER) of larger polyps is relevant because risk of advanced neoplasia or malignancy correlates with tumor size. *En bloc* resection is essential because main predictors for recurrency are tumor size > 20 mm and piecemeal resection[1]. Endoscopic mucosal resection (EMR) is only adequate for *en bloc* resection for lesions < 20 mm[2]. Recurrence rates after *en bloc* EMR are low and reported down to 3%[3]. For lesions > 20 mm piecemeal EMR[4,5] or endoscopic submucosal dissection (ESD) are available. However, recurrence rates after piecemeal EMR are reported between 15%-45%[3,6,7] and ESD still is an advanced technique associated with higher risks for bleeding or perforation in the western world.

Submucosal injection is well investigated and essential for EMR and ESD. By injection a liquid-filled cushion is created, so tumor is lifted and amenable for ER plus underlying tissue is protected against bleeding and perforation[8,9]. Different injection agents have been investigated but saline solution still is the standard solution used for ER[9]. Major limitation of isotonic saline solution is its absorption by the adjacent mucosa. In consequence, submucosal cushion disappears quickly[8-10], frequent re-injections are necessary and prolonged procedure times are the consequences. Different viscous and hypertonic solutions have been investigated to prolong maintenance of submucosal cushion and to reduce procedure time[8,10-13]. However, every agent has merits and limitations so optimal agent still is not identified. LiftUp® (Ovesco Endoscopy, Tübingen, Germany) is a new developed agent for submucosal injection consisting of poloxamers. Viscosity of LiftUp® is temperature-dependent and liquid at room temperature. After injection LiftUp® forms a stable and permanent gel cushion.

Grasp and snare techniques using double channel (DC) endoscopes have been investigated to optimize EMR procedure for larger or difficult (*e.g.*, difficult location or reduced lifting-sign) lesions[14-17]. However, resection with DC endoscopes has not

come to daily routine as instruments are more expensive and not widely available. The novel additional working channel (AWC®, Ovesco Endoscopy, Tübingen, Germany) is installed on the endoscope externally and designed for single use.

The aim of this study was to develop a novel technique for endoscopic *en bloc* resection for lesions up to 30 mm. The technique was considered as modified grasp and snare technique and included a new injection agent (LiftUp®) and novel additional working channel (AWC®). The technique was developed *ex vivo* and evaluated *in vivo* (porcine model).

MATERIALS AND METHODS

Additional working channel and instruments

For simultaneous use of a grasping and cutting device an external additional working channel (AWC) was used (AWC®, Ovesco Endoscopy, Tübingen, Germany). AWC® is available (currently in Europe and United States) for endoscopes with diameters 8.5-13.5 mm and shaft lengths 122 cm/185 cm. The device is installed on the outer surface of the endoscope, covered with a plastic sleeve and designed for single use. After attachment AWC® allows use of an additional instrument with diameter up to 2.8 mm (Figure 1). An anchor device (OTSC® Anchor, Ovesco Endoscopy, Tübingen, Germany) was advanced through the conventional working channel and used to improve positioning of the resection snare. For resection an oval monofilament snare (Olympus) with diameter of 35 mm was used and advanced through the AWC.

Injection agent

For submucosal injection a new agent was used (LiftUp®, Ovesco Endoscopy, Tübingen, Germany). Safety of LiftUp® has been shown in a pre-clinical study in domestic pigs. LiftUp® is commercially not yet available. Approval of LiftUp® is pending and expected in early 2019 in Europe. LiftUp® consists of poloxamers (nonionic tensides) with temperature-dependent viscosity. The agent is sterile and premixed with methylene blue and has liquid consistency at room temperature which allows submucosal injection. At body temperature the agent gels within seconds and forms a stable and permanent cushion. LiftUp® was stored in a refrigerator (6-8 degrees celcius) just before submucosal injection. First, 2 mL of saline solution were injected into the submucosa to facilitate injection of LiftUp®. Injection of LiftUp® was performed with an inflation device (Inflation Device, Accura Medizintechnik GmbH, Germany) and conventional injection needle (diameter 0.7 mm).

Ex vivo model

EMR+ was developed *ex vivo* (October – December 2017). Explanted pig stomach was opened by incision (Figure 2A) and imaginary lesions were created by coagulation (Figure 2B) using a template (circular, diameter 30 mm). After preparation stomach was closed and connected to EASIE-R1 simulator (EndoSim, Bolton, United States) to be accessible to endoscopy (Figure 2C). Primary goal in this setting was to develop a concept of EMR+ (*e.g.*, positioning of instruments, injection/resection technique). EASIE-R 1 was filled with warm water and before resection the lesion (cushion) was additionally flushed with warm water endoscopically to ensure correct temperature. Before resection temperature was measured on the inner and outer surface of stomach.

In vivo model

After developing concept of EMR+ *ex vivo*, technique was transferred and evaluated *in vivo* (domestic pigs, April – July 2018). Main outcome measurements were: Procedure time, macroscopic *en bloc* resection and adverse events. *In vivo* study was conducted at the facility of experimental surgery of the University of Tübingen, Germany (Institut für experimentelle Chirurgie, Universitätsklinikum Tübingen, Tübingen, Germany) after approval from the local authority/institutional animal care and use committee (Regierungspräsidium Baden-Württemberg, Germany, approval number C1/15). Three domestic pigs with a median weight of 81.5 kg were used. The animals were fasted from solid food for 48 hours prior to surgery but were allowed full access to water and milk. Preanesthesia sedation consisted of ketamine 2 mg/kg and xylazine 2 mg/kg. General anesthesia was achieved using isoflurane, nitrous oxide and oxygen following endotracheal intubation. Continuous pulse oximetry and electrocardiogram were carried out throughout the procedure. All procedures were performed with the animal in supine position. With the animal under general anesthesia, gastric lavage was performed and imaginary lesions were created by coagulation using a template (circular, diameter 30 mm). The template was introduced into the stomach endoscopically and extracted after coagulation. After

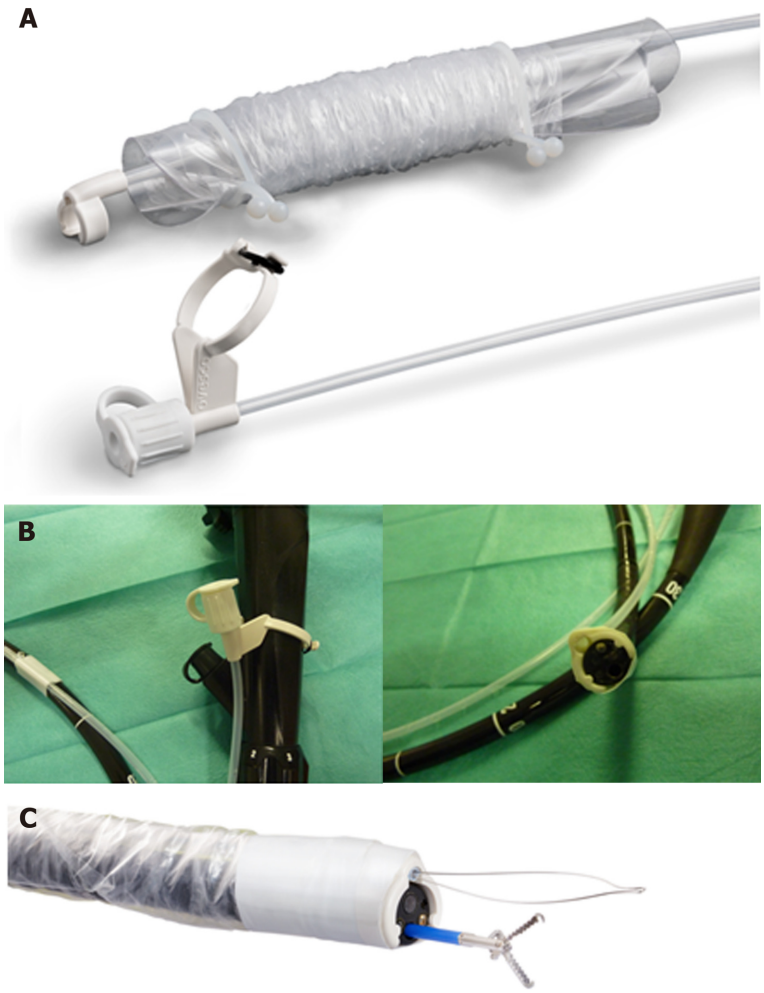

Figure 1 Illustration of AWC®. Distal and proximal site uninstalled (A) and installed (B). C: Fully installed AWC® with advanced grasp and snare device.

resection, specimens were stretched and pinned onto a histology platform and examined for size and resection margins. Complications were managed endoscopically. Periprocedural bleeding was managed by coagulation, perforations were managed by OTSC application. In the first animal additional laparotomy was used to further evaluate EMR+. One animal was used for several resections. All animals were euthanized immediately after the resections using intravenous pentobarbital.

RESULTS

Ex vivo model

EMR+ was developed *ex vivo* (Figure 3). Resections were performed in the area of the greater curvature (endoscope in a relatively straight position). Initially, 2 ml of saline solution were injected into the submucosa to facilitate injection of LiftUp®. Then 5-8 mL of LiftUp® were used for submucosal injection to elevate the lesions (Figure 3A). The snare was advanced through the AWC. The anchor device (advanced through the conventional working channel) was used to improve positioning of the snare (Figure 3B). The lesion was pulled with the anchor and snare was closed (Figure 3C). Before resection the lesion was pushed back using the anchor to avoid perforation (Figure 3D). Using this protocol, 22 resections were performed *ex vivo* (Figure 4, Video 1). Median time for injection was 3 min (range 2-5, SD 0.86) and measured from injection to complete lifting of lesion and flushing with warm water. Median time for resection was 4 min (range 2-9, SD 1.57) and measured from snare opening to extraction of resection specimen. Median time of EMR+ (injection and resection) was 7 min (range 5-11, SD 1.68). Median size of specimen was 30 mm × 26 mm × 11 mm and ranged

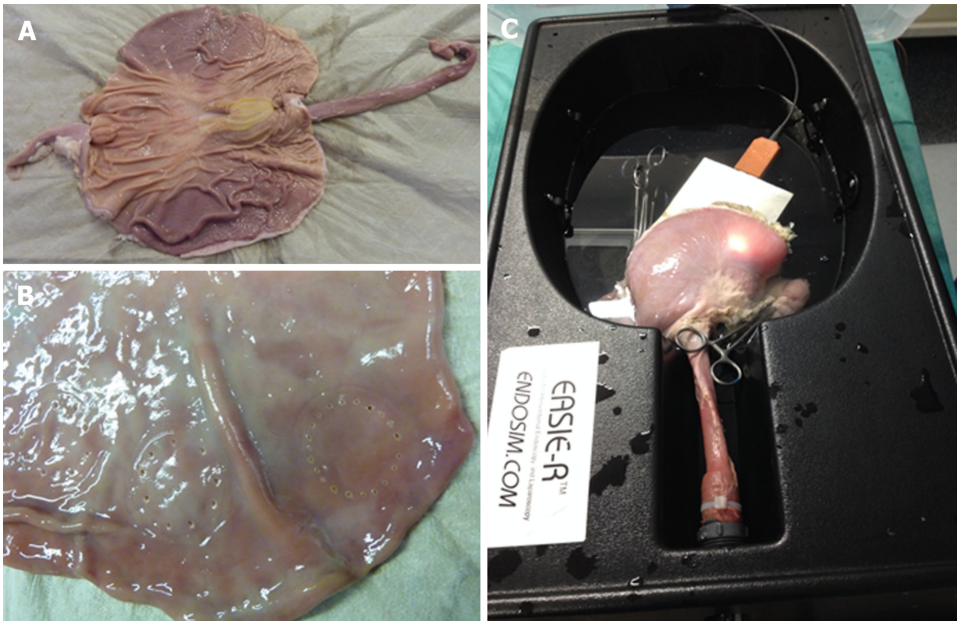

Figure 2 ***Ex vivo*** **model.** A: Opened pig stomach; B: Circular coagulation; C: Stomach connected to EASIE-R1 simulator.

between 22 mm × 20 mm × 7 mm to 40 mm × 33 mm × 14.4 mm (Table 1).

In vivo

After EMR+ was developed *ex vivo* the technique was transferred and evaluated *in vivo* (three domestic pigs). Resections were performed in the area of the greater curvature (endoscope in a relatively straight position). In the first animal perforations were observed due to excessive use of the anchor (Figure 3C). Perforations were managed by OTSC application. In consequence, laparotomy was used to further evaluate endoscopic technique in the same animal. It was observed that it is essential to push back the lesion with the anchor before resection (Video 2). The "Push Back" maneuver avoids inversion of the muscular layer into the lumen and subsequently protects from perforation (Figure 3D). After developing this last essential step of EMR+ *in vivo* no further perforations were observed.

13 resections were performed *in vivo* (animal two and three). Illustration of resection specimens and resection technique is shown in Figure 5 and Video 3. Median time for injection was 2 min (range 1-6, SD 1.23) and measured from injection until complete lifting of lesion. Median time for resection was 3 min (range 2-10, SD 2.47) and measured from snare opening to extraction of resection specimen. Median time of EMR+ (injection and resection) was 5 min (range 3-12, SD 2.72). Median size of specimen was 35 mm × 35 mm × 11 mm and ranged between 30 mm × 30 mm × 12 mm to 40 mm × 38 mm × 13.5 mm. Resection was macroscopic complete in 12/13 cases (92.3%). Major adverse events were not observed. In one case (7.7%) minor periprocedural bleeding was observed and managed by coagulation (Table 2).

DISCUSSION

This study describes a novel resection technique for endoscopic *en bloc* resection (EMR+). The technique was considered as modified grasp and snare technique and included two major components. For submucosal injection a new agent (LiftUp®, Ovesco Endoscopy, Tübingen, Germany) with temperature-dependent viscosity was used. Efficacy and safety of LiftUp® has been shown recently in a preclinical study[18]. Once injected, LiftUp® forms a stable and permanent gel cushion which allows ER without re-injection. The agent is not yet commercially available but approval is pending and suspected in early 2019 in Europe. For resection a novel additional working channel (AWC®, Ovesco Endoscopy, Tübingen, Germany) was used. Successful clinical use of AWC® has been reported recently[19]. AWC® allows use of an additional working tool and is installed on the endoscope externally. Resection was performed as grasp and snare technique and included simultaneous use of an anchor device and monofilament resection snare. EMR+ was first developed and evaluated *ex vivo* (explanted pig stomach) and later transferred and evaluated *in vivo* in domestic pigs. In this study, EMR+ allowed for *en bloc* resection specimens up to 40 mm in

Table 1 Results of endoscopic mucosal resection *ex vivo*

Resection	Specimen L × B × H (mm)	Time injection[1] (min)	Time resection[2] (min)	Time EMR+ (min)
1	30 × 27 × 10	4	7	11
2	25 × 24 × 10.4	3	3	6
3	30 × 24 × 9.2	3	3	6
4	22 × 20 × 7	4	3	7
5	31 × 25 × 13.3	3	3	6
6	35 × 25 × 11.6	2	4	6
7	34 × 29 × 12.7	2	3	5
8	40 × 33 × 14.4	3	2	5
9	29 × 25 × 8.8	3	4	7
10	32 × 26 × 10.3	4	3	7
11	30 × 25 × 11.4	3	2	5
12	30 × 26 × 9.6	2	9	11
13	30 × 28 × 12,4	2	4	6
14	25 × 22 × 8.5	3	4	7
15	30 × 29 × 10.5	5	3	8
16	36 × 30 × 13.5	3	4	7
17	33 × 30 × 16.6	4	5	9
18	32 × 28 × 14.4	2	5	7
19	25 × 25 × 12.7	3	4	7
20	26 × 22 × 6.5	4	5	9
21	29 × 29 × 11.5	4	4	8
22	37 × 30 × 10.1	2	4	6
Median	30 × 26 × 11	3	4	7

[1]Time from injection to complete lifting of lesion and flushing with warm water.
[2]Time from snare opening to extraction of resection specimen (all resections were performed in the area of the greater curvature).

diameter (median size *ex vivo*: 30 mm × 26 mm × 11 mm, median size *in vivo*: 35 mm × 35 mm × 11 mm). *In vivo*, macroscopic complete resection could be achieved in 92.3%. Median procedure time was fast (5 min *in vivo*). After developing final concept of EMR+ major adverse events were not observed. In one case (7.7%) minor periprocedural bleeding was observed *in vivo* and managed by coagulation.

Endoscopic *en bloc* and R0-resection is essential for adequate treatment of mucosal neoplasia and prevention of recurrency. However, EMR only is adequate for lesions > 20 mm and ESD is associated with higher risks for complications, especially in the western world. In consequence, new techniques for endoscopic *en bloc* resection for lesions > 20 mm are needed. Ideal resection technique should be effective and safe but as well fast and easy to perform.

Submucosal injection is essential for EMR and ESD. Different injection agents have been investigated but saline solution still is the standard solution used for ER[9]. Major limitation of isotonic saline solution is its fast absorption by the adjacent mucosa. To facilitate and maintain cushion formation other viscous and hypertonic solutions such as hydroxyethyl starch, sodium hyaluronate solution, 50% dextrose or succinylated gelatin have been investigated[8,10-13] but optimal agent is not defined or identified. Using viscous and hypertonic solution resulted in lower volumes to inject[10-12], longer duration of submucosal elevation and shorter procedure times[10,11] compared to saline solution. A recent meta-analysis (five randomized controlled trials, 504 patients) showed higher rates of *en bloc* resection and lower rates of residual lesions compared to saline solution when viscous and hypertonic solutions were used for EMR and polyps > 20 mm[9]. Rates of adverse events were similar.

Other agents with temperature-depended viscosity have been developed and investigated. Combination of hyaluronic acid, chondroitin sulfate and poloxamer 407 (Ziverel, Norgine, United Kingdom) showed prolonged submucosal elevation and absence of tissue damaging in a porcine model[20]. Combination of water, medium chain triglycerides, sodium chloride, polyoxyl-15-hydroxystearate and poloxamer 188 (Eleview®, Cosmo pharmaceuticals NV, Dublin, Ireland) showed prolonged submucosal elevation and safe application for EMR/ESD in preclinical[21] and clinical[22] trials. However, prolonged submucosal elevation (described up to 60 min)

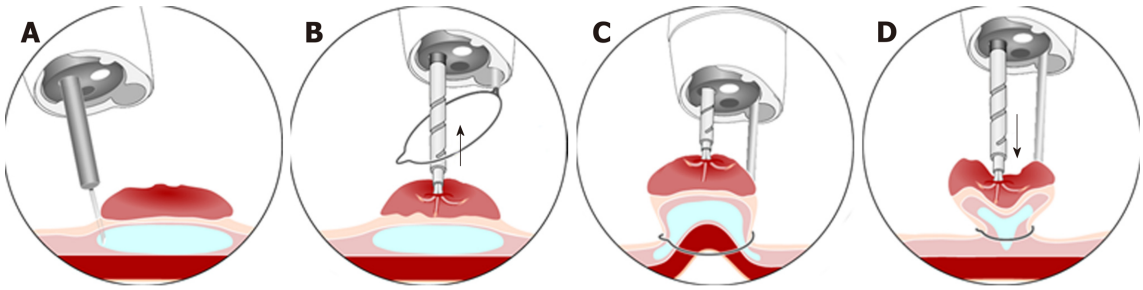

Figure 3 Illustration of endoscopic mucosal resection. A: Submucosal injection; B: Positioning of anchor device and snare; C: Lesion is pulled with anchor device and snare is closed; and D: Lesion is pushed back ("Push Back maneuver") and snare fully closed. Lesion is ready for resection.

could not be confirmed clinically. Submucosal elevation was observed for 1-15 min and for ESD re-injections were still necessary[22]. Eleview® is approved as injection agent for ER in USA and Europe. In a recent study, Eleview® was compared with saline solution in a randomized double-blind setting[23]. Patients undergoing EMR for ≥ 20 mm colorectal non-pedunculated lesions were randomized 1:1 and 226 patients were included (mean lesion size 32 mm ± 12.4 mm). In the Eleview® arm total volume needed for EMR was significantly lower (approximately reduction of 50%). A trend for faster procedure times and higher *en bloc* resection rates was observed under Eleview® but statistical significance was not reached. Remarkably, macroscopic complete *en bloc* resection was only observed in 18.6% (Eleview®) *vs* 10.9% (saline solution). Rate of adverse events were similar in both arms. The agent for submucosal injection used in our study (LiftUp®) is comparable to Ziverel and Eleview® as agent includes poloxamers. In our *ex vivo* model duration of submucosal elevation using LiftUp® was observed for approximately one hour. However, submucosal lifting was not examined systematically and might be biased by inconsistent conditions of temperatures in the *ex vivo* model. *In vivo*, duration of submucosal lifting was not measured because study was focused on resection technique. The required volumes of LiftUp® were comparable to volumes of Eleview® used in the porcine model of Spadaccini *et al*[21].

Grasp and snare techniques have been investigated to optimize EMR procedure for lesions > 20 mm and were first described in 1976[24]. Double channel (DC) endoscopes allow simultaneous use of two different tools e.g. grasping device and resection snare. Using this technique, lesions in difficult locations or lesions with reduced lifting after submucosal injection can be resected[14-17]. The technique also allows reducing procedure time[25]. However, resection with DC endoscopes has not come to daily routine as instruments are more expensive and not widely available. The novel additional working channel (AWC®) used in our study provides an alternative option using two different endoscopic tools simultaneously. AWC® is designed for single use and installed on the endoscope externally. Different installations of AWC® allow variable positions of both working channels in contrast to DC endoscopes. Our modified grasp and snare technique (EMR+) could be accomplished with AWC® without observing technical problems.

Our study has strengths and limitations. Major strength of our study is a systematic development of a modified grasp and snare resection technique (EMR+) using two novel components (LiftUp® and AWC®). Major aim of this study was to develop a novel technique for endoscopic *en bloc* resection and proofing concept *in vivo*. Imaginary lesions had to be created in the stomach by circular coagulation. Major limitation of our study is the resection of regular mucosa in contrast to apparent mucosal neoplasia. Morphological features of lesions or existing fibrosis have a high impact on resectability. In consequence, clinical studies are needed to further evaluate EMR+. Notably, comparative trials (*e.g.*, EMR+ *vs* ESD or EMR+ *vs* EMR with AWC® or EMR+ *vs* EMR with LiftUp®) are needed to further evaluate potential advantage of EMR+ over other resection techniques.

In conclusion, EMR+ is a novel modified grasp and snare technique for endoscopic *en bloc* resection. The technique includes two novel components (LiftUp® and AWC®) and was evaluated *in vivo* (porcine model). The technique appeared to be effective and safe and was easy and fast to perform in the porcine model. EMR+ needs to be further evaluated clinically in comparative trials.

Table 2 Results of endoscopic mucosal resection *in vivo*

Resection	SpecimenL × B × H (mm)	Time injection[1] (min)	Time resection[2] (min)	Time EMR+ (min)	Adverse events	Macroscopic complete
1	40 × 35 × 10	2	6	8	-	Yes
2	40 × 35 × 11	6	3	9	-	Yes
3	40 × 38 × 13	2	6	8	-	Yes
4	40 × 38 × 13	2	10	12	-	Yes
5	30 × 30 × 12	2	6	8	-	No
6	35 × 35 × 11	2	4	6	-	Yes
7	40 × 40 × 11	2	2	4	-	Yes
8	35 × 35 × 9	1	2	3	-	Yes
9	35 × 35 × 13	2	2	4	-	Yes
10	35 × 38 × 10	3	2	5	-	Yes
11	40 × 35 × 14	1	2	3	-	Yes
12	35 × 35 × 9	2	3	5	Minor bleeding[3]	Yes
13	35 × 35 × 8	2	2	4	-	Yes
Median	35 × 35 × 11	2	3	5	-	-

[1]Time from injection to complete lifting of lesion.
[2]Time from snare opening to extraction of resection specimen (all resections were performed in the area of the greater curvature).
[3]Management by coagulation.

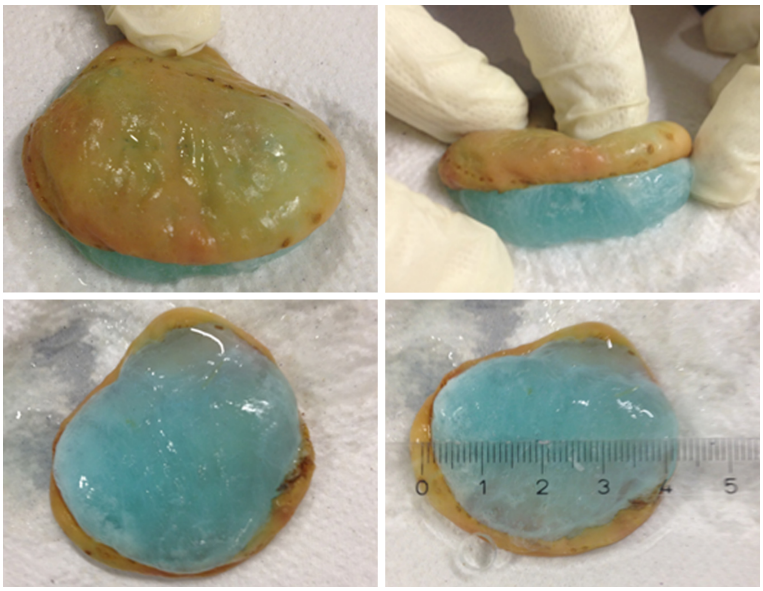

Figure 4 Example of endoscopic mucosal resection specimens (*ex vivo* model).

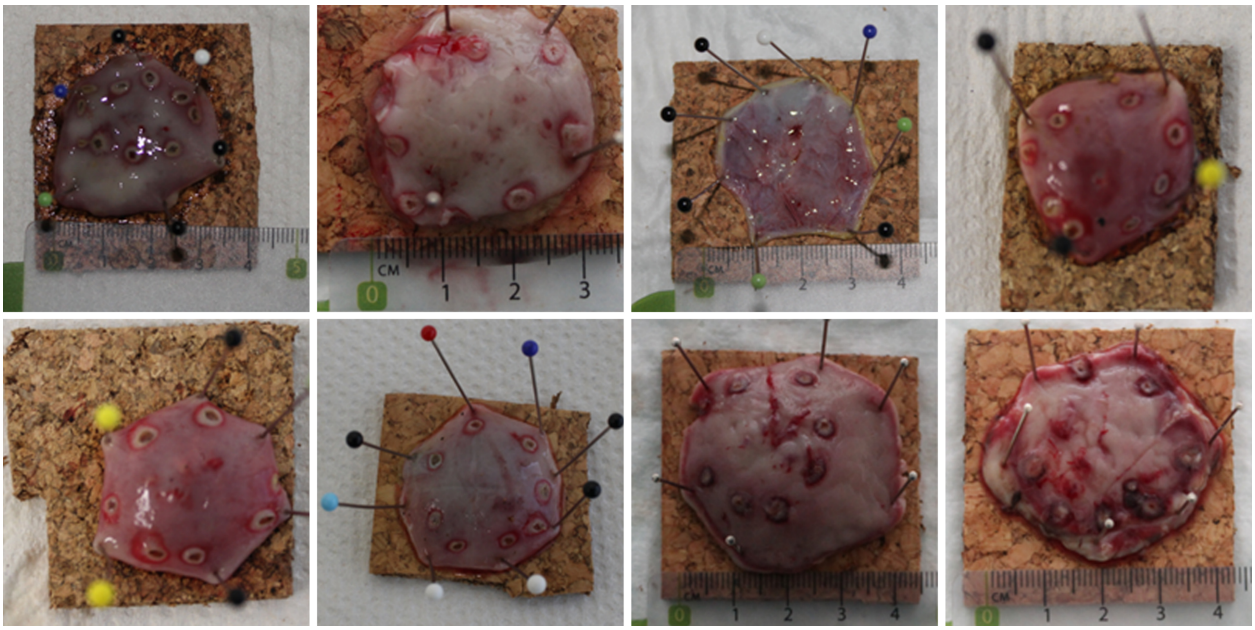

Figure 5 Example of endoscopic mucosal resection specimens (*in vivo* model).

ARTICLE HIGHLIGHTS

Research background

Endoscopic *en bloc* and R0-resection is essential for adequate treatment of mucosal neoplasia. EMR is fast and safe but only adequate for lesions up to 20 mm of size. For lesions > 20 mm ESD is available. However, especially in the western world this technique might not be widely available and associated with higher risks for complications and longer procedure times.

Research motivation

To provide a fast and safe *en bloc* resection technique for lesions > 20 mm we developed a modified grasp and snare technique (EMR+) in a porcine model. We presumed that a novel technique might be interesting especially when ESD expertise is not available.

Research objectives

Major objective was to develop an effective, safe and fast technique for endoscopic *en bloc* resection for lesions > 20 mm of size.

Research methods

EMR+ was first (October – December 2017) developed *ex vivo* in an explanted pig stomach. The technique included two novel components and was considered as a modified grasp and snare technique. We used an additional working channel (AWC®, Ovesco Endoscopy, Tübingen, Germany) to facilitate simultaneous application of a resection and grasping device. For submucosal injection we used a new agent with temperature-dependent viscosity (LiftUp®, Ovesco Endoscopy, Tübingen, Germany). EMR+ was then (April – July 2018) further evaluated *in vivo* (porcine model, stomach).

Research results

During the study period, 22 resections were performed *ex vivo* and 13 resections were performed *in vivo*. Median procedure time was fast (7 min *ex vivo*, 5 min *in vivo*) and median size of resections specimens was 30 mm × 26 mm × 11 mm/35 × 35 × 11 mm *ex vivo*/*in vivo*. Resection was macroscopically complete *in vivo* in 92.3%. Major adverse events were not observed.

Research conclusions

EMR+ is a novel modified grasp and snare technique for endoscopic *en bloc* resection. The technique allowed safe and fast resection for lesions > 20 mm of size and was easy to perform in the porcine model. The novel injection agent allowed for sufficient protection of the muscular layer. Major limitation of our study was resection of regular mucosa in the stomach (imaginary lesions were created by circular coagulation).

Research perspectives

To better define the role of EMR+ clinical and comparative trials are needed. Further studies need to address resection of apparent mucosal neoplasia in different anatomic locations.

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ORIGINAL ARTICLE

Basic Study

MiR-205 mediated APC regulation contributes to pancreatic cancer cell proliferation

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Abstract

BACKGROUND

Pancreatic cancer is a deadly malignancy with aggressive properties. MicroRNAs (miRNAs) participate in the pathogenesis of a variety of diseases and molecular processes by targeting functional mRNAs. Nevertheless, the regulatory role of miRNAs in signaling pathways involved in pancreatic cancer remains largely unknown.

AIM

To explore the molecular regulation involved in pancreatic cancer and potential mechanisms of miR-205.

METHODS

Microarray analysis was performed to investigate the expression profile of miRNAs in pancreatic cancer. Expression of miR-205 was validated by qRT-PCR. Target prediction and functional enrichment analysis were employed to seek potential target genes of miR-205 and potential functions of these genes. The target binding of miR-205 and adenomatous polyposis coli (APC) was validated by luciferase reporter assay. APC protein expression in pancreatic cancer was validated by qRT-PCR and Western blot. Proliferation was evaluated by MTT and colony formation assays.

RESULTS

A large number of miRNAs with altered expression were identified in pancreatic cancer. MiR-205 was significantly up-regulated. APC was found to be a validated target of miR-205 and down-regulated in pancreatic cancer. Proliferation experiments showed that miR-205 could promote cell proliferation in pancreatic cancer by targeting APC.

CONCLUSION

The above findings suggested that miR-205 mediated APC regulation contributes

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to pancreatic cancer development, which could be considered as a novel prognostic biomarker for clinical care.

Key words: Pancreatic cancer; Microarray; MiR-205; Adenomatous polyposis coli; Proliferation

Core tip: A large number of microRNAs with altered expression were identified in pancreatic cancer. MiR-205 was found to be significantly up-regulated in pancreatic cancer. Adenomatous polyposis coli (APC) was found to be a validated target of miR-205 and down-regulated in pancreatic cancer. Proliferation experiments showed that miR-205 could promote cell proliferation in pancreatic cancer by targeting APC.

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INTRODUCTION

Pancreatic cancer is a severe malignancy with a five-year survival rate of less than 5% worldwide, due to its late detection, metastasis, and resistance to treatment such as chemotherapy and radiation therapy[1-3]. There are over 60 types of genetic mutations in pancreatic cancer according to previous studies, and these mutations have been related to several signaling pathways. Nevertheless, the regulation of these pathways in pancreatic cancer remains largely unknown[4-6]. Therefore, the exploration of molecular mechanisms involved in pancreatic cancer will be necessary and useful to improve its current therapy status.

In recent years, microRNAs (miRNAs) are emerging as important regulators in cancer development and play important roles in many physiological and pathological processes such as tumor growth, biosynthesis, immune regulation, and drug resistance[7-9]. MiR-205 has been found to play a role in various cancers[10,11], but there has been no relevant report in pancreatic cancer. Adenomatous polyposis coli (APC) is a tumor suppressor protein that is involved in biological processes including transcriptional activation, apoptosis, cell migration, and cell adhesion[12,13]. Besides, APC has been found to have an important role in pancreatic cancer in a previous study[14].

In the present study, microarray analysis was used to explore the differentially expressed miRNAs in pancreatic cancer. It was found that miR-205 was up-regulated in both pancreatic cancer tissue samples and cell lines, whereas APC was significantly down-regulated. Target prediction of miR-205 showed that there are potential targets that are involved in various signaling pathways. Furthermore, we confirmed that miR-205 could promote cell proliferation in pancreatic cancer by targeting APC *in vitro*. Taken together, our findings suggest that miR-205 might be used as a potential therapeutic target in human pancreatic cancer.

MATERIALS AND METHODS

Study participants and cell lines

Human pancreatic cancer tissue samples before treatment and adjacent healthy pancreatic tissue samples were obtained from Handan Central Hospital with patients' consent and were histologically verified. This study was approved by Handan Central Hospital and was performed in accordance with the Helsinki Declaration. HPDE6 (control) and SW1990/PANC-1/BXPC-3 cell lines were purchased from Tianjin Saier Biotechnology Company (Tianjin, China) and maintained in identical conditions with 10% fetal bovine serum (FBS) (Sigma, MO, United States).

Cell culture and transfection

Cells were cultured in RPMI 1640 (Hyclone, CA, United States) supplemented with FBS, streptomycin, and penicillin in a humidified chamber at 37 °C. Transfection was performed using Lipofectamine 2000 reagent in accordance with the manufacturer's instructions. The transfection efficiency was assessed by detecting the fluorescence of red fluorescent protein expressed by the transfection vector.

Microarray and bioinformatics analysis

The cancer samples and controls were analyzed through Agilent microRNA microarray (v14.0). First, the raw data presented as gProcessedSignal were normalized. The differential expression was filtered by fold change > 2 and *P*-value < 0.05, and all bioinformatics computations were performed using R script[15]. The prediction of miRNA targets was performed with miRDB[16] and targetScan[17]. Functional analysis was performed with KOBAS[18] software.

Luciferase reporter assay

The 3'-untranslated region (UTR) of APC containing miR-205 binding sites was cloned into the pGL3-Basic luciferase vector (Promega, Madison, United States) to generate APC wild type (wt) and mutated to generate APC mutant (mut). After transfection, cells were incubated in suitable conditions for 24 h. The activity of luciferase was measured using the Luciferase Reporter Assay Kit (Promega, Madison, United States) in accordance with the manufacturer's instructions.

Quantitative real-time reverse-transcription PCR

In accordance with the manufacturer's protocol, total RNA was isolated from each sample with Trizol (Invitrogen, CA, United States) and treated with DNase I (Invitrogen, CA, United States) to remove residual DNA. Then, RNA was reverse-transcribed into cDNA. MiRNAs were reverse-transcribed using the Mir-XTM miRNA Synthesis Kit (Clontech, Shanghai, China) according to the manufacturer's protocol. For miRNA targets, the primary transcript levels were determined with the SYBR Green Master. The sequence-specific primers for the target genes were retrieved from PrimerBank database. MiRNAs and mRNAs were normalized into U6 and GAPDH, respectively.

Western blot assay

Pancreatic cancer cells were lysed in ice-cold lysis buffer using the protein-extraction reagent (Roche, Mannheim, Germany). To determine the concentration of total protein, BCA Protein Assay (ThermoFisher, Shanghai, China) was used. According to the manufacturer's protocol, Western blot analysis was performed with antibodies specifically against APC and GAPDH (Proteintech, China). The experiment was independently repeated three times.

MTT and colony formation assays

After 24 h transfection of miR-205 mimic and inhibitor, cells were put into 96-well plates for 12 h at a density of 3×10^3 viable cells/well. MTT assay was conducted on a spectrophotometer (Shimadzu, Columbia, SC, United States) at 490 nm to observe cell viability. For colony formation assay, the treated cells were plated and cultured in 6-well plates for 2 wk. After paraformaldehyde (Saier Biotechnology, Tianjin, China) was applied to these cells, the number of colonies was counted as cells were stained with crystal violet (Saier Biotechnology, Tianjin, China).

RESULTS

Overview of patient subjects

A total of 52 pancreatic cancer patients who received examination during their stay in Handan Central Hospital from July 2014 to November 2017 were collected. After ruling out other relevant diseases, 41 patients aged < 87 years were included in the experiment group, including 16 women and 25 men. The age, height, weight, and tumor stage were recorded as shown in Table 1.

Expression profiling of miRNAs in pancreatic cancer tissues shows that miR-205 is up-regulated

To explore the pancreatic cancer-related miRNAs, microarray analysis was performed on five cancer tissue samples and five healthy control samples. The data demonstrated that a list of miRNAs were differentially expressed in pancreatic cancer ($P < 0.05$, fold change ≥ 2) (Figure 1A), including 79 up-regulated and 128 down-regulated miRNAs. Furthermore, we sorted out top 20 differentially expressed miRNAs with relatively large differences, including miR-205-3p, miR-216a, miR-216b,

Table 1 Basic characteristics of pancreatic cancer patients

Variable	Patients
Age (yr)	57.21 ± 4.36
Height (cm)	165.08 ± 3.12
Weight (kg)	56.89 ± 6.94
Tumor stage (%)	
T1-T2	91 (n = 37)
T3-T4	8 (n = 4)

Note: The data above are expressed as the mean ± SD.

miR-148b, miR-30a, miR-6130, miR-155, miR-5704, miR-222, miR-221, miR-21, miR-631, miR-181a, miR-6754-3p, miR-6817-5p, miR-3928-5p, miR-6805-5p, miR-199a-3p, miR-4726-5p, and miR-6845-3p. The hierarchical clustering analysis was performed to demonstrate their expression patterns, as shown in Figure 1B. Among these miRNAs, miR-205 expression level was significantly increased in pancreatic cancer and there has been no relevant report about its mechanisms of action.

Tumor-promoting effect of miR-205 in pancreatic cancer cells in vitro

To further verify the miR-205 expression level, qRT-PCR was performed on patient samples and three pancreatic cancer cell lines as described in the Methods section. MiR-205 showed increased expression in cancer samples compared with healthy tissues (n = 41 each; Figure 2A). Similarly, miR-205 also showed an increased expression level in three pancreatic cancer cell lines compared with HPDE6 cells (Figure 2B). MTT assay was performed in PANC-1 cells and control cells, and the results demonstrated that miR-205 overexpression in PANC-1 cells could notably increase the growth rate while an opposite result was observed in miR-205 down-regulated PANC-1 cells, as shown in Figure 2C. We then performed colony formation assay to assess its potential impact on cell proliferation. The results showed that proliferation of PANC-1 cells was increased after transfection with miR-205 mimic, as shown in Figure 2D. Collectively, these findings demonstrated that miR-205 may exert a tumor-promoting effect in pancreatic cancer.

MiR-205 target prediction and functional analysis

In order to investigate the molecular mechanism of miR-205, we performed target prediction and functional enrichment analysis of the targets using bioinformatics tools. A total of 168 targets were mapped to KOBAS database and subjected to GO/pathway analysis. According to the GO enrichment results, these genes participate in the regulation of cellular components, biological processes, and molecular functions. The bar chart shows that these genes are related to plasma membrane part, cell projection, and neuron part in the cellular components category, and are involved in signaling, cell communication, and developmental process in the biological processes category. Moreover, the molecular functions category showed that these genes mainly play a role in signaling and transmembrane receptor activity (Figure 3). According to the pathway analysis results, the target genes are related to cytokine-cytokine receptor interaction, regulation of IFNA signaling, and the TGF-β signaling pathway (Figure 4). Furthermore, we noticed that APC is a potential target of miR-205, which has been discovered to play an important role in the development of pancreatic cancer.

APC is down-regulated in pancreatic cancer

We evaluated the expression level of APC in HPDE6 and three pancreatic cancer cell lines by qRT-PCR assay. Lower expression of APC was observed in pancreatic cancer cell lines but not in HPDE6 cell line (Figure 5A). Meanwhile, we also evaluated the protein level of APC in these cell lines using Western blot analysis, and the results demonstrated that APC protein level was notably decreased in pancreatic cancer cell lines (Figure 5B). Since APC showed an opposite expression pattern with miR-205, it might be a potential target of miR-205.

MiR-205 promotes cell proliferation in pancreatic cancer cells by targeting APC

To confirm that APC is a target of miR-205, luciferase reporter assay was performed. The 3′-UTR of APC wild-type or mutant was cloned, as shown in Figure 6A. The results indicated that miR-205 mimic could dramatically decrease the luciferase activity of wild-type vector, but had no effect on the mutant (Figure 6B) in PANC-1

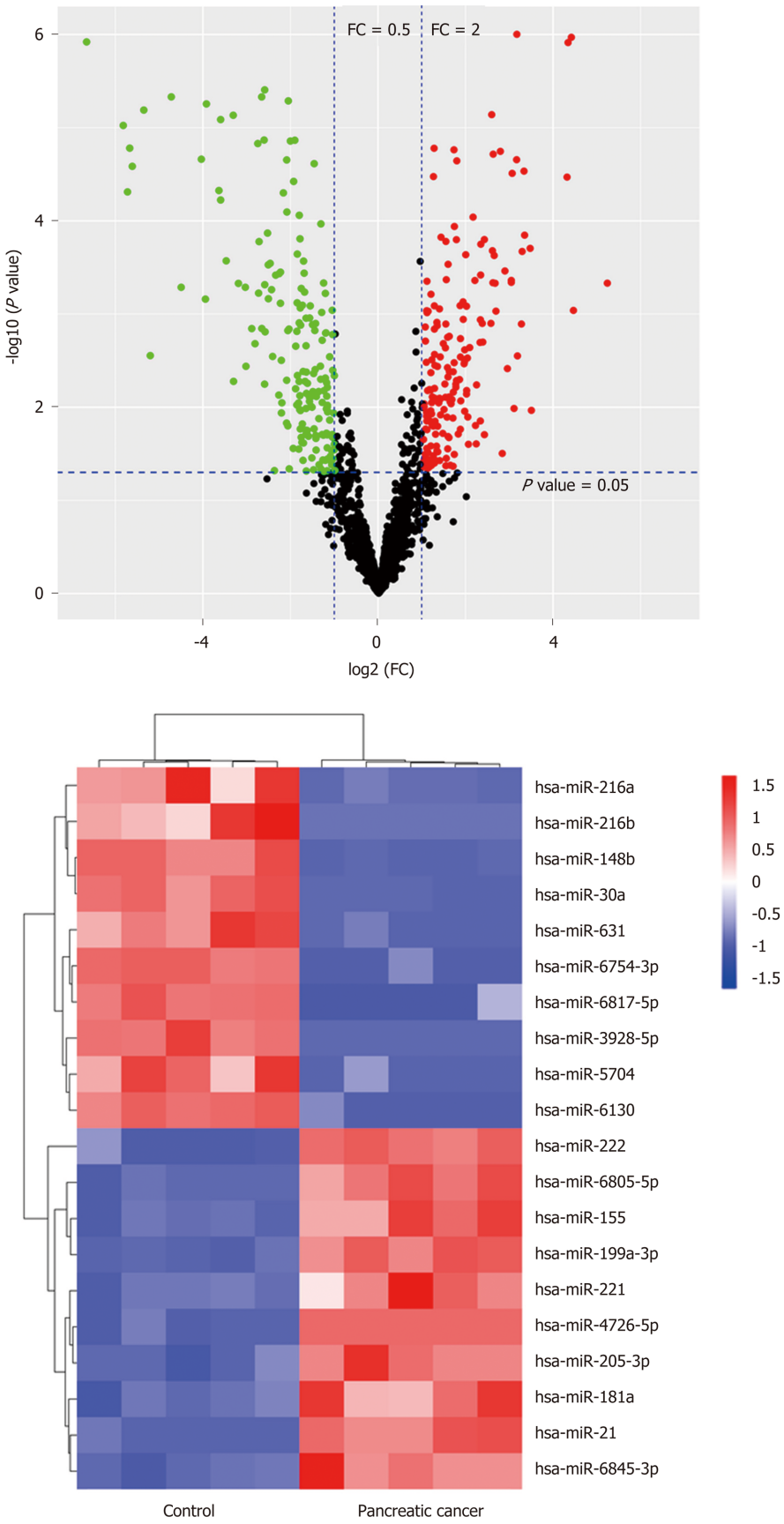

Figure 1 The miRNA expression profile in pancreatic cancer. A: The volcano plot was constructed using *P*-values and fold change values; B: The clustered heatmap showed the top 20 differentially expressed miRNAs between the control and pancreatic cancer groups. Red indicates the up-regulated expression and green/blue indicates the down-regulated expression.

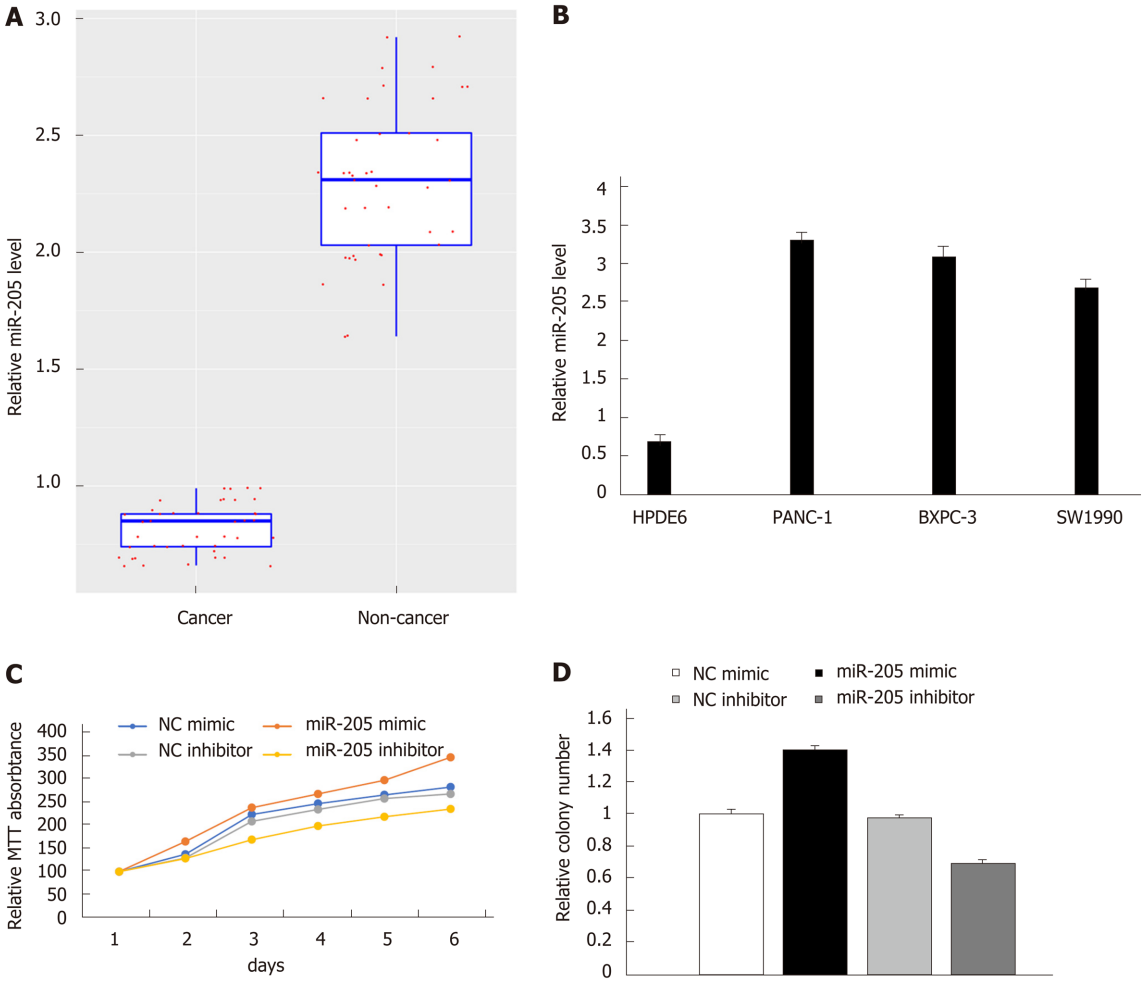

Figure 2 Detection of expression of miR-205 in pancreatic cancer tissues and cell lines by qRT-PCR. A: MiR-205 was up-regulated in pancreatic cancer tissues (n = 41); B: MiR-205 was up-regulated in pancreatic cancer cell lines (PANC-1, BXPC-3, and SW1990) compared with normal human pancreatic duct epithelial cell line HPDE6 (P < 0.05); C: MTT assay. Cell viability was significantly increased in cells with overexpression of miR-205 compared with control cells in a time-dependent manner; D: Colony formation assay. The effect of miR-205 overexpression on cell proliferation was evaluated.

cells. Furthermore, we found that APC mRNA level in miR-205 mimic treated PANC-1 was decreased while an opposite result was observed in miR-205 inhibitor treated cells (Figure 6C). Since APC protein was reported to participate in the development of pancreatic cancer, MTT assay was then carried out in APC overexpressing PANC-1 cells, and the results demonstrated that the promoting effect of miR-205 on pancreatic cancer cell proliferation was reduced (Figure 6D and E). These results indicated that miR-205 directly inhibits APC expression by binding to its 3′-UTR in pancreatic cancer cells. Moreover, miR-205 promotes the proliferation of pancreatic cancer cells by targeting APC.

DISCUSSION

Pancreatic cancer, an aggressive malignancy with a five-year survival rate of less than 5%[2], is a multi-genic disease that develops in a stepwise manner. The treatment of pancreatic cancer is often very difficult due to the impact of drug resistance and metastasis[1]. MiRNAs are a group of small, non-coding RNA molecules, which have been investigated as novel therapeutic targets in cancer[19]. The main mechanism for miRNAs to exert their function is down-regulating the expression or inducing degradation of target genes by binding to the 3′-UTR of target genes in mammals[8,17].

Microarray assay is a convenient and efficient technique to explore the genome-wide gene expression[20]. In this study, 207 miRNAs were found to be abnormally expressed in pancreatic cancer by microarray analysis, including 79 up-regulated and 128 down-regulated miRNAs. These aberrantly expressed miRNAs may provide valuable resources for cancer research. Among these miRNAs, several miRNAs have

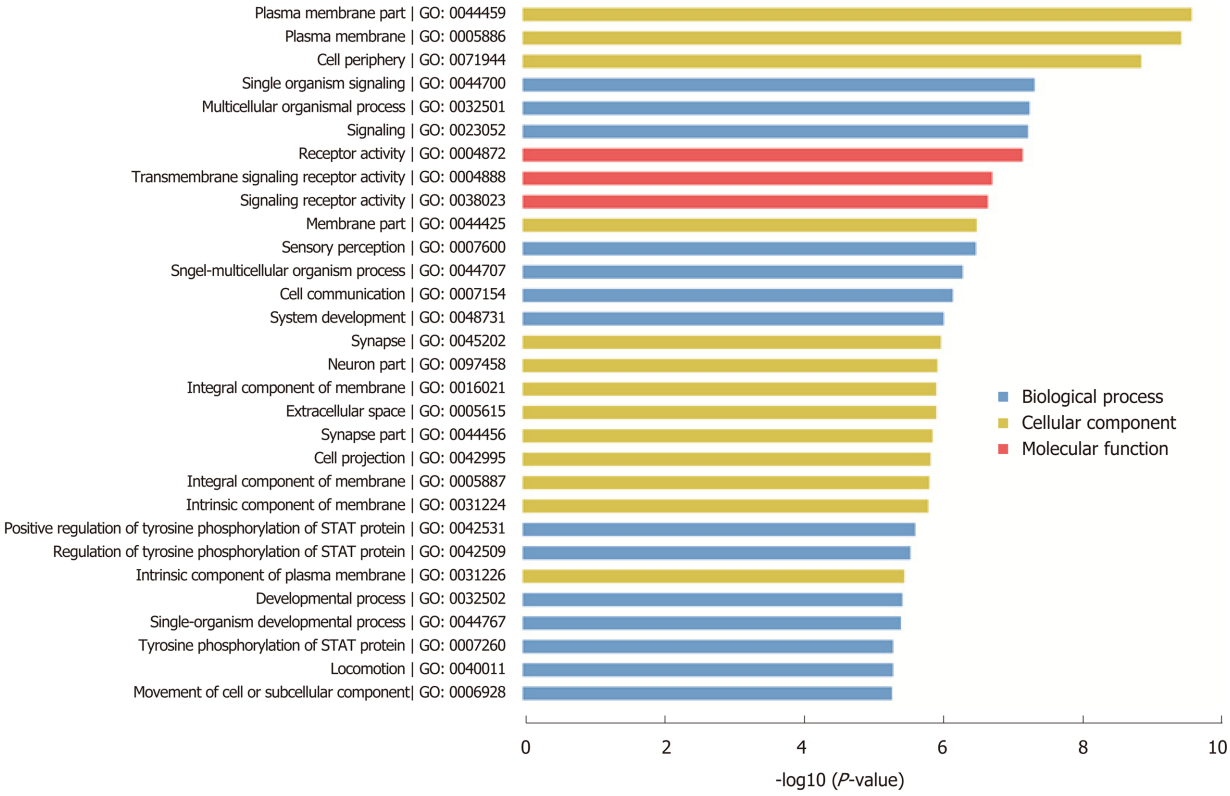

Figure 3 GO pathway analysis of the target genes of miR-205.

been studied in previous research. For instance, miR-216 was identified to be down-regulated in pancreatic cancer, which is consistent with previous result[21], and miR-221 was found to promote proliferation and enhance cell cycle progression[22]. MiR-205 was found to play a role in various cancers, including breast cancer and prostate cancer[10,11], but there has been no relevant report in pancreatic cancer. We found that miR-205 showed increased expression in pancreatic cancer and could promote cell proliferation *in vitro*. The target prediction of miR-205 and functional enrichment analysis of the targets identified the genes involved in various functions and pathways, including cytokine−cytokine receptor interaction, regulation of IFNA signaling, the Wnt signaling pathway, and the TGF-β signaling pathway. Among them, the Wnt signaling pathway was demonstrated to regulate crucial aspects of cell fate determination, cell migration, and organogenesis. A previous study found that mutations cause Wnt pathway activation in human cancers[23]. As one of the miR-205 targets, APC acts as a tumor suppressor protein and participates in transcriptional activation, apoptosis, cell migration, and cell adhesion[12,13]. We confirmed that miR-205 promoted cell proliferation by targeting APC in pancreatic cancer.

In summary, our results revealed the expression profile of miRNAs in pancreatic cancer. The expression of miR-205 was up-regulated in pancreatic cancer whereas APC was significantly down-regulated. Target prediction of miR-205 and KOBAS enrichment analysis identified the genes involved in various functions and pathways. Furthermore, we confirmed that miR-205 could promote cell proliferation in pancreatic cancer by targeting APC. Our findings provide informative knowledge for the potential therapeutic use of miR-205 in human pancreatic cancer.

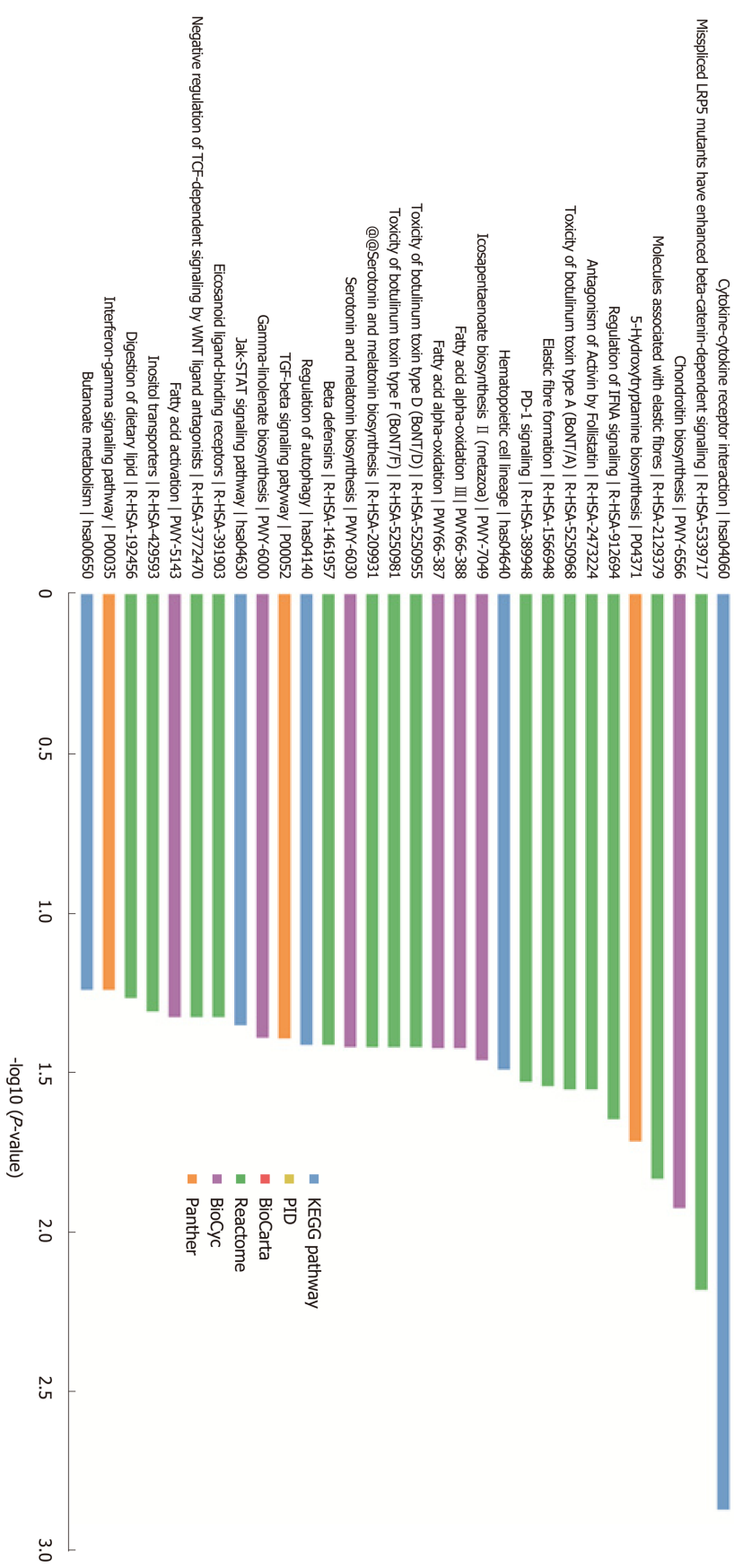

Figure 4 Pathway analysis of the target genes of miR-205.

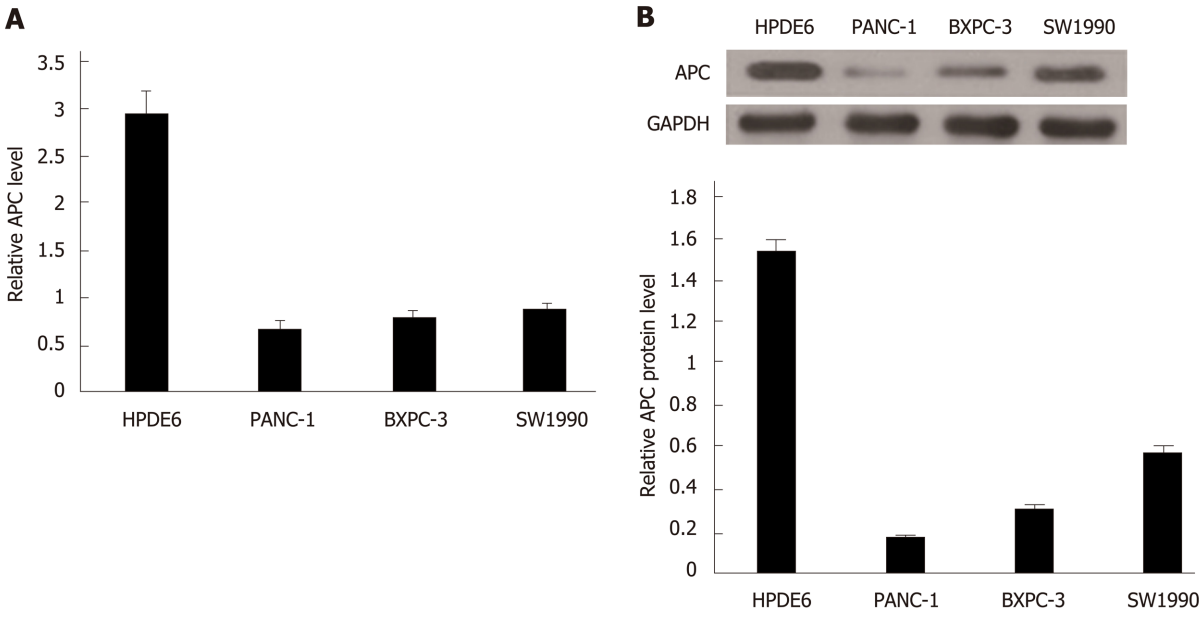

Figure 5 Expression of adenomatous polyposis coli in pancreatic cancer cell lines. A: mRNA level; B: Protein level, $P < 0.05$. APC: Adenomatous polyposis coli.

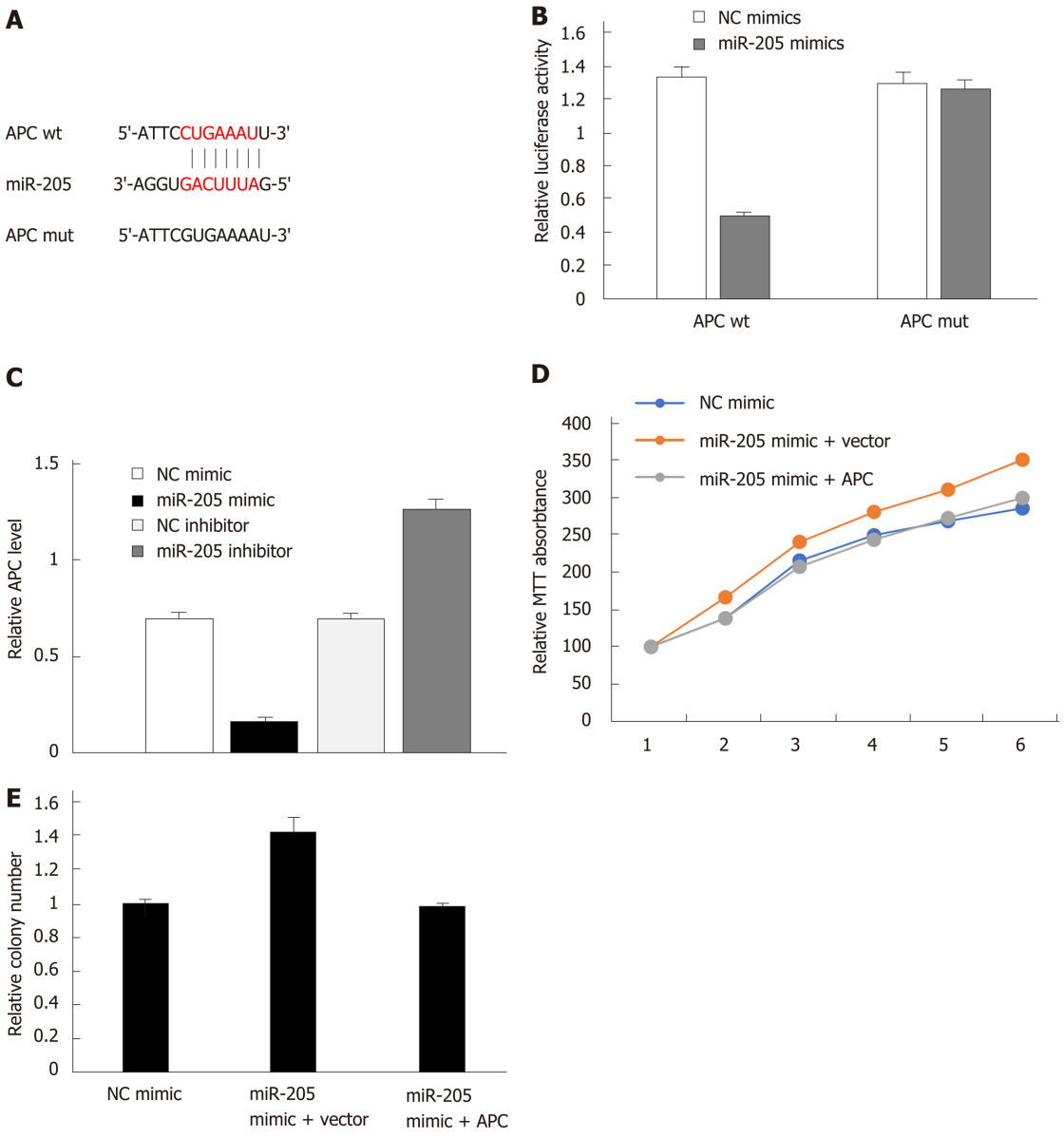

Figure 6 MiR-205 promotes proliferation of pancreatic cancer cells by targeting adenomatous polyposis coli. A: Predicted binding sites of miR-205 in adenomatous polyposis coli (APC). The fragment of wild-type or mutant 3'-UTR of APC was cloned into the luciferase reporter vector; B: Luciferase activities measured at 48 h post transfection; C: APC mRNA expression was decreased in miR-205 mimic treated PANC-1 cells but increased in miR-205 inhibitor treated cells; D and E: The promoting effect of miR-205 on proliferation was reduced in pancreatic cancer cells overexpressing APC, as measured by MTT and colony formation assays. APC: Adenomatous polyposis coli; wt: Wild-type; mut: Mutant.

ARTICLE HIGHLIGHTS

Research background

Pancreatic cancer is known as a deadly malignancy in the world, and a sufficient treatment for the disease has not been found yet. We aimed to explore the regulatory mechanisms of microRNAs (miRNAs) in pancreatic cancer.

Research motivation

As a group of non-coding RNAs, miRNAs were found to paly important roles in human disease. In this study, we aimed to explore the miRNAs involved in pancreatic cancer and potential regulatory mechanisms of miR-205, which may contribute to pancreatic cancer treatment.

Research objectives

MiRNA expression pattern in pancreatic cancer and potential regulatory mechanisms of miR-205 and adenomatous polyposis coli (APC) were analyzed. The findings may contribute to clinical care of pancreatic cancer.

Research methods

Microarray analysis was used to explore the genome-wide miRNA expression profile in pancreatic cancer. QRT-PCR and Western blot were performed to validate gene expression. Bioinformatics analysis was performed to predict target genes and their potential functions. Dual luciferase reporter assay was used to validate the binding of miR-205 and APC. Proliferation was evaluated by MTT and colony formation assays.

Research results

A large number of differentially expressed miRNAs were identified in pancreatic cancer. MiR-205 was significantly up-regulated while APC was down-regulated in pancreatic cancer. Dual luciferase reporter assay showed that APC is a validated target of miR-205. Moreover, miR-205 could promote cell proliferation in pancreatic cancer by targeting APC.

Research conclusions

This study, for the first time, revealed that miR-205 mediated APC regulation contributed to pancreatic cancer development. Microarray analysis was used to fully disclose the genome-wide miRNAs expression profile in pancreatic cancer. Proliferation experiment showed that miR-205 could promote cell proliferation in pancreatic cancer cells by targeting APC, which could be considered as novel prognostic biomarkers for future clinical care.

Research perspectives

The aberrantly expressed miRNAs identified in pancreatic cancer may provide valuable resources for future cancer research.

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ORIGINAL ARTICLE

Case Control Study

Comparison of outcomes between complete and incomplete congenital duodenal obstruction

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Author contributions: Gfroerer S, Theilen TM, Esmaeili A, and Rolle U contributed to study conception and design, acquisition, analysis and interpretation of data, and final approval of the version of the article to be published; Gfroerer S drafted of the article; Theilen TM, Esmaeili A, and Rolle U contributed to critical revisions related to the important intellectual content of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the University Hospital Frankfurt.

Informed consent statement: Patients and parents were not required to give informed consent for the study because the analysis used anonymous data that were obtained after the completion of treatment.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

STROBE statement: The guidelines of the STROBE Statement have been adopted.

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Abstract

BACKGROUND

Congenital duodenal obstruction (CDO) can be complete (CCDO) or incomplete (ICDO). To date there is no outcome analysis available that compares both subtypes.

AIM

To quantify and compare the association between CCDO and ICDO with outcome parameters.

METHODS

We retrospectively reviewed all patients who underwent operative repair of CCDO or ICDO in our tertiary care institution between January 2004 and January 2017. The demographics, clinical presentation, preoperative diagnostics and postoperative outcomes of 50 patients were compared between CCDO (n = 27; atresia type 1-3, annular pancreas) and ICDO (n = 23; annular pancreas, web, Ladd´s bands).

RESULTS

In total, 50 patients who underwent CDO repair were enrolled and followed for a median of 5.2 and 3.9 years (CCDO and ICDO, resp.). CCDO was associated with a significantly higher prenatal ultrasonographic detection rate (88% versus 4%; CCDO *vs* ICDO, $P < 0.01$), lower gestational age at birth, lower age and weight at operation, higher rate of associated congenital heart disease (CHD), more extensive preoperative radiologic diagnostics, higher morbidity according to Clavien-Dindo classification and comprehensive complication index (all $P \leq 0.01$). The subgroup analysis of patients without CHD and prematurity showed a longer time from operation to the initiation of enteral feeds in the CCDO group

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($P < 0.01$).

CONCLUSION
CCDO and ICDO differ with regard to prenatal detection rate, gestational age, age and weight at operation, rate of associated CHD, preoperative diagnostics and morbidity. The degree of CDO in mature patients without CHD influences the postoperative initiation of enteral feeding.

Key words: Congenital duodenal obstruction; Duodenal atresia; Duodenal stenosis; Prenatal ultrasonographic detection rate; Clinical presentation; Preoperative diagnostics; Adverse events; Outcome

Core tip: Outcomes of complete congenital duodenal obstruction (CCDO) and incomplete (ICDO) have rarely been compared. The present study is the first to report on this issue based on a series of patients who represent a broad spectrum of pathologies in either group. The current results show significant differences between CCDO and ICDO with regard to prenatal detection rate, preoperative diagnostics, postoperative enteral feeds, length of hospital stay and morbidity according to Clavien-Dindo classification and the comprehensive complication index.

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INTRODUCTION

Congenital duodenal obstruction (CDO) accounts for approximately one-half of all intestinal obstructions in newborns and is reported to occur in 1 of 2500 to 10000 births[1,2]. CDO represents a spectrum of congenital anomalies. Corresponding duodenal pathologies are subdivided into congenital duodenal anomalies with either complete or incomplete obstruction (Figure 1). Complete congenital duodenal obstruction (CCDO) originates from duodenal atresia type 1 to 3 and annular pancreas. Incomplete congenital duodenal obstruction (ICDO) occurs on the basis of a web (perforated diaphragm), Ladd´s bands, annular pancreas, preduodenal portal vein, superior mesenteric artery syndrome and duplication cyst. CCDO is diagnosed antenatally to a varying degree based on the detection of a characteristic double bubble sign. However, ICDO is most often missed during prenatal ultrasound examination[3]. The overall neonatal survival rate of patients with CDO has gradually increased over past few decades[4]. Survival is currently reported to be approximately 96%[5,6]. Mortality is primarily attributed to complex congenital heart disease (CHD)[4]. Delayed transition to full enteral nutrition has been associated with CHD and prematurity[5]. In addition to CHD and prematurity influencing the postoperative course, there is limited evidence that the degree of duodenal obstruction may have an impact on postoperative outcome[7]. However, to date an outcome analysis comparing subgroups of patients with CCDO and ICDO is not yet available. The aim of this study was to clarify differences in clinical outcomes between CCDO and ICDO.

MATERIALS AND METHODS

After approval of study protocols by the local institutional review board committee (number 85/17), we conducted a retrospective analysis of a series of 50 consecutive patients with CCDO or ICDO, as identified through International Classification of Diseases (ICD-10, Version 2017) codes, who underwent operative repair between January 2004 and January 2017 at our institution. Data including demographic data, preoperative clinical presentation and findings, pathologic findings, operative variables, postoperative outcomes and individual profile of postoperative adverse

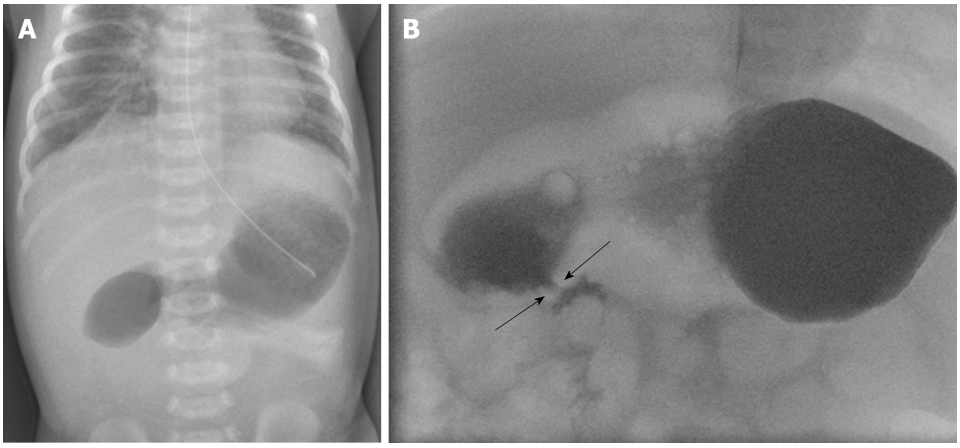

Figure 1 Radiographic images of complete and incomplete congenital duodenal obstruction. A: Complete congenital duodenal obstruction, the plain abdominal X-ray of a newborn infant with duodenal atresia type 1 displays a characteristic double bubble sign; B: Incomplete congenital duodenal obstruction, contrast study of a 2 month old infant with duodenal web (arrows).

events, were retained in a database. Demographics included gender, gestational age at birth, age at operation, weight at operation and associated anomalies. Clinical presentations were specified and comprised vomiting, failure to thrive, intolerance of age-appropriate per oral intake, constipation, postprandial discomfort, acute life-threatening event and intolerance to solid food. Failure to thrive was defined as a child´s weight being below the 5th percentile, a drop of more than 2 major percentile lines, or a weight for height being lower than the 5th percentile[8]. Constipation was defined according to the Diagnostic Criteria for Functional Constipation (Rome IV)[9]. Preoperative diagnostics to indicate operative repair were plain abdominal X-ray, upper gastrointestinal (UGI) contrast study and gastroduodenoscopy. Pathologies of CCDO were allocated to diagnoses of atresia type 1 (membrane), atresia type 2 (fibrous cord), atresia type 3 (gap)[10] and annular pancreas. The findings of ICDO were assigned to annular pancreas, web and Ladd´s bands. Additional intestinal pathologies were specified by the following diagnoses: Intestinal malrotation, second distal stenosis and Meckel´s diverticulum. Intestinal malrotation was present when the duodenal loop and the cecocolic loop lacked their normal 270° counterclockwise rotation. Operative variables included operative time (abdominal incision to close of the abdominal wound; including time for correction of additional abdominal pathologies), operative procedures and additional operative procedures. In cases of malrotation where the dorsal peritoneal mesenteric fixation appeared narrow and put the bowel at risk for the development of a volvulus, Ladd´s procedure was performed. The question of whether to proceed with an appendectomy was an individual decision of the surgeon. The attending senior surgeon determined the operative approach. Laparoscopic repair of CDO was performed by the first author in patients weighing > 1700 g at operation. The operative approach was implemented irrespective of preoperative radiologic findings or associated congenital anomalies. Open access for CDO repair was achieved *via* a transverse right upper quadrant incision. Laparoscopic CDO repair was performed using a transumbilically placed 5 mm 30° camera and two 3.5 mm working trocars, one placed in the upper left quadrant and the second in the right mid abdomen. For duodenoduodenostomy, predominantly diamond-shaped anastomoses were performed; simple oblique[11] and parallel anastomoses[12] were also recently used depending on the individual duodenal anatomy. Tapering duodenoplasty was not performed in either group. All open procedures were performed by, or under the direct supervision of, the first, third or last author. Details of postoperative outcomes included the following parameters: time from operation to initiation of feeds (day of initiation of feeds was the day on which feeding per orally or via nasogastric tube was initiated); time from operation to full feeds (day of achievement of full feeds was the day on which parenteral nutrition was ceased); length of postoperative hospital stay (not including the day of operation, but including the day of discharge); reoperation rate (reoperation was defined as a repetition of a surgical operation undertaken due to lack of success of the first attempt). All postoperative adverse events were recorded in detail per patient and scored according to Clavien-Dindo classification[13]. The Clavien-Dindo classification consists of 7 grades (I, II, IIIa, IIIb, IVa, IVb and V); it focuses on the therapeutic consequences of the single most severe complication occurring in a patient in a given episode. In addition the comprehensive complication

index (CCI) was calculated. The CCI represents a sensitive measure of the overall morbidity in a single score achieved by inclusion of all complications after surgery[14]. The CCI ranges from 0 (no complication) to 100 (death) and was calculated using the CCI calculator available online (www.assessurgery.com).

Postoperative care and follow up

A nasogastric tube was left postoperatively for gastric decompression. All patients with an enterotomy were allowed nothing by mouth on the day of operation and were allowed to receive enteral feeding on postoperative day 1. All patients without an enterotomy were allowed to receive enteral feeding on the day of operation. After commencement of enteral feeding, all patients received nutritional increments based on clinical observations, irrespective of the operative approach. Green gastric fluid postoperatively during preprandial routine aspiration of the nasogastric tube in an otherwise unremarkable clinical course was regarded as a normal finding due to the insufficient closure of the pyloric muscle, and feeding increments were continued. UGI contrast studies were not performed on a routine basis postoperatively. Patients underwent clinical outpatient follow-up within 4 wk after discharge. All patients were scheduled for regular follow-up at least once per year.

Statistical analysis

A biomedical statistician performed the statistical review of the study. For the summary of normal distributed continuous variables, the mean and standard deviation were calculated. For comparison, we used two-sample *t*-tests. Continuous data with another type of distribution or an unknown distribution are presented as median with range, and the Wilcoxon rank sum test was applied for comparison. We used Fisher's exact test to compare categorical variables. Testing was done based on a 5% significance level. Median follow-up was calculated using the reverse Kaplan-Meier estimate. We used statistical software R version 3.4.0 for analysis, R Foundation for Statistical Computing, Vienna, Austria (www.R-project.org).

RESULTS

A total of 50 patients underwent surgical repair of CDO. The patient cohort consisted of a group of 27 patients with CCDO and 23 patients with ICDO. Table 1 displays demographic data and the associated congenital anomalies of both groups. Patients with CCDO that underwent operative repair had a lower gestational age at birth, younger age and lower weight at operation, and had a higher rate of associated CHD. Figure 2 displays the absolute frequencies of operative repairs with the corresponding age at operation for 50 patients with CCDO or ICDO. Of the patients with ICDO, 48% (n = 11) were operated beyond the neonatal period. Patients´ diagnoses of this subgroup (n = 11) were Ladd´s bands (n = 6), duodenal web (n = 4) and annular pancreas (n = 1). Of the patients with ICDO, 13% underwent primary operative repair at 3.4 years or later. This late repair affected all pathologies of ICDO that were evident in this study. Table 2 compares the rates of prenatal ultrasonographic detections of CCDO and ICDO and lists preoperative diagnostics. Of patients with CDO, 49 of 50 had fetal ultrasound screening (98%). One pregnancy did not have prenatal maternal care. The overall prenatal detection rate of CDO was 49% (24 of 49 patients). For patients with CCDO, the prenatal detection rate was 88%; it was 4% for ICDO ($P \leq 0.01$). In all patients with CCDO, preoperative plain abdominal X-ray was sufficient to indicate operative repair. In contrast, all patients with ICDO received a diagnostic UGI contrast study in which 4 patients (17%) underwent an additional diagnostic gastroduodenoscopy to indicate operation. In all patients with prenatally unsuspected CDO (complete group n = 4; incomplete group n = 22), postnatal clinical presentations were studied. Vomiting was the most frequent recorded preoperative finding (n = 24, 92%). All patients who vomited showed a yellow-greenish to green discoloration of the vomit at some point between birth and operation, as observed by parents or nursing staff. Table 3 displays intraoperative pathologic findings in the CCDO and ICDO group. Table 4 compares operative variables of the CCDO and ICDO group. Operative time was similar in both groups. Duodenoduodenostomy was the most frequent procedure in both the CCDO group (93%) and the ICDO group (35%, $P < 0.01$). Duodenal freeing from obstructive ligaments and the Ladd´s procedure were both performed as a single or an adjunct surgical maneuver. Table 5 shows variables of postoperative outcomes for patients with CCDO or ICDO. Durations from operation to initiation and completion of enteral feeds and length of hospital stay were longer in the CCDO group. Morbidity according to median (range) CCI was higher in the CCDO group [8.7 (0.0-100) *vs* 0.0 (0.0-33.7 in the ICDO group, $P<0.01$)]. In an attempt to reduce confounding a subgroup analysis was performed and

outcome parameters were additionally calculated under exclusion of patients with CHD and prematurity. Subgroup analysis revealed a difference between the CCDO and ICDO groups with regard to the parameter time from operation to initiation of feeds. Table 6 lists all adverse events recorded during the entire individual follow-up period for 50 patients undergoing operative repair of CCDO or ICDO.

DISCUSSION

Our study suggests that outcomes of patients with CCDO and ICDO differ significantly. This article, to our knowledge, is the only paper focusing specifically on differences between patients with CCDO and ICDO. According to our results, patients with CCDO had a significantly higher prenatal detection rate, lower gestational age at birth and lower age and weight at operation. Operative repair in the CCDO group was indicated solely on the basis of a plain abdominal X-ray without the need for UGI contrast study. Patients with CCDO had a higher rate of associated CHD, had a longer duration from operation to both initiation and achievement of full feeds, had a longer hospital stay and had a higher morbidity according to Clavien-Dindo classification and CCI in comparison to patients in the ICDO group. In a subgroup of patients without associated CDH and prematurity patients with CCDO had a delayed initiation of enteral feeds in comparison with the ICDO group.

Our study is the first to deliver a differentiated prenatal detection rate of CCDO and ICDO based on an analysis of patients who underwent operative repair. While the overall detection rate was 48% we found a significant difference between CCDO and ICDO (detection rate 88% *vs* 4% respectively). Previously, several authors have conducted studies analyzing prenatal ultrasonographic findings of CDO. However, data based on a wide spectrum of CDO pathologies are scarce. Savran *et al*[15] analyzed 15 patients with duodenal atresia that had undergone operative repair over a period of 6 years at a single center. In their retrospective analysis, the calculated prenatal detection rate was 67%. Only 12 of 15 (80%) pregnant women had a prenatal ultrasonographic screening; ICDO was not analyzed. A study by Kim *et al*[16] reported a prenatal detection rate of 81.4% based on 59 pregnant women and neonates that underwent surgical repair of CDO. A limiting factor of the latter study was the restriction of patients to neonatal age. Our current study included all patients undergoing surgical repair of CDO irrespective of their age in order to gain a more realistic prenatal ultrasonographic detection rate. Due to the long period of observation, our data revealed a substantial number of patients with ICDO (23/50, 46%). The results of our present study suggest that a prenatal detection rate calculated on the basis of patients restricted to the neonatal period is likely to favor the depiction of CCDO. In our current case series, the proportion of patients with ICDO was slightly higher than previously reported (28%-37%)[1,5,17]. This may be attributed to the fact that in recent years, our surgical center has built up collaborations with regional pediatric hospitals, which do not employ pediatric surgeons.

An important finding of our study was that patients with ICDO frequently suffered a considerable delay between birth and diagnosis of CDO. Nearly one half of patients (48%) in the ICDO group underwent operative repair of CDO beyond the neonatal period; 13% were corrected beyond 3 years of age. In the literature, there is rare reporting of children that underwent delayed operative repair of CDO[18]. The results of our retrospective analysis raise the question whether delayed diagnoses of ICDO might be underreported. Patients presenting with chronic vomiting with or without failure to thrive and intolerance of age-appropriate per oral intake need to be assessed with conscious awareness of possible yet undiagnosed ICDO. This is equally attributable both to undiagnosed congenital lesions and the wide spectrum of acquired lesions of the adults` duodenum[19,20,21].

In our study, patients with CCDO had a lower gestational age at birth and lower age and weight at operation. In a previous study that compared duodenal atresia with duodenal web, age and weight at operation differed significantly, with those in the duodenal atresia group having the lowest age and weight and those with duodenal web having the highest age and weight[7]. However, no information was provided regarding differences in age and weight between the groups at birth.

Our finding that UGI contrast-enhanced X-ray examinations are frequently necessary to diagnose ICDO is in line with previous studies[1,22]. However, statistical analysis between ICDO and CCDO had not been previously performed. Our assessment of associated congenital anomalies corresponds well to a large previous analysis of patients with duodenal atresia and stenosis[4]. In simplified terms, approximately 50% of patients with CDO have associated congenital anomalies, CHD in 40% and trisomy 21 in 30%. However, previous studies did not differentiate

Table 1 Demographic data for 50 patients with complete or incomplete congenital duodenal obstruction undergoing operative repair

	Complete	Incomplete	*P* value
	n = 27	*n* = 23	
Gender (male:female), *n* (%)	12 (44):15 (56)	12 (52):11 (48)	0.78
Gestational age at birth (wk)	36.0 (31.3-42)	38.7 (30.1-40.1)	0.01[a]
No CHD + GA ≥ 37 wk (wk)	38.6 (38.3-39.0), *n* = 4	39.3 (37.1-40.1), *n* = 15	0.34
GA < 37 wks (patients), *n* (%)	14 (52)	5 (22)	< 0.05[a]
Age at operation, AO (d)	1.0 (0-7)	21.0 (3-2790)	< 0.01[a]
No CHD + GA ≥ 37 wk (d)	1.0 (0-7), *n* = 4	21.0 (3-2790), *n* = 15	< 0.01[a]
Weight at operation (kg)	2.54 (1.48-3.84)	3.27 (2.20-13.80)	< 0.01[a]
No CHD + GA ≥ 37 wk (kg)	3.20 (2.98-3.45), *n* = 4	3.92 (2.48-12.80), *n* = 15	0.37
Associated congenital anomalies (patients), *n* (%)	20 (74)	7 (30)	< 0.01[a]
Congenital heart disease (patients), *n* (%)	18 (67)	3 (13)	< 0.01[a]
Trisomy 21 (patients), *n* (%)	11 (41)	4 (17)	0.12
Other anomalies (patients), *n* (%)	10 (37)	6 (26)	0.55
Details	Butterfly vertebrae (1), esophageal atresia (1), hemolytic disease of the newborn (1), hydronephrosis, unilateral (1), bilateral (1), hypothyreosis (5), funnel trachea (1), polydactyly, unilateral (1), Hirschsprung disease (1), atopic eczema (1)	Pes calcaneus (1), biliary duct hypoplasia (1), celiac disease (1), Cornelia de Lange syndrom (1), sleep apnoea (1), ectrodactyly, bilateral (1), hypospadia (1), patent omphalomesenteric duct (1), glutaric aciduria type 1 (1)	

[a]*P* < 0.05; No CHD + GA ≥ 37 wk represents only patients born at gestational age 37 wk or later without congenital heart disease. GA: Gestational age; CHD: Congenital heart disease.

between complete and incomplete duodenal obstruction.

A recent study of patients with CDO revealed that CHD and prematurity are most commonly associated with delayed enteral nutrition[5]. Consequently, in our outcome analysis, we additionally analyzed the subgroup of patients without CHD and prematurity (gestational age ≥ 37 wk). Our subgroup analysis demonstrated significant differences between groups with respect to postoperative initiation of feeds. Achievement of full feeds, length of postoperative hospital stay and morbidity did not differ between CCDO and ICDO in this subgroup. It appears that CHD and prematurity are predominant factors that widely influence postoperative outcome, while in contrast the degree of duodenal obstruction is limited to impact time from operation to initiation of enteral feeding.

The primary strength of this study was that it was based on data derived from a consecutive series of patients who underwent operative repair over a period of more than 13 years with a follow up period between 3.9 and 5.2 years. Duodenal pathologies of our series represented a wide spectrum of both CCDO and ICDO. Our analysis has several limitations, including the retrospective design of the study, small sample size, single institution and limited follow-up period. The difference of age at operation between groups may have influenced enteral feeding. Duodeno-duodenostomy had different frequencies in both groups, however differential impact on groups may be minor because operative time between groups was equal. Our study highlights differences in prenatal detection and postnatal outcome of patients with CCDO and ICDO. Our results suggest that future stratified outcome analyses of CDO should be performed with special attention to CHD, prematurity and the degree of duodenal obstruction.

In conclusion, our results indicate that outcome parameters between CCDO and ICDO differ significantly. Patients with CCDO have a longer postoperative hospital stay associated with more adverse events compared to ICDO. Patients with ICDO frequently suffer considerable delays to diagnosis and operative repair of their congenital malformation. Efforts should to be undertaken to improve pre- and postnatal detection of ICDO in order to reduce preoperative morbidity and the delay to operative repair.

Table 2 Prenatal ultrasonographic detection rate and preoperative diagnostics for 50 patients with complete or incomplete congenital duodenal obstruction, and clinical presentations for 26 patients with prenatally unknown complete or incomplete congenital duodenal obstruction undergoing operative repair

	Complete	Incomplete	*P* value
	n = 27	*n* = 23	
Fetal US screening, *n* (%)	26[1] (96)	23 (100)	1
Prenatally suspected by US (yes:no), *n* (%)	23 (88):3 (12)	1 (4):22 (96)	< 0.01[a]
Clinical presentation all prenatally unknown CDO	*n* = 4[2]	*n* = 22	
Vomiting, *n* (%)	4 (100)	20 (91)	1
Failure to thrive, *n* (%)		13 (59)	
Intolerance of age-appropriate p.o. intake, *n* (%)		10 (45)	
Constipation, *n* (%)	1 (25)	7 (32)	1
Postprandial discomfort/pain/restlessness, *n* (%)		5 (23)	
ALTE (aspiration, apnea, bradycardia), *n* (%)		1 (5)	
Intolerance to solid food, *n* (%)		1 (5)	
Preoperative diagnostics	*n* = 27	*n* = 23	
Plain abdominal X-ray, *n* (%)	27 (100)	1 (4)	< 0.01[a]
Upper GI contrast study, *n* (%)	0	23 (100)	< 0.01[a]
Gastroduodenoscopy, *n* (%)	0	4 (17)	0.04[a]

[a]*P* < 0.05;
[1]One maternity in the complete group was unsupervised (no prenatal ultrasound screening);
[2]*n* = 4 is sum of three prenatally unsuspected patients plus one patient without prenatal ultrasound. US: ultrasound; p.o.: Per oral; ALTE: Acute life-threatening event; GI: Gastrointestinal; CDO: Congenital duodenal obstruction.

Table 3 Pathologic findings of 50 patients with complete or incomplete congenital duodenal obstruction undergoing operative repair

	Complete	Incomplete	*P* value
	n = 27	*n* = 23	
Atresia type 1-membrane, *n* (%)	10 (37)		
Type 2-fibrous cord, *n* (%)	1 (4)		
Type 3-gap, *n* (%)	3 (11)		
Annular pancreas, *n* (%)	15 (56)	3 (13)	< 0.01[a]
additionally to type 3 atresia, *n* (%)	2 (7)		
Web, *n* (%)		9 (39)	
Ladd´s bands, *n* (%)		11 (48)	
Additional intestinal pathologies			
Intestinal malrotation, *n* (%)	16 (59)	19 (83)	0.12
Second distal stenosis, *n* (%)	0	1 (4)	
Meckel´s diverticulum, *n* (%)	2 (7)	2 (9)	1

[a]*P* < 0.05.

Table 4 Operative variables and surgical procedures for 50 patients with complete or incomplete congenital duodenal obstruction undergoing operative repair

	Complete	Incomplete	*P* value
	n = 27	*n* = 23	
Operative time (min), *n* (%)	168 (75)	163 (101)	0.85
Procedure			
Duodenoduodenostomy, *n* (%)	25 (93)	8 (35)	< 0.01[a]
Excision of membrane/web and duodenoplasty (Mikulicz), *n* (%)	2 (7)	4 (17)	0.39
Duodenal freeing, *n* (%)	15 (56)	13 (57)	1
Ladd´s procedure, *n* (%)	6 (22)	9 (39)	0.23
Additional procedures			
Jejunoplasty (Mikulicz) for second distal stenosis	0	1 (4)	0.46
Appendectomy, *n* (%)	5 (19)	13 (57)	< 0.01[a]
Resection of Meckel`s diverticulum, *n* (%)	2 (7)	2 (9%)	1
Laparoscopic approach, *n* (%)	12 (44)	16 (70)	0.09
Conversion to open approach, *n* (%)	1 (8)	2 (13)	1

[a]*P* < 0.05.

Table 5 Postoperative outcomes for 50 patients with complete or incomplete congenital duodenal obstruction undergoing operative repair

	Complete	Incomplete	*P* value
	n = 26[1]	*n* = 23	
Time from OP to initiation of feeds (d)	3.0 (0-12)	1.0 (0-3)	< 0.01[a]
No CHD + GA ≥ 37 wk (d)	4 (2-12), *n* = 4	1 (0-3), *n* = 15	< 0.01[a]
Time from OP to full feeds (d)	12.0 (5-22)	6.0 (1-13)	< 0.01[a]
No CHD + GA ≥ 37 wk (d)	10.5 (5-22), *n* = 4	6 (3-11), *n* = 15	0.09
Length of postop. hospital stay (d)	25 (7-40)	9 (3-24)	< 0.01[a]
No CHD + GA ≥ 37 wk (d)	15.5 (7-25), *n* = 4	8 (3-21), *n* = 15	0.14
	n = 27	*n* = 23	
Morbidity (Clavien-Dindo grade I-V), *n* (%)	15 (56)	2 (9)	< 0.01[a]
No CHD + GA ≥ 37 wk, *n* (%)	1 (25), *n* = 4	1 (7), *n* = 15	0.39
Surgical morbidity, *n* (%)	7 (26)	1 (4)	0.06
No CHD + GA ≥ 37 wk, *n* (%)	1 (25), *n* = 4	0 (0), *n* = 15	0.21
Nonsurgical morbidity, *n* (%)	12 (44)	1 (4)	< 0.01[a]
No CHD + GA ≥ 37 wk, *n* (%)	0 (0), *n* = 4	1 (7), *n* = 15	1
Mortality, *n* (%)	1 (3.7)	0 (0)	1
Reoperation, *n* (%)	3 (12)	0	0.24
Comprehensive complication index	8.7 (0.0-100)	0.0 (0.0-33.7)	< 0.01[a]
No CHD + GA ≥ 37 wk	0 (0-58.4), *n* = 4	0 (0-8.7), *n* = 15	0.30
Follow-up (yr)	5.2 (0.4-13.8)	3.9 (0.8-13.1)	0.41

[a]*P* < 0.05.
[1]Parameters time from operative to feeds and length of postoperative hospital stay were calculated from *n* = 26 since one patient in the complete group died during initial in-patient treatment (severe cardiac decompensation); reoperation was defined as a repetition of a surgical operation undertaken due to lack of success of the first attempt over the whole period of observation; reasons for reoperation included (initially missed) Ladd´s bands or anastomotic leakage of the duodenoduodenostomy; other adverse events that needed an operative intervention (*i.e.*, pleural drainage) are found in Table 6. No CHD + GA ≥ 37 wk represents only patients born at gestational age 37 wk or later without congenital heart disease. GA: Gestational age; CHD: Congenital heart disease.

Table 6 Postoperative adverse events graded according to Clavien-Dindo classification for 50 patients with complete or incomplete congenital duodenal obstruction undergoing operative repair

	Clavien-Dindo grade	Postoperative adverse event	Patient No.	Frequency of occurence, *n* (%)
Complete	I	Icterus prolongatus	5	1 (2)
		Hyperbilirubinemia	11	1 (2)
		Transient trocar hernia	16	1 (2)
	II	Surgical site infection	5	1 (2)
		Central line infection	3, 6, 39	3 (6)
		Enteritis, Dehydration	2	1 (2)
		Gastroesophageal reflux	22, 32	2 (4)
		Pneumonia	27, 32	2 (4)
		Pericardial effusion	27	1 (2)
		Cardiac insufficiency, ACE inhibitor	31	1 (2)
		Subclavian malpuncture, transfusion	38	1 (2)
		Enterocolitis	43	1 (2)
	IIIa	Gastric bleeding	40	1 (2)
	IIIb	Colon perforation	1, 25	2 (4)
		Colostomy closure	1	1 (2)
		Mesocolonic hernia	1	1 (2)
		Missed Ladd´s bands	22, 32	2 (4)
		Hematothorax, pleural drainage	38	1 (2)
		Anastomotic leakage	40	1 (2)
	IVb	Cardiac failure, multiorgan dysfunction	40	1 (2)
	V	Death	40	1 (2)
Incomplete	I	Postoperative vomiting (> 7 d)	46	1 (2)
	IIIb	Diagnostic gastroduodenoscopy	46	1 (2)
	IIIb	Incisional hernia	2	1 (2)

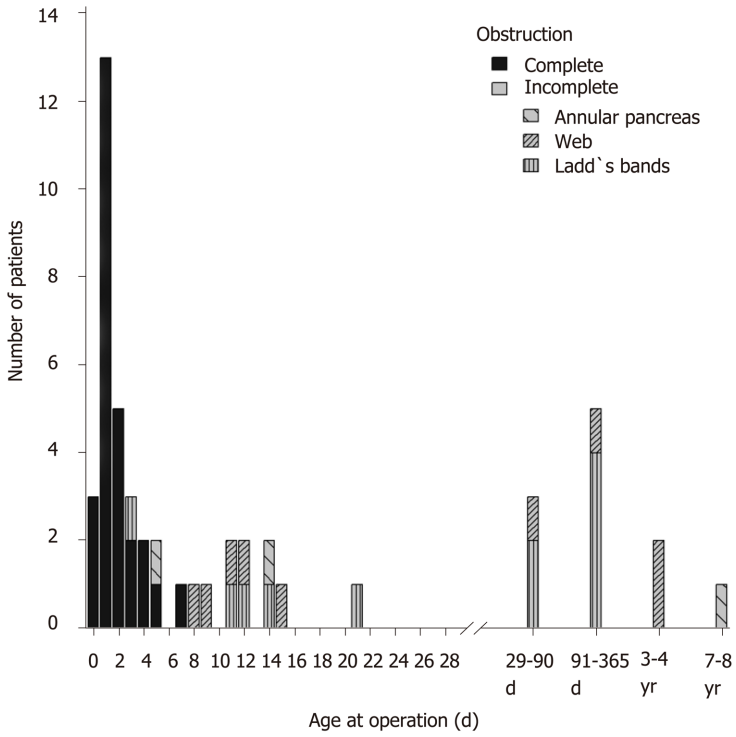

Figure 2 Absolute frequencies of operative repairs and corresponding age at operation for 50 patients with complete or incomplete congenital duodenal obstruction.

ARTICLE HIGHLIGHTS

Research background

Congenital duodenal obstruction (CDO) can be complete (CCDO) or incomplete (ICDO). To date there is no outcome analysis available that compares both subtypes.

Research motivation

Anatomically, CDO is subdevided into CCDO and ICDO. The clinical observation shows that outcomes between patients with CCDO and ICDO differ substantially.

Research objectives

The objective of this study was to analysis and compare the association between CCDO and ICDO with outcome parameters.

Research methods

We retrospectively reviewed all patients who underwent operative repair of CCDO or ICDO in our tertiary care institution between January 2004 and January 2017. The demographics, clinical presentation, preoperative diagnostics and postoperative outcomes of 50 patients were compared between CCDO (n = 27) and ICDO (n = 23).

Research results

CCDO was associated with a significantly higher prenatal ultrasonographic detection rate, lower gestational age at birth, lower age and weight at operation, higher rate of associated congenital heart disease, more extensive preoperative radiologic diagnostics, higher morbidity according to Clavien-Dindo classification and comprehensive complication index. The subgroup analysis of patients without congenital heart disease (CHD) and prematurity showed a longer time from operation to the initiation of enteral feeds in the CCDO group.

Research conclusions

This study showed that CCDO and ICDO differ with regard to prenatal detection rate, preoperative diagnostics, postoperative enteral feeds, length of hospital stay and morbidity according to the Clavien-Dindo classification and the comprehensive complication index. The degree of CDO in mature patients without CHD influences the postoperative initiation of enteral feeding.

Research perspectives

Efforts should to be undertaken to improve pre- and postnatal detection of ICDO in order to reduce preoperative morbidity and the delay to operative repair.

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ORIGINAL ARTICLE

Retrospective Study

Effect of low-dose aspirin administration on long-term survival of cirrhotic patients after splenectomy: A retrospective single-center study

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Abstract

BACKGROUND

Cirrhosis is a major risk factor for the development of hepatocellular carcinoma (HCC). Portal vein thrombosis is not uncommon after splenectomy in cirrhotic patients, and many such patients take oral anticoagulants including aspirin. However, the long-term impact of postoperative aspirin on cirrhotic patients after splenectomy remains unknown.

AIM

The main purpose of this study was to investigate the effect of postoperative long-term low-dose aspirin administration on the development of HCC and long-term survival of cirrhotic patients after splenectomy.

METHODS

The clinical data of 264 adult patients with viral hepatitis-related cirrhosis who underwent splenectomy at the First Affiliated Hospital of Xi'an Jiaotong University from January 2000 to December 2014 were analyzed retrospectively. Among these patients, 59 who started taking 100 mg/d aspirin within seven days were enrolled in the aspirin group. The incidence of HCC and overall survival were analyzed.

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RESULTS

During follow-up, 41 (15.53%) patients developed HCC and 37 (14.02%) died due to end-stage liver diseases or other serious complications. Postoperative long-term low-dose aspirin therapy reduced the incidence of HCC from 19.02% to 3.40% after splenectomy (log-rank test, $P = 0.028$). Univariate and multivariate analyses showed that not undertaking postoperative long-term low-dose aspirin therapy [odds ratio (OR) = 6.211, 95% confidence interval (CI): 1.142-27.324, $P = 0.016$] was the only independent risk factor for the development of HCC. Similarly, patients in the aspirin group survived longer than those in the control group (log-rank test, $P = 0.041$). Univariate and multivariate analyses showed that the only factor that independently associated with improved overall survival was postoperative long-term low-dose aspirin therapy [OR = 0.218, 95%CI: 0.049-0.960, $P = 0.044$].

CONCLUSION

In patients with viral hepatitis-related cirrhosis, long-term post-splenectomy administration of low-dose aspirin reduces the incidence of HCC and improves the long-term overall survival.

Key words: Aspirin; Splenectomy; Prognosis; Hepatocellular carcinoma; Overall survival

Core tip: Anticoagulant therapy reduces the incidence of post-splenectomy portal thrombosis and improves prognosis by inhibiting thrombus formation. This study was to investigate the effect of postoperative long-term low-dose aspirin therapy on the development of hepatocellular carcinoma and long-term survival of cirrhotic patients after splenectomy. Post-splenectomy long-term administration of low-dose aspirin reduced the incidence of hepatocellular carcinoma and improved the long-term overall survival in patients with viral hepatitis-related cirrhosis. Thus, long-term low-dose aspirin therapy should be recommended to cirrhotic patients with hypersplenism after splenectomy.

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INTRODUCTION

Splenectomy, a common surgical treatment for cirrhosis with portal hypertension and hypersplenism, can effectively reduce portal pressure, relieve symptoms, and improve liver function[1,2]. It is often used in patients with viral hepatitis-related chronic liver cirrhosis. However, portal thrombosis is not uncommon after splenectomy, documented at 4.8% to 51.5% of cases[3,4]. Previous studies revealed that portal thrombosis could induce portal hypertension, increase postoperative complications, and result in long-term poor prognosis[5-8]. Therefore, the treatment for portal vein thrombosis after splenectomy is particularly significant.

Anticoagulant therapy reduces the incidence of post-splenectomy portal thrombosis by inhibiting thrombus formation. In this regard, many cirrhotic patients take oral anticoagulants including low-dose aspirin after splenectomy[9,10]. However, the long-term impact of postoperative aspirin on cirrhotic patients after splenectomy remains unknown. The purpose of this study was to investigate the effect of low-dose aspirin therapy on HCC development and long-term overall survival in patients who underwent splenectomy for cirrhosis-related portal vein hypertension and hypersplenism.

MATERIALS AND METHODS

Study population

From January 2000 to December 2014, a total of 1662 patients were diagnosed with cirrhosis-related hypersplenism and portal hypertension at the First Affiliated Hospital of Xi'an Jiaotong University. Among them, 295 (17.75%) patients underwent splenectomy, of whom 31 (10.51%) were excluded because they had serious coagulation disorders, cardiovascular diseases, or malignant tumors, or used warfarin or low-molecular-weight heparin after surgery instead of aspirin. The remaining 264 patients were enrolled in this study. Among these patients, 109 took aspirin after surgery. Those who did not start taking it within seven days after surgery, who took less than one year, or who did not follow the doctor's advice were excluded. Finally, 59 patients were included in the aspirin group. This group of patients took aspirin daily at a basic dose of 100 mg. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University and performed in accordance with the provisions of the Helsinki Declaration. No written informed consent was obtained for the retrospective nature of this study.

Data collection

All clinical variables of these patients were obtained from the electronic medical record system. The general clinical data collected in this study included age, gender, hepatitis status, and underlying concurrent diseases. Laboratory results were collected on the first day after admission, containing routine blood count, liver function, coagulation test, alpha fetoprotein (AFP), and Child-Pugh score. Intraoperative blood loss, spleen size and volume, surgery methods, hospitalization stay, and postoperative complications were also obtained. Portal vein thrombosis was checked by ultrasonography after splenectomy during hospitalization, and anticoagulation information included the initial use of the drugs and detailed name of the drugs.

Follow-up

All patients were followed until October 2017. The median follow-up time was 54 (interquartile range: 40, 87.6) mo. The follow-up content mainly included aspirin drugs, clinical manifestations, laboratory examination, and ultrasound imaging findings. All patients received the relevant follow-up. The overall survival (OS) was recorded from the surgery time to last follow-up, and hepatocellular carcinoma (HCC) occurrence was recorded from the surgery to the last time without tumor. HCC was diagnosed based on imaging results and laboratory tests. To reduce the follow-up bias, two researchers completed the work independently.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or median (min-max). Categorical variables are expressed as frequency and percentage. To calculate the difference between two groups, the Student's *t*-test or Wilcoxon test was used for continuous variables and the chi-squared test or Fisher's exact test for categorical data. For three or more groups, analysis of variance was used. Survival curves were estimated using the Kaplan–Meier method and statistical differences were calculated by the log-rank test. If statistical significance was found by univariate analysis, the factor will continue to be calculated through the multivariate log-regression model. All statistical analyzes were performed using PASW Statistics 18.0 software (IBM Corporation, Armonk, NY, United States). Survival curves have been beautified with Graphpad prism 6.0 software (GraphPad Software, Inc. La Jolla, United States). $P < 0.05$ was considered statistically significant.

RESULTS

Patient demographics and characteristics

The demographics and baseline clinical characteristics of the 264 patients are shown in Table 1. The average age of the patients was 45 years (range: 20-67 years), and there were 194 (73.48%) males and 70 (26.52%) females. Among all the patients, 248 (93.94%) had hepatitis B virus (HBV) infection, 14 (5.30%) had hepatitis C virus (HCV) infection, and 2 (0.76%) had both HBV and HCV infections; 33 (12.50%) had a history of alcohol consumption and 65 (24.62%) had a smoking history; 58 (21.97%) and 21 (7.95%) had hypertension and diabetes, respectively; 71 (26.89%) had a platelet count below 30 ($\times 10^9$/L) at admission. The average values of fibrinogen and alpha fetoprotein (AFP) at admission were 1.89 g/L (range: 0.60-5.36 g/L) and 10.83 mg/L

(range: 0.76-140.90 mg/L), respectively. At admission, 80 (30.30%) cases had Child-Pugh grade A liver function, 165 (62.50%) had Child-Pugh grade B, and 19 (7.20%) had Child-Pugh grade C. The average amount of bleeding during surgery was 425 mL (range: 50-2000 mL). The spleen volume and spleen size were 1410 (range: 156-4896 mm^3) and 158 (range: 12-230 mm), respectively. Two hundred and twenty-eight (86.36%) patients underwent open laparotomy and the other 36 (13.64%) patients underwent laparoscopic surgery. The mean length of hospital stay was 27 d (range: 11-125 d). Among these patients, 47 patients (17.80%) developed portal vein thrombosis during hospitalization after splenectomy. A total of 59 patients, including 21 who developed portal vein thrombosis and 38 who did not, were given 100 mg/d aspirin within seven days after surgery for at least one year.

Effect of postoperative long-term low-dose aspirin therapy on the development of HCC

In this cohort, 41 (15.53%) patients developed HCC during follow-up and Kaplan–Meier analysis showed that the incidence of HCC in patients with postoperative aspirin (log-rank test, $P = 0.028$) was significantly lower than that in patients without aspirin (Figure 1). Univariate and multivariate analyses demonstrated that not taking postoperative aspirin ($P = 0.016$) was the independent risk factor for the development of HCC after splenectomy (Table 2).

Effect of postoperative long-term low-dose aspirin therapy on overall survival after splenectomy

At the end of follow-up, 37 (14.02%) patients died due to end-stage liver diseases or other serious complications. Overall survival rates at 3, 5, and 10 years after splenectomy were 93.18%, 89.77%, and 87.12%, respectively (Table 3). It could be seen that the overall survival of patients in the aspirin group were significantly better than that of the patients who did not receive early postoperative aspirin after surgery (log-rank test, $P = 0.041$, Figure 2). Next, we used univariate and multivariate analyses to explore factors affecting overall survival after splenectomy. As shown in Table 3, the only factor that was independently associated with overall survival was early postoperative aspirin therapy ($P = 0.044$). And other factors such as gender, age > 60 years, underlying liver diseases, Child-Pugh score, surgical approach, and spleen volume did not show a statistically significant effect on overall survival.

DISCUSSION

Cirrhotic patients who underwent splenectomy are at a high risk of developing thrombosis[11]. Due to its convenient administration and relatively low bleeding risk, low-dose aspirin is often used after splenectomy[12]. However, the long-term effects of low-dose aspirin in this specific patient population have not been clarified. Here, we found for the first time that long-term low-dose aspirin use after splenectomy significantly reduced HCC incidence and improved overall survival in cirrhotic patients with hypersplenism.

Splenectomy is a routine surgical procedure[1]. Many studies have indicated that splenectomy improved liver function, delayed hepatic fibrosis, corrected cytopenia, and expanded treatment options for the underlying liver disease[13]. Thus, it is commonly used to treat hypersplenism for patients with cirrhosis. Liver cirrhosis is a major risk factor for HCC[14-16]. Hypersplenism is correlated with an increased risk of HCC in patients with post-hepatitis cirrhosis and splenectomy might reduce HCC risk in those patients[17,18]. A recent retrospective study of 2678 cirrhotic patients with hypersplenism showed that 33.0% of cirrhotic patients who did not undergo splenectomy developed HCC, while only 17.3% of those who underwent splenectomy developed HCC[18]. In the current cohort of 264 cirrhotic patients who underwent splenectomy, a total of 41 (15.5%) developed HCC during follow-up, which is consistent with the early report.

Taking a low-dose aspirin daily has been shown to decrease the risk of developing or dying from many types of cancer[19-21]. A recent study[22] on the chemopreventive effect of aspirin on HCC and death due to chronic liver disease showed that any aspirin use at baseline was associated with a reduced risk of both HCC development and mortality. Non-aspirin NSAID users, on the other hand, were not at a reduced risk of developing HCC[20,23]. The anticancer effects of aspirin are mediated through several interconnected mechanisms[24,25]. Aspirin blocks the production of COX1 and COX2, inhibits WNT-β-catenin signaling, and inactivates platelets and the host immune response[26-28]. Chronic or prolonged inflammation can create an environment in which cancer thrives. Chronic viral hepatitis is the major cause of HCC. Immune-

Table 1 General clinical characteristics of the patients

Clinical characteristic	Median (range)/*n* (%)
Demographic feature	
Age (yr)	45 (20-67)
Gender (male:female)	194:70
Underlying disease	
HBV	248 (93.94)
HCV	14 (5.30)
HBV and HCV	2 (0.76)
Coexisting condition	
Drinking	33 (12.50)
Smoking	65 (24.62)
Hypertension	58 (21.97)
Diabetes	21 (7.95)
Laboratory results	
Leucocytes (10^9/L)	2.66 (0.60-59.00)
Platelet count (<30 × 10^9/L)	71 (26.89)
Hemoglobin (g/L)	97 (18-175)
ALT (>40 U/L)	91 (34.47)
AST (>40 U/L)	124 (46.97)
Albumin (<35 g/L)	125 (47.35)
Total bilirubin (>17 μmol/L)	184 (69.70)
Creatinine (μmol/L)	66 (15-188)
PT (>17 s)	79 (29.92)
APTT (>45 s)	77 (29.17)
INR (>1.2)	179 (67.80)
Fibrinogen (g/L)	1.89 (0.60-5.36)
AFP (mg/L)	10.83 (0.76-140.90)
Child-Pugh score	
Child A	80 (30.30)
Child B	165 (62.50)
Child C	19 (7.20)
Intraoperative and postoperative features	
Intraoperative blood loss (mL)	425 (50-2000)
Spleen volume (mm^3)	1410 (156-4896)
Spleen size (mm)	158 (12-230)
Surgical method	
Laparoscopic surgery	36 (13.64)
Open laparotomy	228 (86.36)
Portal vein thrombosis	47 (17.80)
Postoperative aspirin	59 (22.35)
Length of hospital stay	27 (11-125)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; APTT: Activated partial thromboplatin time; INR: International normalized ratio; AFP: Alpha fetoprotein; ICU: Intensive care unit.

mediated inflammatory responses are considered to be the predominant cause of HCC transformation during chronic viral hepatitis. The combined anti-platelet and anti-inflammatory effects of aspirin may specifically prevent inflammation-associated tumorigenesis under such conditions[16,29]. Oral administration of aspirin can be used for long-term treatment of patients at risk of thrombosis. Thus, in cirrhotic patients with hypersplenism, daily low-dose aspirin therapy should be recommended after splenectomy.

The major strength of our study was the long-term follow-up. However, there were also some limitations in the present study. First, the data in this study originated from

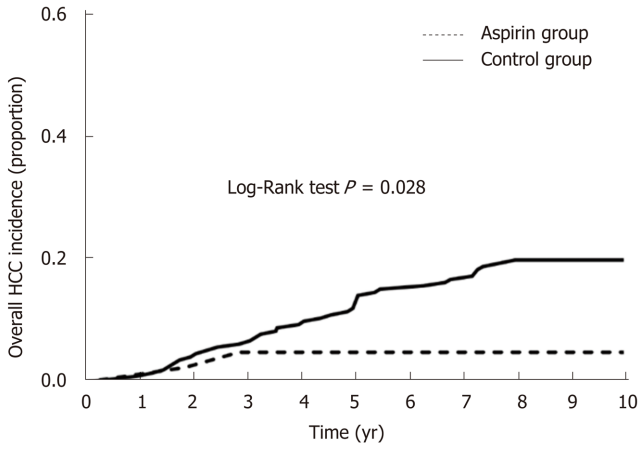

Figure 1 Effect of postoperative long-term low-dose aspirin therapy on the development of hepatocellular carcinoma in cirrhotic patients after splenectomy. Differences in hepatocellular carcinoma (HCC) development between cirrhotic patients who received long-term low-dose aspirin (aspirin group) and those who did not (control group) were compared. The incidence of HCC was assessed by the Kaplan-Meier method and compared by the log-rank test. HCC: Hepatocellular carcinoma.

a single center, therefore the sample size was relatively small and the incidence of postoperative mortality and morbidity was low. For instance, a relatively small proportion of patients died during follow-up, which may have limited the robustness of the multivariable analysis for adjustment for confounding factors. Second, we only considered the long-term use of low-dose aspirin after splenectomy as anticoagulant therapy in this study; however, some patients, especially those who developed portal vein thrombosis, also received other anticoagulants for a short period of time. More data are needed to investigate the long-term effects of other anticoagulants after splenectomy. Third, only viral hepatitis-related cirrhotic patients were enrolled in this study. Therefore, whether long-term low-dose aspirin has the same effect in preventing HCC development in patients with alcohol-related cirrhosis needs to be determined. Moreover, whether taking a low-dose aspirin daily reduces the risk of developing HCC in cirrhotic patients without splenectomy also warrants further investigation. Finally, due to the retrospective nature of this study, the results were subject to some uncontrollable biases, so further prospective studies would be necessary.

In summary, post-splenectomy long-term administration of low-dose aspirin reduces the incidence of HCC and improves the long-term overall survival in patients with viral hepatitis-related cirrhosis. Thus, long-term low-dose aspirin therapy should be recommended to cirrhotic patients with hypersplenism after splenectomy.

Table 2 Univariate and multivariate analyses of risk factors for the development of hepatocellular carcinoma after splenectomy

Variable	Univariate analysis		Multivariate analysis	
	P-value	OR (95%CI)	*P*-value	OR (95%CI)
Gender (male/female)	0.067	2.348 (0.942-5.853)	0.088	2.287 (0.884-5.919)
Age > 60 yr	0.946	1.045 (0.292-3.742)		
Hypertension (yes/no)	0.222	0.628 (0.298-1.325)		
Diabetes (yes/no)	0.187	3.941 (0.514-30.211)		
Drinking (yes/no)	0.432	0.689 (0.276-1.717)		
Smoking (yes/no)	0.791	0.902 (0.421-1.933)		
Platelet count at admission (< 30 × 10^9/L)	0.434	1.337 (0.646-2.764)		
ALT (> 40 U/L)	0.543	1.237 (0.632-2.459)		
AST (> 40 U/L)	0.063	1.910 (0.966-3.775)	0.323	1.460 (0.690-3.092)
Albumin (< 35 g/L)	0.155	0.612 (0.312-1.203)		
Total bilirubin (> 17 μmol/L)	0.683	1.169 (0.553-2.471)		
PT (> 17 s)	0.581	1.221 (0.601-2.477)		
APTT (> 45 s)	0.297	1.452 (0.721-2.924)		
INR (> 1.2)	0.063	2.555 (0.949-6.881)	0.077	2.496 (0.904-6.892)
Child-Pugh score	0.106	1.218 (0.959-1.548)		
Surgical method (LS *vs* OS)	0.094	0.285 (0.066-1.236)	0.297	0.446 (0.098-2.033)
Intraoperative blood loss (mL)	0.184	0.998 (0.995-1.001)		
Spleen volume (mm^3)	0.994	1.000 (1.000-1.000)		
Spleen size (mm)	0.129	0.993 (0.983-1.002)		
Postoperative early aspirin (yes/no)	0.010	6.696 (1.567-28.616)	0.016	6.211 (1.412-27.324)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; LS: Laparoscopic surgery; OS: Open surgery.

Table 3 Univariate and multivariate analyses of risk factors for overall survival

Variable	Univariate analysis		Multivariate analysis	
	P-value	OR (95%CI)	*P*-value	OR (95%CI)
Gender (male/female)	0.104	1.859 (0.896-3.856)		
Age > 60 yr	0.895	1.090 (0.303-3.919)		
Underlying liver disease				
Hypertension (yes/no)	0.709	1.168 (0.517-2.638)		
Diabetes (yes/no)	0.491	1.497 (0.474-4.726)		
Coexisting condition				
Drinking (yes/no)	0.331	0.539 (0.156-1.871)		
Smoking (yes/no)	0.648	0.823 (0.356-1.902)		
Platelet count at admission (< 30 × 10^9/L)	0.649	0.837 (0.388-1.804)		
ALT (> 40 U/L)	0.061	0.510 (0.253-1.030)	0.495	0.710 (0.266-1.897)
AST (> 40 U/L)	0.057	0.500 (0.245-1.021)	0.617	0.772 (0.279-2.132)
Albumin (< 35 g/L)	0.012	2.583 (1.236-5.398)	0.737	1.158 (0.492-2.724)
Total bilirubin (> 17 μmol/L)	0.260	0.620 (0.270-1.425)		
PT (> 17 s)	0.053	0.492 (0.240-1.010)	0.496	0.750 (0.328-1.715)
APTT (> 45 s)	0.907	0.955 (0.444-2.054)		
INR (> 1.2)	0.371	0.668 (0.276-1.617)		
Child-Pugh score	0.008	0.422 (0.222-0.800)	0.181	1.728 (0.775-3.857)
Surgical method (LS *vs* OS)	0.068	6.562 (0.871-49.440)	0.157	4.393 (0.566-34.110)
Intraoperative blood loss (mL)	0.131	0.999 (0.998-1.000)		
Spleen volume (mm^3)	0.634	1.000 (1.000-1.001)		
Spleen size (mm)	0.563	1.003 (0.993-1.013)		

Postoperative early aspirin (yes/no)	0.017	0.170 (0.040-0.731)	0.044	0.218 (0.049-0.960)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin time; APTT: Activated partial thromboplatin time; INR: International normalized ratio; LS: Laparoscopic surgery; OS: Open surgery.

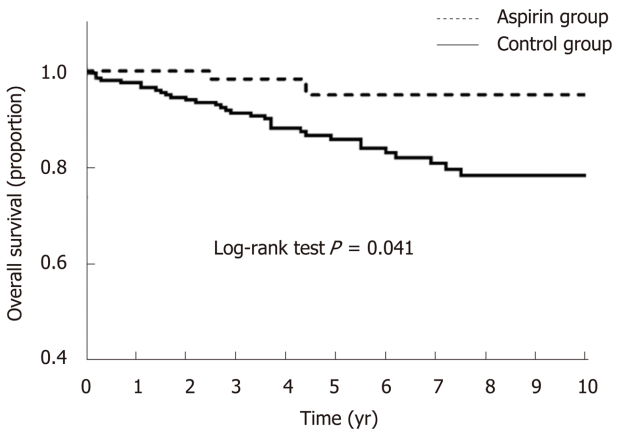

Figure 2 Effect of postoperative long-term low-dose aspirin therapy on overall survival of cirrhotic patients after splenectomy. Differences in overall survival rates between cirrhotic patients who received long-term low-dose aspirin (aspirin group) and those who did not (control group) were compared. The survival rate was assessed by the Kaplan-Meier method and compared by the log-rank test.

ARTICLE HIGHLIGHTS

Research background

Cirrhosis is a major risk factor for the development of hepatocellular carcinoma (HCC). Portal vein thrombosis is not uncommon after splenectomy in cirrhotic patients, and many such patients take oral anticoagulants including aspirin. However, the long-term impact of postoperative aspirin on cirrhotic patients after splenectomy remains unknown.

Research motivation

The motivation of this research was to investigate the effect of low-dose aspirin therapy on HCC development and long-term overall survival in patients who underwent splenectomy for cirrhosis-related portal vein hypertension and hypersplenism.

Research objectives

The main objectives of this study was to investigate the effect of postoperative long-term low-dose aspirin on the development of HCC and long-term survival of cirrhotic patients after splenectomy.

Research methods

The clinical data of 264 adult patients with viral hepatitis-related cirrhosis who underwent splenectomy at the First Affiliated Hospital of Xi'an Jiaotong University from January 2000 to December 2014 were analyzed retrospectively. Among these patients, 59 who started taking 100 mg/d aspirin within seven days were enrolled in the aspirin group. The incidence of HCC and overall survival were analyzed.

Research results

Forty-one (15.53%) patients developed HCC and 37 (14.02%) died due to end-stage liver diseases or other serious complications in this study. Postoperative long-term low-dose aspirin therapy reduced the incidence of HCC from 19.02% to 3.40% after splenectomy. Univariate and multivariate analyses showed that not undertaking postoperative long-term low-dose aspirin therapy was the only independent risk factor for the development of HCC. Similarly, patients in the aspirin group survived longer than those in the control group. Univariate and multivariate analyses showed that the only factor that was independently associated with improved overall survival was postoperative long-term low-dose aspirin therapy.

Research conclusions

Post-splenectomy long-term administration of low-dose aspirin reduces the incidence of HCC and improves the long-term overall survival in patients with viral hepatitis-related cirrhosis.

Research perspectives

Long-term low-dose aspirin therapy should be recommended to cirrhotic patients with hypersplenism after splenectomy. Further prospective and multi-center studies should be

performed to verify our conclusions.

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ORIGINAL ARTICLE

Prospective Study

Comparison of the use of wireless capsule endoscopy with magnetic resonance enterography in children with inflammatory bowel disease

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Author contributions: Hijaz NM has designed the research study under the guidance of Attard TM and Colombo JM. Hijaz NM supervised the recruitment, safety and timed performance of every single aspect of study procedures. Hijaz NM has collected, processed, computed and summarized all the data. Attard TM and Colombo JM have participated in the capsule endoscopy reading of the study. Mardis NJ has participated in reading the magnetic resonance imaging of the study. Hijaz NM, Attard TM, Friesen CA analyzed the data statistically. Hijaz NM wrote the paper and then revised with guidance of Attard TA, Colombo JM, Friesen CA and Mardis NJ.

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Abstract

BACKGROUND

Magnetic resonance enterography (MRE) and wireless capsule endoscopy (WCE) are equally accepted modalities for noninvasive screening of small bowel involvement (SBI) in children with Crohn's disease (CD) and indeterminate colitis (IC) albeit there is a paucity of data comparing the two and thereby guiding the clinician in selecting the ideal diagnostic approach. Therefore, the goal of this study is to provide additional evidence for capsule endoscopy role in the evaluation of established Crohn's disease exacerbation compared to MRE in relation to Pediatric Crohn's Disease Activity Index (PCDAI), and histological indices.

AIM

To prospectively compare the findings of MRE and WCE and their agreement with PCDAI or histology in children with CD or IC.

METHODS

Consecutive patients diagnosed with CD and IC were screened for inclusion. After informed consent, patient's demographic and clinical data was abstracted. The current pediatric disease activity index (PCDAI) and endoscopic findings were included. Patients underwent MRE and WCE including preprocedural patency capsule within a maximum of 7 d of each other. Pathological presence of active small bowel disease in ileal and duodenal biopsies were collected if the endoscopy was performed within 2 mo of the WCE study. Patients who failed to pass the PC were excluded from the study. WCE was read by two different experienced gastroenterologists (Attard TM and Colombo JM) blinded to each other's findings and to the findings on MRE (Mardis NJ). Agreement between

Clinical trial registration statement: The clinical trial is registered with ClinicalTrials.gov, using identifier NCT02182947. Details can be found at https://clinicaltrials.gov/ct2/show/NCT02182947.

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

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WCE reviewers, WCE and MRE findings and concordance between positive PCDAI and SBI based on MRE compared with WCE was computed.

RESULTS

Forty-five patients were included in the study, 18 withdrew and 27 (20 males and 20 CD), mean age (standard deviation) 13.46 (2.4) years, completed the study protocol. There were no instances of capsule retention. Concordance between gastroenterologist reviewers was excellent for the diagnosis of small intestinal CD with good correlation between the two Lewis scores ($r = 0.875$, $P < 0.001$). Concordance between WCE and MRE was poor (69%). In CD patients, when both MRE and WCE were compared using PCDAI > 10 as the standard reference reflecting active small intestinal CD, the sensitivity of MRE and WCE were 100% and 83% respectively and the specificity of MRE and WCE were 57.14% and 78.6%, respectively. If the histology in ileum or/and duodenum was used as the reference for active small bowel involvement, WCE had a higher specificity as compared to MRE (83.3% *vs* 50%). In patients with Crohn's disease, those with a positive PCDAI (> 10) were more likely to have a positive WCE as compared to those with a negative PCDAI (83% *vs* 21%; $P = 0.018$).

CONCLUSION

We suggest that MRE and WCE have a complementary role in the assessment of SBI in CD. WCE detected SBI with a much higher specificity while MRE had a higher sensitivity.

Key words: Crohn's disease; Wireless capsule endoscopy; Inflammatory bowel disease; Magnetic resonance enterography; Small bowel involvement; Small bowel disease; Indeterminate colitis; Pediatric; Children

Core tip: There are a number of prospective adult studies and few in pediatrics comparing magnetic resonance imaging (MRE) to wireless capsule endoscopy (WCE) in identifying small bowel (SB) Crohn's disease (CD) that showed no significant difference in the diagnostic yield and accuracy of MRE and WCE in established non-stricturing crohns disease or suspected and established CD together. This study is the first prospective study in children with established inflammatory bowel disease in the United States assessing and comparing the roles of MRE and WCE in identifying SB disease involvement in relation to clinical and histological indices.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder primarily involving the gastrointestinal tract. Although any part of the gastrointestinal tract may be involved, proximal small intestinal involvement is more common in pediatric patients than in adult patients with a prevalence of up to 20% [1]. The effects of small intestinal involvement in CD are variable and may include obscure abdominal pain, nutritional sequelae resulting in growth delay, iron deficiency anemia, stricture formation, and potentially small bowel obstruction[1,2]. Proximal small bowel (SB) involvement in CD is associated with a more aggressive disease course and an increased need for surgery[3,4]. Therefore, accurate determination of SB involvement (SBI) in pediatric CD is crucial for optimal patient management[3,4].

Current clinical guidelines include suggested modalities to identify SBI and determine management plans[5]. Available options include small bowel series, computed tomography enterography (CTE), small bowel wireless capsule endoscopy (WCE), gadolinium enhanced magnetic resonance imaging (GAD MRI), and small

bowel contrast enhanced ultrasound (US). The choice of modality is largely determined by available resources, radiation exposure risk, physician and institutional preferences. MRE and contrast enhanced US are radiation free, while other radiologic modalities entail a risk of radiation exposure[6]. WCE may entail a risk of capsule retention. The risk of capsule retention resulting in obstruction is increased in the context of stricturing or fistulizing disease in CD and has been estimated at 2.6%[7] but may be greatly mitigated by patency capsule screening[8]. Magnetic resonance enterography (MRE) and small intestine contrast ultrasound (SICUS) have diagnostic effectiveness comparable to other radiological modalities for evaluation of CD patients[1,2,9]. However, both studies have their own limitations. MRE is limited by expense, the availability of the requisite equipment and software, variable expertise in interpretation of the findings, and (potentially) the need for sedation in pediatric population. SICUS is similarly affected by being operator dependent with the requisite need of accumulated expertise and heightened need for cooperation during the study that can limit its use in pediatric populations[10].

Other diagnostic modalities have been evaluated in comparison to WCE in several pediatric and adult inflammatory bowel disease (IBD) studies. Table 1 summarizes the adult and pediatric studies comparing different modalities to WCE. The studies conducted in children with IBD were mostly retrospective and aimed at evaluating the role of MRE and WCE for detection of SB disease. They concluded that MRE and WCE were comparable with similar sensitivities[11]. Only three prospective studies (all European) in pediatric IBD have compared WCE and MRE modalities in identifying SB disease involvement. Two were studies in established CD[9,12] and one in suspected CD[13] and again, they suggested that the tests appear complementary for detection of active CD. The current study is the first prospective study in children with established IBD in the United States assessing the roles of MRE and WCE in identifying SB disease involvement in IBD. This study provides evidence for capsule endoscopy role in the evaluation of established disease exacerbation in patients with IBD in relation to MRE.

The primary goals of this study are to prospectively compare the diagnostic yield, concordance rate, sensitivity and specificity between MRE and WCE findings and their agreement with the Pediatric Crohn's Disease Activity Index (PCDAI) or with histological small bowel involvement in children with known IBD; CD or IC. Secondary goals are to assess the performance of each of the modalities (MRE, WCE and PCDAI) in relation to each other in order predict the results of the compared tests and to assess the correlation between Lewis capsule endoscopy score and PCDAI.

MATERIALS AND METHODS

Patient selection

This study was a prospective single blinded comparison study of a cohort of pediatric patients with established indeterminate colitis (IC) or CD at a tertiary referral pediatric IBD center. The diagnosis of CD was confirmed by using widely validated clinical, endoscopic, and histological criteria. The study was approved by the ethics committee of the hospital IRB #13080263 and written informed assent/consent was obtained from all children and their parents. Study participants were enrolled if they were 4-18 years of age inclusive with an established diagnosis of IC or CD and planned to have an MRE as part of standard of care. Patients were excluded if they had recent intestinal tract surgery, resection involving small bowel, gastrointestinal obstruction or ileus, swallowing disorders, esophageal stricture, nonsteroidal anti-inflammatory drugs or prokinetic medication use in the 4 wk prior to enrollment, inability to swallow the capsule, or if they had an electro-medical device or pacemaker. Demographic and clinical data were recorded including subject demographics, medical and surgical history, imaging results, initial disease presentation, and patient current clinical status which was used to calculate the PCDAI. The PCDAI score is considered positive (active disease) if ≥ 10 and negative (inactive disease) if < 10 (Table 2).

Patency capsule

All patients swallowed a patency capsule (PC; size 11 mm × 26 mm) to assess small bowel patency. All patients with confirmed passage of PC in the first 40 h underwent WCE (Pillcam™ SB Capsule, Given Imaging Ltd, Israel 11 mm × 26 mm) within 1 wk of completion of MRE. Patients excluded from the study if they failed to swallow or pass the PC. WCE was read by two different experienced gastroenterologists, each with > 10 years of experience (Attard TM and Colombo JM) blinded to each other's findings and to the findings on MRE (Mardis NJ). The PCDAI was recorded from the

Table 1 Summery of studies comparing imaging modalities to capsule endoscopy

Author /year / type	Country	Age group/ total No.	Patient population	Modalities compared to CE	Results
Albert 2005[14]	Germany	Adults/52	Established and suspected CD	MRE	Diagnostic yield of WCE is superior to MRE (+ve MRE 32/52 *vs* +ve WCE 25/27)
Golder 2006 prospective[15]	Germany	Adults/16	Established CD	MRE	Diagnostic yield of WCE is similar to that of MRE (+ve MRE 9/15 *vs* +ve WCE 11/15), but the WCE is superior in detecting proximal SB disease
Tillack 2008 prospective[16]	Germany	Adults/19	Established CD	MRE	Diagnostic yield of WCE is similar to that of MRE (+ve MRE 18/19 *vs* +ve WCE 18/19) but the WCE is superior in detecting proximal SB disease
Dionisio 2010 prospective Metanalysis[17]	Europe, Canada, Israel and United States	All ages/ 428	Established and suspected CD	CTE and SBFT and MRE	Diagnostic yield of WCE is superior to that of CTE and SBR in suspected CD but it is similar to MRE in suspected and established CD
Crook 2009 prospective[18]	Switzerland	Adults/5	Suspected CD	MRE	Diagnostic yield of WCE is similar to that of MRE and complementary to each other
Bocker 2010 prospective[19]	Germany	Adults/21	Established and suspected CD	MRE	Diagnostic yield of WCE is similar to that of MRE (+ve MRE 6/21 *vs* +ve WCE 9/21) but the WCE is superior in detecting proximal SB disease
Jensen 2011 prospective[20]	Denmark	Adults/93	Established and suspected CD	MRE	Diagnostic yield of WCE is similar to that of MRE(+ve MRE 24/80 *vs* +ve WCE 22/80) but the WCE is superior in detecting proximal SB disease
Wiarda 2011 prospective[21]	The Netherlands	Adults/38	Established and suspected CD	MRE	Diagnostic yield of WCE is similar that of MRE (+ve MRE 16/38 *vs* +ve WCE 6/25)
Kopylov 2015 prospective[22]	Israel	Adults/77	Established CD	MRE	Diagnostic yield of WCE is similar to that of MRE (+ve MRE 40/52 *vs* +ve WCE 42/52) but the WCE is superior in detecting proximal SB disease
Gonzalez Suarez 2017 retrospective[23]	Spain	Adults/47	Established and suspected CD	MRE	WCE is superior to MRE in detection of small bowel lesions mainly proximal(+ve WCE 36/47 *vs* +ve MRE 21/47)
Di Nardo 2010 prospective[24]	Italy	Peds/117	Established and suspected CD	MRI and SICUS	reclassifying indeterminate colitis (IC) into CD (60%), detection of CD lesions in known CD (41%) and establishing new diagnosis in suspected CD (50%)

Casciani 2011 prospective[13]	Italy	Peds/60	suspected CD	MRE	Diagnostic yield of WCE is similar to that of MRE (+ve MRE 19/37 *vs* +ve WCE 10/60)
Gralnek 2012 prospective[25]	Israel	Peds /18	Established and suspected CD	No studies compared	
Kovanlikaya 2013[11] retrospective	United States	Peds/23	Established and suspected CD	MRE	Sensitivity of MRE 75% was similar to WCE 77.8%
Aloi 2015 prospective[9]	Italy	Peds/25	Established and suspected CD	MRE and SICUS	Diagnostic yield of WCE is similar to that of MRE and SICUS (+ve MRE 15/25 *vs* +ve SICUS 16/25 *vs* +ve WCE 16/25) but the WCE is superior in detecting proximal SB disease
Oliva 2016 prospective[12]	Italy	Peds/38	Established CD	MRE and SICUS	Diagnostic yield of WCE is similar to that of MRE and SICUS (+ve MRE 19/38 *vs* +ve WCE 19/38 *vs* +ve SICUS 21/38) but the CCE is superior in detecting proximal SB disease

WCE: Wireless capsule endoscopy; CCE: Colon capsule endoscopy; SBR: Small bowel radiography; CTE: Computed tomography enterography; MRE: Magnetic resonance enterography; SICUS: Small intestinal contrast ultrasonography; CD: Crohn's disease; IC: Indeterminate colitis; Peds: Pediatric; +ve: Positive.

most recent medical chart and laboratory data. Blood samples for hemoglobin and hematocrit, erythrocyte sedimentation rate, C-reactive protein (CRP), and albumin were collected within 7 d if these labs were not obtained in the last 2 wk prior to WCE.

MRE

MRE examinations were performed as a standard of care by using a whole body magnetic resonance imaging unit (Children's Mercy Hospital, Kansas City, MO, United States) with an 8-channel abdominal phased-array coil. A benefiber dissolved in liquid with weight-based dosing was used as the intraluminal oral contrast agent. Intravenous contrast was administered to reduce SB peristalsis and to prolong luminal distention. Axial and coronal T1 weighted images with fat suppression were performed. When the distention quality was inadequate, images were reobtained 30 minutes after the ingestion of a more appropriate dose for age of fiber water solution. Axial T2, axial diffusion and coronal true cine images were obtained.

One radiologist retrospectively reviewed the MRE for all subjects to provide a consistent assessment of the extent of SB activity for each subject. Patients with a MRE score of >3 were considered to have positive MRE study[20]. The score was modified in this study to exclude counting colonic segment involvement in the overall radiological score (maximum score is 13). Evaluated findings included SB wall thickness (0-3 mm or 3-6 mm, > 6mm), SB wall enhancement after intravenous contrast media (none, mild or severe), mucosal and serosal enhancement suggestive of mesenteric fatty infiltration, strictures (defined as luminal narrowing to be less than 10 mm), increased mesenteric vascularity close to the inflamed bowel loop, mesenteric lymphadenopathy, the presence of fistula, stricture or abscess and the number of SB segments involved (duodenal, jejunal and ileal)[9]. MRE score used is provided in supplemental material.

WCE

The capsule images were independently interpreted by two gastroenterologists with > 10 years of experience in capsule studies. To optimize the visualization of the jejunum and ileum of the CE, after an overnight fast, patients ingested Polyethylene Glycol 3350 PEG before they swallowed the capsule (PEG doses adjusted based on age: 34 g in 480 mL clear liquid if age of the subject was < 5 year, 51 g in 720 mL if 5-10 years, 68 g in 960 mL if >10 years). The CE used in this study was the PillCam™ SB video capsule (Given Imaging, Medtronics Ltd, Yokneam, Israel). It measures 11 mm × 26 mm and it weighs less than 4 g. This capsule was ingested orally in all patients except for one patient who was scheduled to have endoscopy on the same day, so the capsule was deployed by esophagogastroduodenoscopy. Capsule retention is defined as a

Table 2 Highlights baseline characteristics of patient's demographics and clinical and endoscopic descriptions

	All patients CD and IC *n* = 27	CD *n* = 20
Age at diagnosis year	13.46 (2.40)	13.48 (2.02)
Male %	74%	75%
Medications ratio (%)		
Biological alone or combination therapy	12/27 (44.4%)	11/20 (55%)
Immune modulators with no biologic combination	8/27 (30%)	5/20 (25%)
5 ASA +- steroids	4/27 (15%)	3/20 (15%)
Steroids alone	2/27 (7%)	0/20 (0%)
Antibiotic alone	1/27 (4%)	1/20 (5%)
Phenotype%		
Inflammatory	93%	93%
Stricturing	7%	7%
Duration of disease year	1.7 (2.32)	2.1 (2.57)
BMI percentile	57 (32.9)	58.18 (35.83)
PCDAI	10.2 (12.5)	9.8 (11.6)
SB transit time min	233 (115.4)	241(184.99)
Days between MRE and WCE days	4.19 (1.88)	4 (1.90)

Baseline characteristics of all patients expressed in mean (SD) and the ratio (percentage). CD Crohn's disease, IC indeterminate colitis, ASA amino salicylate, SB small bowel, BMI body mass index, MRE magnetic resonance enterography, PCDAI pediatric Crohn's disease activity index WCE wireless capsule endoscopy.

failure of the passage of the capsule from the gastrointestinal tract for ≥ 2 wk[20]. The examination was incomplete if the capsule did not reach the cecum by the end of the study. Images were considered as negative (or inactive) if no abnormalities were seen and as positive (or active) if clear abnormalities of the SB mucosa (ulcerations > 3, erosions, polyps, vascular lesions, and bleeding lesions were seen). White lesions within a crater with surrounding erythema were considered ulcers, whereas small superficial white lesions, even with surrounding erythema, were considered erosions[24]. If no abnormalities or non-specific findings (such as erythematous spots or mucosal damage) were seen, the examination was considered non-specific or normal. All capsule readers were blinded to each other's findings or radiological MRE images but were aware of the patient's medical history and laboratory testing. In addition, evaluators used the capsule endoscopy data collection form including the Lewis scoring system that is automatically calculated and included in the RAPID™ software[26]. The Lewis score is a WCE ranking of inflammatory activity into three levels based on erythema, stenosis, edema and erosions in small intestinal tertiles: (1) No disease or clinically insignificant disease (LS < 135); (2) Mild disease (135 ≤ LS ≤ 790); and (3) Moderate or severe disease (LS > 790). Any WCE with Lewis score more than 135 is considered positive[26].

Histological findings

A subgroup of 15 of the 27 patients had pathology specimens available for review within 2 mo of the WCE study [mean 3.9 wk, standard deviation (SD) = 2.58]. Pathology specimens from the terminal ileum and duodenum were evaluated as they are considered the accepted reference standard to determine active CD in the SB.

Histology findings were considered positive if the subject had final impression of chronic active ileitis or duodenitis or if there was a description of at least one of the chronic changes (architectural changes, increase in lamina propria mononuclear cells and lamina propria PMNs) together with at least one of activity histology findings (epithelial damage, intraepithelial PMNs in surface epithelium, cryptitis, crypt abscess, erosions/ulcers, or granulomas) in either ileal or duodenal biopsies. This is based on the histological remission definition proposed by a systemic review with absence of neutrophils in crypt and lamina propria, basal and lamina propria plasma cells and eosinophils[27] and the in the diagnosis guidelines for CD[2]. The histology grading used is provided in the supplemental material.

Statistical analysis

Descriptive data was expressed as the mean [± standard deviation (SD)] for the continuous variables. Categorical data were expressed as frequencies and per-

centages. A Chi square with the Fisher correction was used to evaluate the differences for categorical variables when appropriate. Statistical significance is expressed as $P < 0.05$

For each of the 2 methods evaluated (MRE and WCE), sensitivity, specificity, negative predictive value, positive predictive value, and accuracy were determined by the available PCDAI and histological findings from the terminal ileum and duodenum. The Fisher exact test was used to evaluate the performance of each method in relation to another. Exact binomial 95% confidence intervals were also reported. The sample size of 34 children was estimated as having an 80% power to detect 23% difference in IBD small intestinal MRE findings and WCE detection rate. This size was estimated based on our previous retrospective study[24].

The Pearson correlation coefficient was utilized to assess agreement between Lewis capsule endoscopy score and PCDAI. All *P* values were 2 sided with statistical significance evaluated as statistical significance $P < 0.05$. All analyses were performed in SPSS Version 19.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Forty-five subjects with the diagnosis of CD or IC were enrolled. Twenty-seven patients completed all of the procedures of the study, 20 with CD (74%) and 7 with IC (26%). Eighteen patients were excluded because of inability to swallow PC (4/18), failure to pass PC (3/18) or failure to follow or complete study procedures (3/18), screen failure (1/18) or elective withdrawal from study (7/18).

Concordance between gastroenterologist reviewers for the diagnosis of small intestinal CD was excellent with strong correlation between the two Lewis score ($r = 0.875$, $P < 0.001$). The studies were incomplete in 3 patients. Two of these demonstrated active CD and one was negative. The patient with a negative incomplete study was excluded. There were no capsule retentions in any of the studies. All capsules passed within 2 wk of the WCE and no surgical interventions were needed. The mean small intestinal transit time was comparable (260.2 min, 218.2 min, P = NS) for WCE positive and negative studies respectively. The Pearson correlation coefficient between average Lewis score between both reviewers and PCDAI is very poor ($r = 0.12$, P = NS). Agreement rates for positive WCE, MRE, and PCDAI for the total subject group is shown in Figure 1. Agreement rates for positive WCE, MRE, and SB Histology for the 14 patients in which the histology was available are shown in Figure 2.

The concordance rate between WCE and MRE was poor (69%) in collectively matched positive and matched negative subjects. The concordance rate between MRE and WCE is shown in Figure 3 in all subject patients (CD and IC) and in Figure 4 in CD only patients.

Histology was available for fifteen patients within 2 mo of the WCE study (mean 3.9 wk and SD = 2.58) and 8 of them demonstrated active CD histology in the ileum and one in the duodenum. For one of the patients who has diagnosis of IC with positive histology, the WCE interpretation was discrepant between reviewers and this patient was dropped from the analysis leaving 14 patients analyzed in the histology comparison and 26 total patients. In CD patients, when both MRE and WCE were compared using PCDAI > 10 as the standard reference reflecting active small intestinal CD, the sensitivity of MRE and WCE were 100% and 83% respectively and the specificity of MRE and WCE were 57.14% and 78.6%, respectively. If the histology in ileum or/and duodenum was used as the reference for active small bowel involvement, WCE had a higher specificity as compared to MRE (83.3% *vs* 50%). See Table 3.

When all IBD patients were taken collectively, there was no statistically significant relationship between the performance of either MRE or WCE with PCDAI or with each other. However, in patients with CD, those with a positive PCDAI (> 10) were more likely to have a positive WCE as compared to those with a negative PCDAI (83% *vs* 21%; $P = 0.018$). There was no significant difference in the frequency of a positive MRE comparing those with and without a positive PCDAI. See Table 4.

DISCUSSION

There are several modalities available to screen for small intestinal involvement in IBD[1]. However, there is no consensus on a gold standard and it remains controversial whether one of the available examinations is adequate for assessment of SB Crohn's alone or if it should be used in conjunction with other investigative modalities.

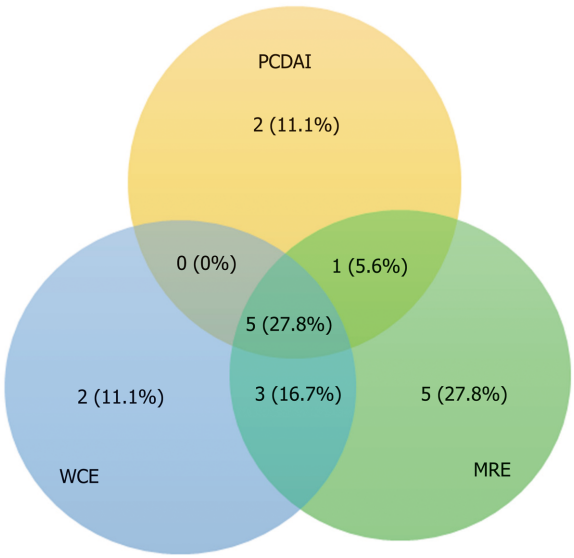

Figure 1 Concordance rate of positive small bowel involvement in the pediatric Crohn's disease activity index, positive magnetic resonance imaging, and wireless capsule endoscopy modalities in all patients *n* = 26. PCDAI: Pediatric Crohn's disease Activity Index; MRE: Magnetic resonance enterography; WCE: Wireless capsule endoscopy.

There are several prospective adult studies comparing MRE to WCE in identifying SB Crohn's which conclude that there is no significant difference in the diagnostic yield and accuracy of MRE and WCE in established non-stricturing CD[15,16,28] or suspected and established CD together[19,20,21]. However, proximal small bowel lesions were more often detected using WCE rather than MRE[16,19,20,21]. Moreover, other prospective studies have shown superiority for WCE[14,23].

The published pediatric studies are far more limited especially ones utilizing MRE as radiological modalities[9,12,13] and they have evaluated heterogeneous groups of IBD patients[9,13,24]. Because there is no consensus on the best screening tool for SB in CD, most of the previous studies evaluated the performance of WCE or imaging studies as the measure of diagnostic yield. It is noteworthy that this approach is suboptimal and simply suggests that a test can detect abnormalities rather than confirming its significance.

Our study is one of the first prospective studies in the United States to compare clinical, radiological and histological measures to WCE in assessing SB activity in pediatric IBD specifically CD and indeterminate colitis. The primary focus was on established Crohn's disease and did not include heterogeneous populations with suspected IBD[9,24]. Our study demonstrates excellent inter-observer agreement in the interpretation of WCE, suggesting WCE is highly reproducible.

Because of the absence of a standard criteria for confirming proximal SB CD activity that is feasible and less invasive in children, this study used two different references to compare MRE with WCE. The first was the PCDAI as a global clinical standard for overall disease activity and the second was pathological findings in the ileum and duodenum as histological standards for SBI. We have used PCDAI because the evidence suggested its moderate correlation with pediatric CD activity and endoscopic scores[29,30]. PCDAI < 10 is the standard definition of inactive CD that is used in clinical trials for clinical response to medical therapies[29,30]. Pediatric onset CD runs a more aggressive active disease course, including more extensive disease location, more upper GI involvement and increased need for more aggressive medical therapy, in pediatric studies[31-33]. This is also replicated in adult studies; proximal small bowel involvement should be considered as high risk in terms of CD-related surgery[34-36]. In particular L4 (proximal SB not including TI) disease phenotype was associated with stricturing disease, and significantly increased risk for multiple surgeries[37,38]. Pediatric phenotypes of CD at the time of diagnosis showed 50.9%were affected by CD proximal to the terminal ileum in United Kingdom[39]. In Europe, isolated ileal disease (L1) is reported to be 16% in CD children, or proximal to terminal ileal (L4) in 24% and esophagogastroduodenal (EGD) involvement in 30%[33]. If pediatric CD mostly runs an aggressive and extensive course involving small bowel either in more than half of children, then using PCDAI can arguably be justified to reflect active small bowel disease. However, this is still a limitation in this study

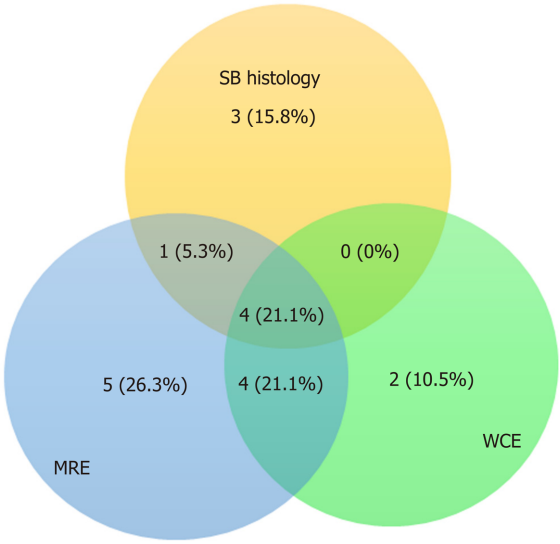

Figure 2 Concordance rate of positive small bowel involvement in wireless capsule endoscopy, magnetic resonance enterography and small bowel histology modalities in only patients with available histology *n* = 14. SB: Small bowel; WCE: Wireless capsule endoscopy; MRE: Magnetic resonance enterography.

because it does not exclude the possibility of bowel disease activity overall and it is not validated to accurately reflect SBI compared to other invasive reliable standards.

Pediatric prospective studies used ileocolonoscopy as the reference standard for identifying active CD in the terminal. Moreover, a consensus reference standard was used to determine active CD in the proximal bowel[9,12]. This consensus is basically made up of clinical expert opinion reviewing the results of available images, labs and capsule endoscopy to decide jejunal and duodenal activity.

The current study showed near similar results for both references. However, there was relatively poor agreement between WCE and MRE in sensitivity or specificity. We found a higher sensitivity for MRE as compared to WCE with both standards. While WCE was more specific than MRE in detecting SB disease, the two modalities were comparable in test accuracy.

Our findings are consistent with previously reported pediatric studies which suggest that MRE and WCE are comparable in accuracy for detecting SB disease[9,13]. In contrast, Oliva and colleagues, in a study of established CD in children, demonstrated slightly better accuracy of colon capsule endoscopy including SB images than MRE and SICUS. [12] Our results are consistent with a recent systemic review by Giles revealing a pooled sensitivity and specificity for MRE for detecting active SB CD of 84% and 97%, respectively, with endoscopy as the reference test[39]. However, the specificity of MRE is much lower in our study at 50%-57%, likely attributed to a smaller sample size.

MRE was found to be a sensitive and specific test with a decent diagnostic yield in a systemic review published in 2013[40]. The higher sensitivity of MRE may be attributed to the low threshold being used in MRI scoring systems in few studies, the inclusion of colonic activity in some of the studies or localization of SB segments based on anatomic sectioning of the images[16,20]. Detection of proximal small bowel inflammation in CD by MRE is challenging. Newer suggested scoring systems such as MRI global score MEGS provide potential accurate evaluation of the SB and strongly correlates with inflammation detected with fecal calprotectin and with pan-intestinal inflammatory activity[41] but it is very time consuming and cumbersome limiting practicality[42-44]. Moreover, terminal ileum MRI index of Activity (MaRIA) score has been developed but it did not address perfectly the activity of the proximal SB disease[42].

Our study has uniquely modified the score reported by Jensen and discounted colonic involvement to accurately focus on scoring only small bowel findings in term of enhancement, thickening, vascular, lymphatic or fatty mesenteric changes or presence of SB complications (abscess, fistula, stricture) with same cut off > 3 to robust SB MRI score. Whether this modified score has a clinical significance is yet to be validated. This certainly suggests the need for standardizing MRI scoring, especially in children. Until a validated score is universally accepted, the possibility of MRE false positive results and the possibility of an overestimated positive yield MRE

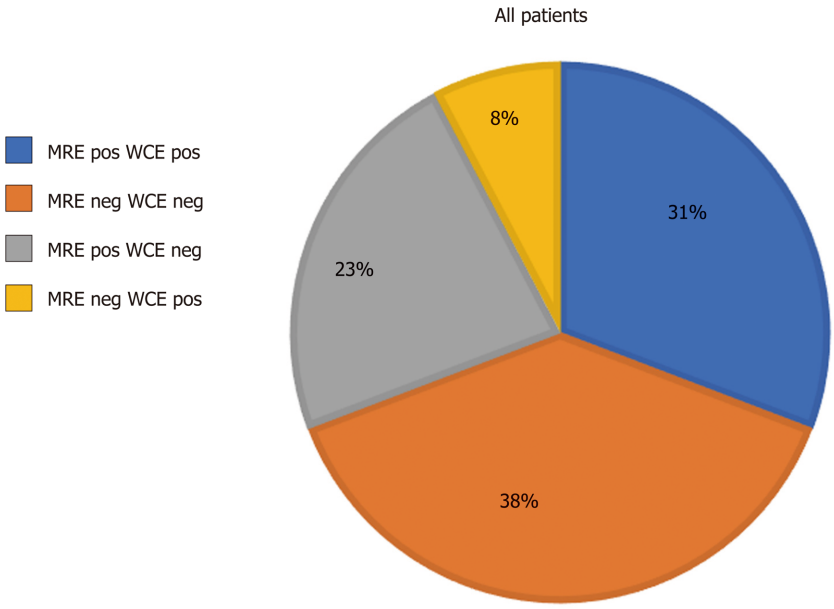

Figure 3 Concordance rate of magnetic resonance imaging and wireless capsule endoscopy in all patients. WCE: Wireless capsule endoscopy; MRE: Magnetic resonance enterography; Pos: Positive; Neg: Negative.

should be taken into consideration.

In the current study, the specificity of WCE was higher than that of MRE (83% *vs* 50%) which contrasts with what has been reported in an established CD population (94% in WCE *vs* 89% in MRE)[12]. Specificities of both WCE and MRE in the current study were lower than that reported in pediatric patients with suspected or established CD populations[12,13] and disagreed with Aloi *et al*[9] who found MRE to be more specific than WCE (89% *vs* 72%, respectively). Our results differed with other published studies likely because of the heterogeneity of populations used in their analysis and possibly to our small sample size. Therefore, WCE may be suggested as a unique confirmatory test in the assessment of mucosal disease activity. WCE has been suggested as a secondary test if MRE is inconclusive[13]. Published expert recommendations state that a negative capsule endoscopy in CD likely excludes the presence of small bowel disease[45].

We were able to make comparison of the performance of pairs of tools (WCE, MRE and PCDAI) with each other in patients with IBD (CD and IC) overall, and in patients with CD only. The performance of one test was not able to predict the results of the other test when WCE was compared to MRE or when MRE was compared toPCDAI. However, in patients with CD, those with a positive PCDAI (> 10) were more likely to have a positive WCE as compared to those with a negative PCDAI (P = 0.018). See Table 4. This suggests that active disease defined with higher PCDAI score, will increase the predictive ability of WCE to be positive and it supports the use of PCDAI routinely in the assessment of SBI along with radiologic or endoscopic modalities.

This current study is limited by lack of an established reference or gold standard that can be used to compare modalities that may result in a confirmation bias. We therefore had to adopt several surrogate indices to determine if either diagnostic modality correlated with SB disease. Additionally, the current study only partially controls for timing of histology which might impact treatment measures that in turn could impact study results from MRE, SBC or both. It also lacks the evaluation of jejunal histology that can be affected in up to 20% of IBD patients. It is however explained by the assumption that histological changes may lag longer than endoscopic findings and microscopic inflammation persists in 25%-37% of cases of endoscopically quiescent CD[27]. Finally, each subject acted as its own control as there was no use of control group population.

Future studies should continue to integrate the use of WCE, low risk imaging modalities and clinical parameters in defining of SBI in children with CD. It will be useful to integrate a composite of these modalities in a practical validated scoring measure that identify SBI in the least invasive approach.

Our study supports the use of the radiation free, less invasive and generally tolerated imaging modalities of WCE and MRE with each having a favorable role in the assessment of SBI in children with established CD. Although the unique ability of the capsule to detect mucosal changes, and similar unique ability of MRE to detect

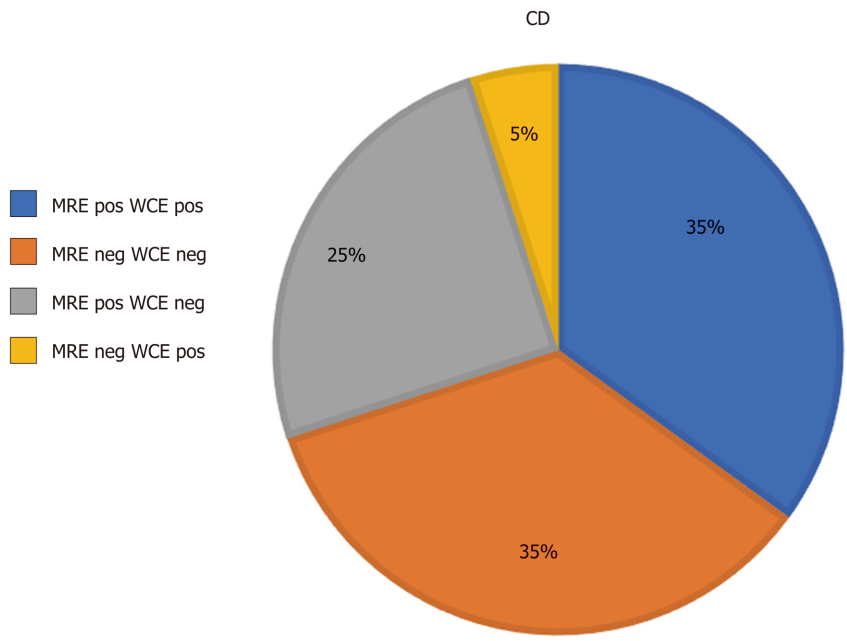

Figure 4 Concordance rate of magnetic resonance imaging and wireless capsule endoscopy in Crohn's disease patients. WCE: Wireless capsule endoscopy; MRE: Magnetic resonance enterography; Pos: Positive; Neg: Negative.

mural changes, there is still need for a standardized scoring system to describe the specificity of these findings. WCE more accurately detected small bowel disease with a much higher specificity while MRE had a higher sensitivity in pediatric IBD. Patients with active CD (PCDAI > 10) were more likely to have a positive WCE as compared to those with a negative PCDAI. Despite the disagreement between the two modalities, accuracy was comparable between MRE and WCE suggesting that they may have a complementary role in the assessment of small bowel disease.

Table 3 Magnetic resonance imaging and wireless capsule endoscopy positivity predictive of small bowel involvement in reference pediatric Crohn's disease activity index > 10 and to histology

	Reference standard is PCDAI > 10 indicate active CD				Reference standard is histology in ileum and duodenum			
	CD only patients (*n* = 20)				Histology available samples only (*n* = 14)			
	MRE		WCE		MRE		WCE	
	Value	95%CI	Value	95%CI	Value	95%CI	Value	95%CI
SEN	100%	54.07% to 100%	83.3%	35.88% to 99.58%	62.50%	24.49% to 91.48%	50.00%	15.70% to 84.30%
SP	57.14%	28.86% to 82.34%	78.6%	49.20% to 95.34%	50.00 %	11.81% to 88.19%	83.33 %	35.88% to 99.58%
PPV	50%	35.32% to 64.68%	62.5%	36.49% to 82.86%	62.50%	38.87% to 81.37%	80.00%	36.99% to 96.46%
NNP	100%		91.7%	64.29% to 98.53%	50.00 %	23.14% to 76.86%	55.56 %	36.43% to 73.17%
Accuracy	70%	45.72 to 88.11%	80.0%	56.34% to 94.27%	57.14%	28.86-82.34%	64.29%	35.14% to 87.24%

SEN: Sensitivity; SP: Specificity; PPN: Positive predictive value; NNP: Negative predictive value; MRE: Magnetic resonance enterography; PCDAI: Pediatric Crohn's Disease Activity Index; WCE: Wireless capsule endoscopy; CD: Crohn's disease.

Table 4 Fischer exact performance of each diagnostic test compared to other modality or pediatric Crohn's disease activity index

Studies compared	All patients (*n* = 26)	CD only (*n* = 20)
MRE and WCE	*P* = 0.428	*P* = 0.373
MRE and PCDAI	*P* = 0.395	*P* = 0.325
WCE and PCDAI	*P* =0.1892	*P* = 0.0181

MRE: Magnetic resonance enterography; PCDAI: Pediatric Crohn's Disease Activity Index; WCE: Wireless capsule endoscopy; CD: Crohn's disease.

ARTICLE HIGHLIGHTS

Research background

Magnetic resonance enterography (MRE) and wireless capsule endoscopy (WCE) are equally accepted modalities for noninvasive screening of small bowel involvement (SBI) in children with Crohn's disease (CD) and indeterminate colitis (IC) and there is a paucity of data comparing the two in children. Thereby guiding the clinician in selecting the ideal diagnostic approach. Many prospective adult studies and few in pediatrics comparing MRE to WCE in identifying small bowel (SB) CD showed no significant difference in the diagnostic yield and accuracy of MRE and WCE in established non-stricturing CD or suspected and established CD together. The current study is the first prospective study in children with established IBD in the United States assessing the roles of MRE and WCE in identifying SB disease involvement in IBD. This study provides evidence for capsule endoscopy role whether it is superior or complementary in the evaluation of established disease exacerbation in patients with IBD in relation to MRE thereby guiding the clinician in selecting the ideal diagnostic approach.

Research motivation

Therefore, the goal of this study is to provide additional evidence and guidance for capsule endoscopy role in the evaluation of established CD exacerbation compared to MRE into relation Pediatric Crohn's Disease Activity Index (PCDAI), and histological indices.

Research objectives

The primary goals of this study are to prospectively compare the diagnostic yield, concordance rate, sensitivity and specificity between MRE and WCE findings and their agreement with the PCDAI or with histological small bowel involvement in children with known IBD; CD or IC. Secondary goals are to assess the performance of each of the modalities (MRE, WCE and PCDAI) in relation to each other in order to predict the results of the compared tests and to assess the correlation between Lewis capsule endoscopy score and PCDAI.

Research methods

Consecutive patients diagnosed with CD and IC were screened for inclusion. After informed consent patient's demographic and clinical data was abstracted. The current pediatric disease activity index (PCDAI) and endoscopic findings were included. Patients underwent MRE and WCE including preprocedural patency capsule within a maximum of 7 d of each other. Pathological presence of active small bowel disease in ileal and duodenal biopsies were collected if the endoscopy was performed within 2 mo of the WCE study. Patients who failed to pass the PC were excluded from the study. WCE was read by two different experienced

gastroenterologists (Attard TM and Colombo JM) blinded to each other's findings and to the findings on MRE (Mardis NJ). Agreement between WCE reviewers, WCE and MRE findings and concordance between positive PCDAI and SBI based on MRE compared with WCE was computed.

Research results

In CD patients, when both MRE and WCE were compared using PCDAI > 10 as the standard reference reflecting active small intestinal CD, the sensitivity of MRE is higher than WCE but specificity of MRE were lower than WCE. If the histology in ileum or/and duodenum was used as the reference for active small bowel involvement which is usually the most reliable reported standard, WCE had a higher specificity as compared to MRE (83.3% *vs* 50%). Concordance between WCE and MRE was poor (69%) whether both agreed positively or negatively. While WCE was more specific than MRE in detecting SB disease, the two modalities were comparable in test accuracy. Specificities of both WCE and MRE in the current study were lower than that reported in pediatric patients with suspected or established CD populations. An active disease defined with higher PCDAI score > 10, will increase the predictive ability of WCE to be positive and it supports the use of PCDAI routinely in the assessment of SBI along with radiologic or endoscopic modalities. The argument remains to be elucidated on what is the gold standard that best identify the SBI in patients with IBD.

Research conclusions

Our study supports the use of the radiation free, less invasive and generally tolerated imaging modalities of WCE and MRE with each having a favorable role in the assessment of SBI in children with established CD. Although the unique ability of the capsule to detect mucosal changes and similar unique ability of MRE to detect mural changes, there is still need for a standardized scoring system to describe the specificity of these findings. WCE more accurately detected small bowel disease with a much higher specificity while MRE had a higher sensitivity in pediatric IBD. Patients with active CD (PCDAI > 10) were more likely to have a positive WCE as compared to those with a negative PCDAI. Despite the disagreement between the two modalities, accuracy was comparable between MRE and WCE suggesting that they may have a complementary role in the assessment of small bowel disease.

Research perspectives

Future studies should continue to integrate the use of WCE, low risk imaging modalities and clinical parameters in defining the best standard to identify SBI in children with CD. It will be useful to integrate a composite of these modalities in a practical validated scoring measure that identify SBI in the least invasive approach.

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SYSTEMATIC REVIEWS

Systematic review of nutrition screening and assessment in inflammatory bowel disease

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Abstract

BACKGROUND

Malnutrition is prevalent in inflammatory bowel disease (IBD). Multiple nutrition screening (NST) and assessment tools (NAT) have been developed for general populations, but the evidence in patients with IBD remains unclear.

AIM

To systematically review the prevalence of abnormalities on NSTs and NATs, whether NSTs are associated with NATs, and whether they predict clinical outcomes in patients with IBD.

METHODS

Comprehensive searches performed in Medline, CINAHL Plus and PubMed. Included: English language studies correlating NSTs with NATs or NSTs/NATs with clinical outcomes in IBD. Excluded: Review articles/case studies; use of body mass index/laboratory values as sole NST/NAT; age < 16.

RESULTS

Of 16 studies and 1618 patients were included, 72% Crohn's disease and 28% ulcerative colitis. Four NSTs (the Malnutrition Universal Screening Tool, Malnutrition Inflammation Risk Tool (MIRT), Saskatchewan Inflammatory Bowel

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Disease Nutrition Risk Tool (SaskIBD-NRT) and Nutrition Risk Screening 2002 (NRS-2002) were significantly associated with nutritional assessment measures of sarcopenia and the Subjective Global Assessment (SGA). Three NSTs (MIRT, NRS-2002 and Nutritional Risk Index) were associated with clinical outcomes including hospitalizations, need for surgery, disease flares, and length of stay (LOS). Sarcopenia was the most commonly evaluated NAT associated with outcomes including the need for surgery and post-operative complications. The SGA was not associated with clinical outcomes aside from LOS.

CONCLUSION
There is limited evidence correlating NSTs, NATs and clinical outcomes in IBD. Although studies support the association of NSTs/NATs with relevant outcomes, the heterogeneity calls for further studies before an optimal tool can be recommended. The NRS-2002, measures of sarcopenia and developments of novel NSTs/NATs, such as the MIRT, represent key, clinically-relevant areas for future exploration.

Key words: Nutrition; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Screening; Outcomes research

Core tip: Malnutrition is highly prevalent amongst patients with inflammatory bowel disease (IBD) and negatively impacts various clinical outcomes. This review highlights the Malnutrition Universal Screening Tool, Malnutrition Inflammation Risk Tool, Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool, Nutrition Risk Screening 2002 and cross-sectional imaging assessments of sarcopenia as promising nutrition screening and assessment tools in IBD. By becoming familiar with and consistently applying these tools we can move towards early recognition, diagnosis and management of malnutrition in clinical practice. Further research will elucidate the optimal tools and the impact of their integration into routine practice on clinical outcomes in IBD.

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INTRODUCTION

Malnutrition is highly prevalent in inflammatory bowel disease (IBD); present in up to 70% of patients with active disease and up to 38% of patients in remission[1-3]. Closely related to malnutrition, sarcopenia is a syndrome defined by the presence of low muscle mass and either decreased muscle strength or physical performance[4]. Sarcopenia and malnutrition represent separate entities but often overlap; notably, the Global Leadership Initiative on Malnutrition, American Society for Parenteral and Enteral Nutrition and European Society for Clinical Nutrition and Metabolism (ESPEN) include components of reduced muscle mass and impaired muscle function in their respective consensus definitions of malnutrition[5-7].

In patients with IBD, sarcopenia and malnutrition have been associated with increased hospitalizations, disease flares, need for surgery, and post-operative complications[8-13]. Early identification of malnourished patients using a two-step approach of nutritional screening and subsequent assessment[6] may allow for earlier intervention and impact on clinical outcomes[14-17]. Recent data from Zhang *et al*[10] showed fewer major complications in patients who received peri-operative enteral nutrition than those who did not (6.5% *vs* 29%, $P = 0.045$). In line with these findings, ESPEN recommends implementing nutrition support therapy in malnourished peri-operative patients with IBD[18].

Nutritional risk screening (NRS) is a process to predict those at risk of malnutrition so that they can be referred to a registered dietitian (RD) for detailed nutritional

assessment and intervention. Nutrition screening tools (NSTs) (*i.e.*, the malnutrition universal screening tool, MUST) are rapid evaluations that can be completed by any member of the medical team whereas nutrition assessment tools (NATs) (*i.e.*, the subjective global assessment, SGA) are usually more detailed and require greater specialized resources[5]. As recent studies have demonstrated a close relationship between malnutrition and sarcopenia, many expert groups now incorporate measures of lean muscle mass within the definition of malnutrition[19,20]. For the purposes of our review, measurements of lean muscle mass and sarcopenia will be classified as a NAT.

To date, there are no published recommendations that exist for use of a specific NST or NAT in IBD[14,18,21]. Although there have been isolated reviews of sarcopenia in IBD[22], a practical approach to nutrition screening and treatment is more extensive than sarcopenia assessment alone. Given the current lack of consensus, high prevalence and the significant health and economic burden of malnutrition in IBD, we performed a systematic review of the available literature surrounding NSTs and NATs for IBD patients, including sarcopenia. In patients with IBD, our aims were to provide a descriptive overview of: (1) The prevalence of abnormalities on NSTs and NATs; (2) Whether the findings on NSTs are associated with abnormalities on NATs; and (3) Whether NSTs or NATs are associated with clinical outcomes. Evidence of clear associations between NSTs and NATs may simplify the nutrition care process, allow for much needed risk stratification and targeted use of limited dietitian resources.

MATERIALS AND METHODS

Data sources/search strategy (Appendix S1)

The initial literature review was completed on December 20, 2017 using the following databases: National Institutes of Health PubMed (1946-present), Ovid MEDLINE (1946-present) and CINAHL Plus (1937-present). Medical library search heading terms were used to combine "nutrition screening", "nutrition assessment", "malnutrition", or "sarcopenia" with either terms of "inflammatory bowel disease", Crohn's/Crohn disease" or "ulcerative colitis". Filters applied included human subjects, English language and adult population (age 16 years and above). An updated search was conducted to identify articles published between December 20, 2017 and January 14, 2019 on PubMed. Further eligible studies were extracted from a review of reference lists of full texts retrieved after initial screening of search results.

Study selection

Initial search results were screened against inclusion and exclusion criteria through review of article titles and abstracts. Inclusion criteria encompassed studies whose population was > 16 years old, had a confirmed diagnosis of IBD [either Crohn's disease (CD) or ulcerative colitis (UC)], and (1) Associated NSTs with a diagnosis of malnutrition using NATs; or (2) Associated either NST or NATs with prospective clinical outcomes. Study designs eligible for inclusion included randomized controlled trials, cross-sectional studies, cohort studies and case control studies.

Records were excluded if a formal NST/NAT was not utilized, if there were no prospective clinical outcomes evaluated and/or the study lacked comparisons between NSTs and NATs. Additionally, studies that utilized body mass index (BMI) as the sole NAT were excluded as previous studies have shown that BMI does not accurately predict body composition in IBD patients[23]. Studies that used NST/NATs based only on laboratory parameters (*i.e.*, CONUT, OPNI) were also excluded. Significant laboratory abnormalities can be seen in IBD patients at baseline due to the inflammatory nature of their illness that do not necessarily accurately reflect nutrition status[24]. Articles that did not have an English translation available were excluded. Articles of interest or that were unclear as to meeting inclusion/exclusion criteria had their full text retrieved and reviewed by two independent reviewers (SL and MN) for eligibility. Disagreements between reviewers were settled through discussions with a third reviewer (PT).

Data extraction

The following data was extracted from each study where possible by an independent reviewer: First author's surname, journal, year of publication, study design (patient selection) and duration, number of participants, underlying disease (CD or UC), patient demographics (age, duration of disease, severity of disease, concomitant treatments), type of NST or NAT used, reported correlations between NST and NAT or NST/NAT, and clinical outcomes.

Quality assessment

As most studies were observational non-randomized non-interventional studies without control groups, quality was assessed with a modified Newcastle-Ottawa assessment scale (NOS)[25]. Of available instruments, the NOS is highlighted as one of the most useful tools for assessing methodological quality and risk of bias in non-randomized studies in the Cochrane Handbook for Systematic Review of Interventions[26]. Study quality was assessed by two independent reviewers utilizing the modified NOS (SL and MN). Disagreements between reviewers were settled through discussions with a third reviewer (PT).

Data synthesis

Statistical results relating to outcomes of interest were retrieved from each study and categorized as per objectives. Authors and a third-party statistician (BV) reviewed all data. Given the heterogeneity of results, they were not suitable for a formal meta-analysis.

RESULTS

Literature search results

The summary of the literature search and selection process is shown in Figure 1. In total, 1782 studies were identified from the initial search after removal of duplicates. An additional 9 studies were identified through review of the full-text of articles of interest. 62 studies were identified for full-text review of which 16 studies met inclusion/exclusion criteria. 31 studies were excluded because they lacked predictive outcomes or comparisons between NST/NATs. 15 studies were excluded as there was no formal NST or NAT utilized in the study or the NST/NAT utilized included only laboratory parameters or was based solely on BMI.

Study populations

Included studies were published between 2015-2018. Seven studies were conducted in Asia[9-11,13,27-29], four in Europe[8,30-32], four in North America[12,33-35], and one in Oceania[36]. In total, 1618 patients with IBD were included from all studies, 1158 (72%) had the diagnosis of CD, 454 (28%) were UC patients and 4 (0.2%) had indeterminate colitis. The age of participants ranged from 16 to 86 years (Table 1).

Nutrition screening or assessment tools

NSTs that were examined in the included studies were the NRS-2002, MUST, Nutritional Risk Index (NRI), Malnutrition Inflammation Risk Tool (MIRT), and the Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool (SaskIBD-NRT)[8,9,13,27,30,35]. Table 2 illustrates the basic components, categories and interpretations of included NSTs.

The NATs evaluated in the studies in this review included the SGA, comprehensive RD and gastroenterologist (GI) assessment, Skeletal Muscle Percentage (SMP), Fat Free Mass Index (FFMI), L3 Skeletal Muscle Index (L3 SMI), Appendicular Skeletal Muscle Indices, Skeletal Muscle Area (SMA), Total Psoas Muscle Area, and the mean Hounsfield unit average calculation (mHUAC) at L3[8-13,28-30,33,35,36]. Table 3 illustrates the basic components, categories and interpretations of included NATs.

Quality assessment results

Given the non-randomized observational design of all studies, with the majority lacking well-defined cohorts, all studies carry a high relative inherent risk of bias. Utilizing the modified NOS scale, half of the studies (8/16) were assessed to be of acceptable quality, scoring four or more stars out of five, with the other half assessed to be of relatively poor-quality scoring three or less stars (Table S2).

What is the prevalence of abnormalities on nutrition screening and assessment?

Five studies utilized various NSTs (MUST, NRI, NRS-2002, and SaskIBD-NRT) to categorize patients ordinally into low, moderate and high nutrition risk categories[9,13,27,30,35]. The most commonly utilized NST was the MUST (4/5 studies) showing 28.0% (n = 115) to be at high nutrition risk (MUST ≥ 2) across a composite of inpatient/outpatient studies[9,13,30,35]. Of the two inpatient studies, both utilizing the NRS-2002, 67.0% (n = 75) of patients were found to be at high nutrition risk (NRS-2002 ≥ 3)[9,13]. Of the three outpatient studies, 29.1% (n = 87) of patients were found to have at least a mild/moderate degree of nutrition risk *via* MUST (score ≥ 1), NRI (score ≥ 97.5) and SaskIBD-NRT (score ≥ 3)[27,30,35] (Table 4).

Ten studies evaluated the presence of sarcopenia in their respective populations, with a total prevalence of 39.5% (n = 477) across all studies[9-12,29-34]. Three studies

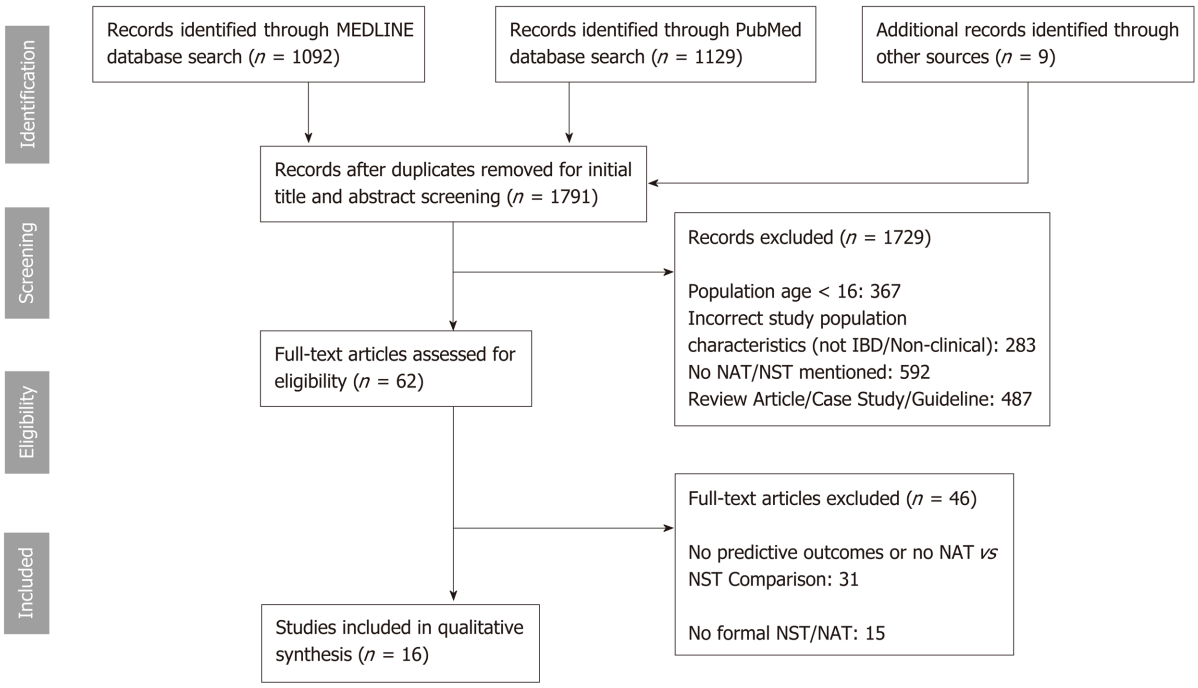

Figure 1 PRISMA flow diagram. IBD: Inflammatory bowel disease; NST: Nutrition screening tools; NAT: Nutrition assessment tools.

utilized the SGA in categorizing patients into well-nourished (SGA-A), mild/moderately malnourished (SGA-B) and severely malnourished (SGA-C) with two of the studies based on an inpatient IBD population. The total proportion of patients diagnosed with some degree of malnutrition based on SGA (SGA B/C) was 61.7% (n = 103)[8,9,13] (Table 5).

How did findings on nutrition screening compare to those on nutrition assessment?

Four studies (25%) included comparisons between an abnormal score on an NST and how that compared to a diagnosis of malnutrition using a NAT[8,9,30,35]. All four NSTs (MUST, NRS-2002, MIRT, and SaskIBD-NRT) showed significant association with NAT measures[8,9,30,35]. In both inpatients and outpatients from two separate studies[9,30], the MUST showed a significant association *via* logistic regression [odds ratio (OR) = 0.934, P = 0.014] and fair inter-rater agreement (Cohen's kappa=0.53) to SMI and FFMI. One study demonstrated poor inter-rater agreement (Cohen's kappa = 0.15) of MUST with com-prehensive RD/GI nutritional assessment among outpatients[35]. NRS-2002 was significantly associated with SMI (OR = 0.928, P = 0.008) in one inpatient study[9]. MIRT also demonstrated significance with a moderate correlation to SGA in one outpatient study (Spearman Rank Correlation = 0.394, P = 0.005)[8]. The SaskIBD-NRT showed strong inter-rater agreement (Cohen's kappa = 0.73) with comprehensive RD/GI assessment in outpatients[35] (Table 6).

Were nutrition screening tools associated with clinical outcomes?

Three studies (18.8%) associated NSTs with clinical outcomes. The NSTs utilized in these studies included the MUST, MIRT, NRS-2002, and NRI[8,13,27], the latter three showing significance[8,13,27]. Baseline MIRT was significantly correlated *via* Spearman rank correlation at 6 mo with hospitalizations (ρ = 0.398, P = 0.003), disease flares (ρ = 0.299, P = 0.030), disease complications (ρ = 0.333, P = 0.015), and need for surgery (ρ = 0.371, P = 0.006)[8]. Interestingly, the study did not find a significant association between MIRT and CDAI or Harvey-Bradshaw index (HBI) scores at 6 mo (P = 0.077 and 0.195 respectively)[8] (Table 7).

NRS-2002 (scores ≥ 3 *vs* ≤ 2) significantly predicted hospital length of stay (P = 0.032), however did not significantly predict the need for surgery (P = 0.109)[13]. A high NRI score (> 97.5) significantly predicted response to infliximab among CD patients (P = 0.037)[27]. MUST was examined in only one study and showed a trend towards significance in predicting length of stay (P = 0.058) and had no significance in predicting need for intestinal resection (P = 0.314)[13] (Table S3).

Were nutrition assessment tools associated with clinical outcomes?

Table 1 Demographics of patients with inflammatory bowel disease included in the studies

Study ID	Total (*n*) (M:F)	CD:UC:ID (*n*)	Age (yr)	BMI (kg/m^2)	Steroid *n* (%)	Immunomodulator *n* (%)	Biologics *n* (%)	Previous resection *n* (%)
Adams *et al*[33]	90 (38:52)	76:14	Median: 35 (26-50)	Median: 22.5	30 (33)	40 (44)	15 (17)	40 (44)
Bamba *et al*[9]	72 (52:19)	43:29	UC Median: 39 (28-55) CD Median: 29 (25-37)	Median: 19.5	-	-	-	25 (35)
Csontos *et al*[30]	173 (92:81)	126:47	Mean: 34.8 ± 12.3	Mean: 23.6	-	-	-	-
Cushing *et al*[34]	89 (53:29)	0:89	Mean: 43 (9 – 86)	Non-sarcopenic: 26 ± 8 Sarcopenic: 23 ± 6	-	33 (37)	26 (29)	-
Fujikawa *et al*[29]	69 (45:24)	0:69:0	Mean: 39.8 ± 14.4	Mean: 20.40 ± 3.65	-	-	-	-
Haskey *et al*[35]	110 (47:63)	75:35	Mean: 39 ± 15	Mean BMI: 26.4 ± 5.8	5 (4.5)	17 (15.5)	17 (15.5)	-
Holt *et al*[36]	44 (20:24)	44:0	Mean: 37.8 ± 14.2	Mean: 23.5	20 (45)	26 (59)	10 (24)	44 (100)
Jansen *et al*[8]	55 (19:36)	55:0	Mean: 40 ± 11	Mean: 24.9	10 (18)	31 (56)	21 (38)	-
O'Brien *et al*[31]	77 (46:31)	52:21:4	Median: 42 (20-80)	Median: 24 (16-37)	42 (55)	-	-	-
Pedersen *et al*[12]	178 (86:92)	127:51	Mean: 42.71 (18-86)	-	86 (48)	63 (35)	42 (24)	178 (100)
Sumi *et al*[27]	16 (12:4)	16:0	Responders median: 34 (18-68) Non-responders median: 31 (23-46)	Responders median: 21.7 Non-responders Median: 16.8	5 (31)	8 (50)	-	9 (56)
Takaoka *et al*[13]	40 (30:10)	40:0	Median: 32.4 (25.3-37.8)	Median:19.2	12 (30)	15 (38)	30 (75)	13 (33)
Thiberge *et al*[32]	149 (68:81)	149:0	Mean: 41.0 ± 17.5	Mean: 22.7 ± 6.1	108	85	86	85
Zhang T *et al*[10]	114 (75:39)	114:0	Mean: 32 ± 11.47	Median: 13.66	-	-	-	114 (100)
Zhang T *et al*[11]	204 (NR)	105:99	NR (min 18; max 65)	Median: 18.41	99 (49)	53 (26)	25 (12)	14 (7)
Zhang W *et al*[28]	138 (86:52)	138:0	Median: 29 (16-60)	Median: 17.9	13 (9)	50 (36)	-	37 (27)

NR: Not reported; CD: Crohn's disease; UC: Ulcerative colitis.

Thirteen studies (81.3%) examined NATs for the prediction of clinical outcomes[8-13,28,29,31-34,36]. The majority of studies (11/13) that evaluated NATs utilized measures of sarcopenia *via* computed tomography of the L3/4 vertebrae or BIA[8-13,28,29,31-34,36]. Five studies evaluated the correlation of sarcopenia with the need for intestinal resection[9,11,31,33,34], with only two demonstrating a significant correlation with need for intestinal resection (P = 0.003 on operation free survival curves)[9,11] (Table 8).

The presence of sarcopenia (*via* L3 SMI or mHUAC) was significantly associated with major post-operative complications with Clavien-Dindo grade (CDG) ≥ 3 in one study (OR = 9.24, P = 0.04) and life-threatening complications (CDG = 4) in another[10,12]. SMP was protective against major (OR 0.588, P = 0.002) and overall (OR = 0.487, P = 0.002) post-operative complications in one study[28] but not another[31]. Additionally the need for post-operative blood transfusions (OR = 1.31, P = 0.014), ICU admissions (OR = 1.32, P = 0.016), post-operative sepsis (OR = 1.325, P = 0.009), post-operative surgical site infections (OR = 4.91, P = 0.03) and deep vein thrombosis (OR = 1.265, P = 0.017) was found to be significantly associated with sarcopenia[12,29]. The need for either surgical or medical rescue therapy (P = 0.02) in patients with acute

Table 2 Components and interpretation of nutrition screening tools

NST	NRS-2002[9]	MUST[9]	NRI[27]	MIRT[8]	SaskIBD-NR[35]
NST components					
	Initial screening	BMI	Serum albumin	BMI	Symptoms (nausea/vomiting/diarrhea/poor appetite > 2 wk)
	BMI	Weight loss (last 3-6 mo)	Present weight/usual weight	Weight loss (last 3 mo)	Weight loss (last month)
	Weight loss (last 6 mo)	Acute disease effect[3]		CRP	Anorexia
	Dietary intake (last week)				Food restriction
	ICU patient				
	Final Screening[1]				
	Weight loss				
	Food intake				
	Disease severity[2]				
NST score indicating risk of malnutrition					
	0 = Low	0 = Low	> 97.5 = No Risk	Score range = 0-8	0-2 = Low risk
	1 = Mild	1 = Medium	83.5-97.5 = Moderate	0 = Lowest	3-4 = Medium risk
	2 = Moderate	≥ 2 = High	< 83.5 = High	8 = Highest	≥ 5 = High risk
	≥ 3 = High				

[1]To be conducted if there is a "YES" to any one of initial screening questions;
[2]Categorized into mild/moderate/severe based on descriptors in Nutrition Risk Screening 2002 Tool;
[3]Patient is acutely ill AND there has been/likely to be no nutrition intake > 5 d. BMI: Body mass index; CRP: C-reactive protein; ICU: Intensive care unit. NST: Nutrition screening tools; NRS-2002: Nutrition Risk Screening 2002; MUST: Malnutrition universal screening tool; NRI: Nutritional Risk Index; MIRT: Malnutrition Inflammation Risk Tool; SaskIBD-NR: Saskatchewan Inflammatory Bowel Disease Nutrition Risk.

severe UC was significantly associated with the presence of sarcopenia[34] (Table S4).

One study demonstrated that various measures of sarcopenia (SMI, SMA) correlated significantly with Mayo disease activity scores[11]. A separate study showed that SMA did not significantly predict endoscopic recurrence (P = 0.096)[36]. Two studies associated SGA with clinical outcomes based on SGA score[8,13] with discordant results. One inpatient study found that SGA did not predict the need for surgery (P = 0.071)[13] but it did predict length of stay (P = 0.008)[13]. A second outpatient study did not find any correlation between SGA and hospitalizations, disease flares, disease complications, or need for surgery[8].

DISCUSSION

This review of the literature is the first to systematically evaluate the use of NSTs and NATs in IBD-their performance in relation to each other and to clinical outcomes. Our review highlights both the adverse clinical implications of malnutrition in IBD as well as the paucity of NST and NAT data available in this population in comparison to other chronic disease populations[37-40]. Although the reviewed studies were not amenable to meta-analysis due to heterogeneity and observational non-randomized, non-controlled study designs, multiple conclusions can still be drawn to summarize the current state and guide future work in the area.

First, our review reinforces the high prevalence of malnutrition in patients with IBD. One in four outpatients and approximately two in three inpatients were found to be at nutritional risk. These results are consistent with prior studies confirming the substantial prevalence of malnutrition in IBD[1,3,22]. Secondly, we evaluated how the findings on Nutrition Screening compared to the findings on Nutrition Assessment. This demonstration of an association between NSTs and NATs is required, to demonstrate face and content validity of the NST for use in screening[41].

There is a limited amount of data available to compare NSTs to NATs. Four NSTs (the MUST, NRS-2002, MIRT and SaskIBD-NRT) showed promise. The MUST includes BMI, unplanned weight loss in the past 3-6 mo and an acute disease effect score. The MIRT measures similar criteria, including BMI, unintentional weight loss and CRP. Therefore, these two tools vary only in the method that acute disease is assessed. The NRS-2002 differs from the two previous tools, as it captures reduced

Table 3 Components and interpretation of nutrition assessment tools

Nutrition Assessment Tools			
SGA[8,9,13]	Comprehensive RD/GI Assessment[35]	BIA[28,30]	CT Scan[9-12,29,31-34,36]
NAT Components			
Nutrient Intake	BMI	SMP	mHUAC
Weight loss	GI symptoms, oral intake	FFMI	L3 SMI
Symptoms affecting oral intake	IBD location, severity, concurrent conditions		L4 TPA
Functional capacity	Surgical history, medications		ASMI
Metabolic requirement	Laboratory parameters (Albumin/Vit D/Iron/Vit B12)		SMA
Physical examination	SCAI, HBS		
NAT interpretation			
A = Well nourished	At risk	Sarcopenia:	Sarcopenia:
B = Mild/moderately malnourished	Not at risk	FFMI:	mHUAC: Lowest sex quartile at level of L3 vertebrae
C = Severely malnourished		Men: ≤ 17 kg/m^2	L3 SMI: Lowest sex quartile, variable between studies (Male: < 42-55 cm^2/m^2; Female: < 35.6-41 cm^2/m^2)
		Women: ≤ 15 kg/m^2	L4 TPA: Lowest sex quartile (Male < 56.7 cm^2/m^2, Female: < 35.6 cm^2/m^2)
		SMP: Continuous variable	ASMI/SMA: Continuous variable

BMI: Body mass index; SCAI: Simple Colitis Activity Index; HBS: Harvey Bradshaw Score; SGA: Subjective Global Assessment; SMP: Skeletal Muscle Percentage; FFMI: Fat Free Mass Index; mHUAC: Mean Hounsfield Unit Area Calculation; ASMI: Appendicular Skeletal Muscle Index; L3 SMI: L3 Vertebrae Skeletal Muscle Index; SMA: Skeletal Muscle Area; IBD: Inflammatory bowel disease; CT: Computed tomography; RD: Registered dietitian; GI: Gastroenterologist.

dietary intake in addition to BMI, weight loss and ICU admission status, and has been validated only in the inpatient population. The SaskIBD-NRT is a novel tool based on patient history evaluating gastrointestinal symptoms and food restriction behaviors commonly seen in the IBD population in addition to the more common screening questions of weight loss and poor oral intake[35]. The SaskIBD-NRT does not capture disease severity and is reliant only on nutrition specific data points to assess risk.

The MIRT and SaskIBD-NRT although not yet compared to SMI in IBD, have shown significant associations with more comprehensive nutritional assessment methods. The MIRT for example demonstrating an association with an abnormal SGA[8]. Similarly, the SaskIBD-NRT showed strong agreement to subsequent comprehensive assessment by RD/GI[35]. This association has not been consistent with one study noting poor inter-rater agreement between MUST and a comprehensive RD/GI assessment[35]. Recognizing sarcopenia as an integral, objective component of malnutrition, both the MUST and NRS-2002 demonstrated a significant association with sarcopenia as measured by the SMI[9]. To summarize, although limited, the data on NSTs is encouraging for a strong association with a diagnosis of malnutrition by NATs (both sarcopenia and more comprehensive NATs).

Thirdly, we evaluated whether NSTs were associated with clinical outcomes. Although traditionally used to determine which patients require further nutritional assessment and therapy, the summary of findings from the current review would suggest that NSTs also hold promise in the prediction of clinical outcomes. Notably, all studies were performed in patients with CD and therefore the results are at this time only generalizable to this population. The outcomes associated with the three NSTs (NRS-2002, NRI and MIRT) were all of clinical were of clinical relevance. For inpatients, the NRS-2002 predicted hospital length of stay[13]. For outpatients, the MIRT correlated well with hospitalizations, disease flares and need for surgery[8,27]. All three NSTs included a component to reflect disease severity. Although this parameter itself can correlate with adverse clinical outcomes, its inclusion in IBD nutrition screening and assessment is appropriate, as disease severity may exacerbate poor oral intake, malabsorption and catabolism. The SaskIBD-NRT (did not include measure of disease severity) has not yet been studied with reference to clinical outcomes.

Notably, the MUST was not associated with clinical outcomes among inpatients. This is perhaps not surprising as the European Society for Clinical Nutrition and Metabolism has recommended against the use of MUST in inpatients, citing concern

Table 4 Proportion of nutrition abnormalities *via* nutrition screening tools

NST	Proportion of low risk patient's *n* (%)	Proportion of mild-moderate risk patient's *n* (%)	Proportion of high-risk patient's *n* (%)	Study ID
MUST	12 (16.7)	27 (37.5)	49 (68.1)	Bamba *et al*[9]
	118 (68.2)	18 (10.4)	37 (21.4)	Csontos *et al*[30]
	93 (84.5)	12 (10.9)	5 (4.5)	Haskey *et al*[35]
	10 (25.0)	6 (15)	24 (60)	Takaoka *et al*[13]
NRI	5 (31.3)	11 (68.8)		Sumi *et al*[27]
NRS-2002	0 (0)	24 (33.3)	48 (66.7)	Bamba *et al*[9]
	13 (32.5)		27 (67.5)	Takaoka *et al*[13]
SaskIBD-NRT	89 (80.9)	12 (10.9)	9 (8.2)	Haskey *et al*[35]

NST: Nutrition screening tools; NRS-2002: Nutrition Risk Screening 2002; MUST: Malnutrition universal screening tool; NRI: Nutritional Risk Index; SaskIBD-NRT: Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool.

regarding confounders from the lack of grading the severity of the acute illness[14]. In other studies, the MUST has been associated with CD severity as measured by the HBI (P = 0.005) on cross-sectional analysis[42]. Further studies utilizing this tool are required to evaluate its use in outpatient IBD populations.

From the available NST data therefore, the NRS-2002 in inpatients, and the MIRT and MUST in outpatients, are promising candidates for further evaluation. This is consistent with previous reviews suggesting NSTs such as the NRS-2002 which use combined simple measures of malnutrition are most appropriate to assess malnutrition in IBD[24]. Further evaluation is needed as it remains unclear whether the associations noted in CD patients will be generalizable to the UC population and, furthermore, if these findings will apply across inpatient and outpatient populations. It is also important to recognize that there are other NSTs that have not yet been explored in the IBD setting, including the patient-generated SGA, and Canadian Nutrition Risk Screening Tool. These screening tools have performed well in other chronic disease populations[43,44]. Further research into the use of patient-led versions of malnutrition screens would also be of interest. Although the studies evaluating patient-led NSTs did not meet eligibility criteria for this review, the patient-led MUST has correlated with a practitioner-led MUST in IBD[45,46] and is in keeping with the utility of these screens in other chronic disease populations[47,48]. As a direct translation to clinical practice, the signal that NSTs predict clinical outcomes supports their importance. In future studies it will be of interest to evaluate the impact of nutrition therapies on NST results and on clinical outcomes.

Lastly, we explored the association between NATs and clinical outcome measures. Notably, most studies correlating NATs and clinical outcomes used measures of sarcopenia as the primary assessment method, in particular the L3 SMI[9,11,28,29]. By adding an additional 6 studies (Zhang 2015, Holt 2017, Cushing 2018, Fujikawa 2017, O'Brien 2018, and Thiberge 2018)[28,29,31,32,34,36] the current review extends the recent sarcopenia focused systematic review carried out by Ryan *et al*[22]. Ryan's group reported a sarcopenia prevalence rate over 40%, similar to the 39.5% seen in our current study. They also concluded that sarcopenia was a significant independent predictor for the need for surgery and it correlated with an increased rate of major post-operative complications, as was seen our study[22].

It must be noted that although measures of sarcopenia are among some of the most objective assessment tools for malnutrition, given the inherent cost, risk of radiation and contrast exposure with computed tomography, research into more practical alternatives such as bed-side ultrasound, is required[49,50]. Moreover, the underlying pathogenesis of sarcopenia remains multifactorial, and may include additional physiological factors independent of malnutrition[51,52]. In the IBD population, active inflammation may be reflective of disease severity and contribute to malnutrition through anorexia, hypermetabolism and malabsorption. Additionally, anorexia, malabsorption and active inflammation underpin some pathophysiological mechanisms of sarcopenia[53]. Nutrition risk screening and assessment is made even more complex with the increasing prevalence of overweight patients with IBD. Over-nourishment and obesity affects up to 55% of patients with IBD in the Western hemisphere[23,54]. In spite of this, decreased muscle mass and micronutrient deficiencies remain prevalent even among the obese population with IBD (*i.e.*, sarcopenic obesity), and are not accurately assessed by traditional nutrition assessment methods[33,55-57].

Table 5 Proportion of nutrition abnormalities *via* nutrition assessment tools

NAT measure				
	Proportion of non-sarcopenic patients *n* (%)	**Proportion of sarcopenic patients *n* (%)**		**Study ID**
Sarcopenia	49 (54.4)	41 (45.6)		Adams *et al*[33]
	42 (58.3)	30 (41.7)		Bamba *et al*[9]
	125 (72.3)	48 (27.7)		Csontos *et al*[30]
	25 (30.5)	57 (69.5)		Cushing *et al*[34]
	51 (73.9)	18 (26.1)		Fujikawa *et al*[29]
	47 (67.1)	30 (38.9)		O'Brien *et al*[31]
	134 (75.3)	44 (24.7)		Pedersen *et al*[12]
	99 (66.4)	50 (33.6)		Thiberge *et al*[32]
	115 (56.4)	89 (43.6)		Zhang *et al*[11]
	44 (35.1)	70 (61.4)		Zhang *et al*[10]
Comprehensive RD/GI Assessment	**Proportion of patients not at risk *n* (%)**	**Proportion of patients at risk of malnutrition *n* (%)**		**Study ID**
	87 (79.1)	23 (20.9)		Haskey *et al*[35]
SGA	Proportion of SGA A	Proportion of SGA B	Proportion of SGA C	Study ID
	8 (11.1)	37 (51.4)	27 (37.5%)	Bamba *et al*[9]
	8 (20.0)	17 (42.5)	15 (37.5%)	Takaoka *et al*[13]
	48 (87.3)	7 (12.7)		Jansen *et al*[8]

NAT: Nutrition assessment tools; RD/GI: Registered dietitian/Gastroenterologist.

Although there is conflicting data on the association of obesity itself with IBD related clinical outcomes[58-61], the syndrome of "sarcopenic-obesity" likely does have implications in predicting relevant clinical outcomes, and warrants further investigation[33].

Additionally, our review of NATs highlights the discordant data regarding the ability of the SGA, a familiar nutritional assessment tool, to predict clinical outcomes in IBD. Notably, a large percentage of IBD patients with decreased body cell mass as determined by BIA and sarcopenia can be missed by SGA alone[50]. In this review, SGA was not significantly associated with clinical outcomes in IBD populations other than length of hospital stay[8,13].

In conclusion, our study has summarized the currently available evidence for NSTs/NATs in the IBD population. Although some studies support the association of NSTs/NATs with specific clinical outcomes, the heterogeneity in study design, lack of data from large cohorts, and lack of comprehensive validation of existing NSTs, does not translate into the recommendation of a single optimal NST or NAT at this time. The high prevalence of malnutrition seen across these recent studies reaffirms the ongoing significance of malnutrition in the IBD population and the need to utilize appropriate NST/NATs. Consistent with guideline recommendations, nutrition screening should be conducted on every patient with IBD both at diagnosis and at least annually, with more frequent measures as needed[18]. Referral should be made to a RD to patients at moderate or high risk of malnutrition for more definitive assessment. The strengths and limitations of the tools have been highlighted in this review. Going forward, clinically relevant research areas include larger scale studies evaluating the assessment of alternate measures of sarcopenia, the development and validation of novel NSTs/NATs, such as the MIRT/SaskIBD-NRT and an assessment of the responsiveness of the tools to measure change with a nutrition intervention. Based on the promising data from these tools, the optimal NST/NAT for the IBD population is likely to be one that takes into account the unique dietary habits and chronic inflammatory nature of this population. It is encouraging to note that the majority of articles included within this review have been published within the last 2 years. We anticipate that continued activity and interest will lead to the development and validation of tools in concert with clinical care pathways, embedding the important processes of nutrition screening and assessment within routine IBD clinic visits.

Table 6 Nutrition screening tools correlating with nutrition assessment tools

NST	Comparative NAT measure	Statistical Variable	Value	Study ID
MUST	FFMI	Cohen's Kappa (low/normal FFMI *vs* low MUST)	κ = 0.53 (95%CI: 0.39-0.67)	Csontos *et al*[30]
	SMI	Logistic Regression (MUST 0,1 *vs* ≥ 2)	OR: 0.934, *P* = 0.014[a]	Bamba *et al*[9]
	RD/GI Assessment	Cohen's Kappa	κ = 0.15	Haskey *et al*[35]
MIRT	SGA	Spearman's Rank Correlation	ρ = 0.394, *P* = 0.005[a]	Jansen *et al*[8]
NRS-2002	SMI	Logistic Regression (NRS-2002 1, 2 *vs* ≥ 3)	OR: 0.928, *P* = 0.008[a]	Bamba *et al*[9]
SaskIBD-NR	RD/GI Assessment	Cohen's Kappa	κ = 0.73	Haskey *et al*[35]

[a]Indicates significant *P* value < 0.05. FFMI: Fat Free Mas Index; SMI: Skeletal Muscle Index; SGA: Subjective Global Assessment; OR: Odds ratio; NST: Nutrition screening tools; NRS-2002: Nutrition Risk Screening 2002; MUST: Malnutrition universal screening tool; SaskIBD-NR: Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool; MIRT: Malnutrition Inflammation Risk Tool; RD/GI: Registered dietitian/Gastroenterologist.

Table 7 Significant nutrition screening tool correlations with clinical outcomes

NST	Comparative outcome measure	Statistical variable	Value	Study ID
MIRT	Hospitalization	Spearman's rank correlation	ρ = 0.398, *P* = 0.003[a]	Jansen *et al*[8]
	Disease flare		ρ = 0.299, *P* = 0.030[a]	
	Disease complications[1]		ρ = 0.333, *P* = 0.015[a]	
	Need for surgery		ρ = 0.371, *P* = 0.006[a]	
NRI	Response to infliximab	Fischer's exact test	*P* = 0.037[a]	Sumi *et al*[27]
NRS-2002	Length of stay (< 28 *vs* ≥ 28 d)	Chi-square test	*P* = 0.032[a]	Takaoka *et al*[13]

[a]Indicates significant *P* value < 0.05);
[1]Newly occurred stenosis, fistula or abscess. NST: Nutrition screening tools; NRS-2002: Nutrition risk screening 2002; NRI: Nutritional risk index; MIRT: Malnutrition inflammation risk tool.

Table 8 Significant nutrition assessment tool correlations with clinical outcomes

NAT	Comparative outcome measure	Statistical analysis	Result	Study ID
SGA	Length of stay in hospital	Chi-square test	*P* = 0.008	Takaoka *et al*[13]
Sarcopenia	Change in IBD disease activity at 6 mo (HBI)	Paired *t*-test (baseline *vs* 6 mo)	Sarcopenic: 0.4 (*P* = 0.80)	Adams *et al*[33]
			Non-sarcopenic: -2.3 (*P* = 0.004)	
	Need for operation (operation free survival curve)	Kaplan-Meier Analysis	*P* = 0.003	Bamba *et al*[9]
			P = 0.003	Zhang *et al*[11]
	Need for operation	Cox-regression (multivariate)	HR 0.318 (0.126-0.802), *P* = 0.015	Bamba *et al*[9]
	Need for any rescue therapy (medical/surgical)	Fischers exact test	*P* = 0.02	Cushing *et al*[34]
		Multivariate logistic regression	OR 3.98 (95%CI 1.12-14.1), *P* = 0.033	
	Post-operative complications (Major)[1]		OR 9.24 (95%CI 1.10-77.50). *P* = 0.04	Zhang *et al*[10]
	UC disease activity (Mayo Score ≥ 6)		OR 8.49 (95%CI 1.80-40.10), *P* = 0.007	Zhang *et al*[11]
	Post-operative surgical site infection		OR 4.91 (95%CI 1.09-23.50), *P* = 0.03	Fujikawa *et al*[29]
	Need for red blood cell transfusion		OR 1.31, *P* = 0.014	Pedersen *et al*[12]
	ICU admission		OR 1.32, *P* = 0.016	
	Post-operative sepsis		OR 1.325, *P* = 0.009	
	Deep vein thrombosis		OR 1.265, *P* = 0.0173	
	Clavien-Dindo grade 4 complication		OR 1.329, *P* = 0.0052	
ASMI	Fecal calprotectin	Spearman's Rank Correlation	ρ = -0.564, *P* = 0.005	Holt *et al*[36]

L3 SMI	UC disease activity (Mayo Score)		ρ = -0.523, $P \leq 0.01$	Zhang *et al*[11]
SMA			ρ = -0.445, $P \leq 0.01$	
SMP	Post-operative complications (Overall)[2]	Multivariate logistic regression analysis	OR: 0.487 (95%CI 0.307-0.772) $P = 0.002$[a]	Zhang *et al*[28]
	Post-op complications (Major)[1]		OR: 0.588 (95%CI 0.422-0.820) $P = 0.002$[a]	

[a]Indicates significant P value < 0.05);
[1]Clavien-Dindo Score ≥ 3;
[2]Clavien-Dindo Score 1-5. HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval; HBI: Harvey-bradshaw index; mHUAC: Mean hounsfield unit area calculation; ASMI: Appendicular skeletal muscle index; SMI: Skeletal muscle index; SMA: Skeletal muscle area; SMP: Skeletal muscle percentage; SGA: Subjective global assessment.

ARTICLE HIGHLIGHTS

Research background

Malnutrition is highly prevalent in patients with inflammatory bowel disease (IBD), however the optimal nutrition screening tools (NST) and nutrition assessment tools (NAT) to detect and diagnosis malnutrition respectively are unclear.

Research motivation

Given the negative clinical and economic impacts of malnutrition in IBD, identification of a simple, accurate and efficient process for identifying malnutrition may allow for increased recognition and earlier nutritional intervention.

Research objectives

To systematically review the prevalence of malnutrition in patients with IBD, whether available NSTs correlate with NATs, and whether NSTs and NATs are predictive of clinical outcomes.

Research methods

PubMed and MEDLINE databases were systematically searched utilizing a comprehensive search strategy. Articles were reviewed and extracted by two independent reviewers against inclusion/exclusion criteria. Included articles underwent quality assessment review utilizing the modified Newcastle Ottawa Scale as well as data extraction, synthesis and review by the authors and a biostatistician.

Research results

A total of 1791 studies were identified from the initial search, 16 of which m*et al*l inclusion criteria and were included for qualitative synthesis. Prevalence of patients at high risk of malnutrition amongst inpatient and outpatient IBD patients as assessed by NSTs ranged from 28%-67%. Sarcopenia was identified in 39.5% of IBD patients. The malnutrition universal screening tool (MUST), Nutrition Risk Screening 2002 (NRS-2002), Malnutrition Inflammation Risk Tool (MIRT) and Saskatchewan Inflammatory Bowel Disease Nutrition Risk Tool (SaskIBD-NRT) all showed significant associations with various NAT measures. Of NSTs, the MIRT, NRS-2002 and NRI demonstrated significance in predicting clinical outcomes of relevant clinical outcomes. Presence of sarcopenia was significantly associated with various clinical and post-operative outcomes. The Subjective Global Assessment was not consistent in its association with clinical outcomes.

Research conclusions

Malnutrition and sarcopenia remain highly prevalent in the IBD population as assessed by currently available NSTs and NATs. No single optimal NST or NAT can be recommended based on our review at this time. Based on current evidence, previously available NSTs including the NRS-2002 and MUST, as well as novel IBD-specific NSTs (MIRT, SaskIBD-NRT) are the most useful to screen for malnutrition in this population. Sarcopenia evaluation (*via* cross-sectional imaging) has promise as a robust nutrition assessment method given its significant associations with clinical outcomes. However, more accurate, practical and cost-effective methods of evaluating sarcopenia in the IBD population outside of conventional methods of body composition analysis should be explored.

Research perspectives

The utility as well as strengths and weaknesses of available NSTs and NATs have been reviewed. Future research is needed to test and validate available tools in the IBD population. The development of novel tools will aid clinicians in identifying, diagnosing and intervening on malnourishment in the IBD patient population.

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