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MINIREVIEWS

Evolution of liver transplant organ allocation policy: Current limitations and future directions

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Abstract

Since the adoption of the model for end-stage liver disease (MELD) score for organ allocation in 2002, numerous changes to the system of liver allocation and distribution have been made with the goal of decreasing waitlist mortality and minimizing geographic variability in median MELD score at time of transplant without worsening post-transplant outcomes. These changes include the creation and adoption of the MELD-Na score for allocation, Regional Share 15, Regional Share for Status 1, Regional Share 35/National Share 15, and, most recently, the Acuity Circles Distribution Model. However, geographic differences in median MELD at time of transplant remain as well as limits to the MELD score for allocation, as etiology of liver disease and need for transplant changes. Acute-on-chronic liver failure (ACLF) is a subset of liver failure where prevalence is rising and has been shown to have an increased mortality rate and need for transplantation that is under-demonstrated by the MELD score. This underscores the limitations of the MELD score and raises the question of whether MELD is the most accurate, objective allocation system. Alternatives to the MELD score have been proposed and studied, however MELD score remains as the current system used for allocation. This review highlights policy changes since the adoption of the MELD score, addresses limitations of the MELD score, reviews proposed alternatives to MELD, and examines the specific implications of these changes and alternatives for ACLF.

Key Words: Model for end-stage liver disease score; Acute-on-chronic liver failure; Regional sharing

Core Tip: Since the adoption of the model for end-stage liver disease (MELD) score for

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organ allocation in 2002, there have been numerous changes to policy in an effort to make organ allocation and distribution more fair and equitable. This review highlights policy changes since the adoption of the MELD score, addresses limitations of the MELD score, reviews proposed alternatives to MELD, and examines the specific implications of these changes and alternatives for acute-on-chronic liver failure.

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INTRODUCTION

Organ allocation for liver transplantation was revolutionized in 2002 by wide adoption of the model for end-stage liver disease (MELD) scoring system, which utilized objective criteria to facilitate equitable organ allocation. Although this system has improved fairness in prioritizing patients for transplantation, important disparities remain. In this review, we discuss current organ allocation policy and future directions through a historical lens, from the pre-MELD era through the development of MELD exception points, regional sharing, and implementation of the MELD-Na score. We conclude with an examination of limitations of the MELD scoring system in assessing mortality in certain patient groups and areas for improvement in current organ allocation policy.

OVERVIEW AND HISTORY OF MELD

Pre-MELD era

Prior to 1997, liver transplant priority was determined by hospitalization status and time on the waiting list. For example, a patient in the intensive care units (ICU) was given priority over a non-ICU hospitalized patient who was given priority over an outpatient. This system was based on subjective criteria that could be manipulated by hospitalizing patients or admitting to the ICU when there was no medical indication, thereby fraudulently giving a patient an advantage over others.

In 1998, United Network for Organ Sharing (UNOS) adopted the Child-Turcotte-Pugh (CTP) scoring system to stratify patients as Status 2A, 2B, or 3 for patients at high risk of death without transplantation, with Status 1 reserved for patients with acute liver failure. The CTP score incorporated objective data into waiting list priority, but still included subjective grading of encephalopathy and ascites which allowed for wide variability and the potential for inappropriately scoring the severity of a patient's condition. The CTP score was originally proposed in 1964 by surgeons Child *et al*[1] as a way to assess operative risk in patients undergoing surgical portosystemic shunt for variceal bleeding—patients were given a subclass score of A-C depending on bilirubin, albumin, ascites, hepatic encephalopathy, and nutritional status[1]. In 1973, Pugh *et al*[2] modified the scoring system by adding prothrombin time and removing nutritional status which became known as the CTP score[2]. In 2000, the United States Department of Health and Human Services released the Final Rule, which mandated that organ allocation should be based upon medical urgency that is determined by objective and reproducible data and that access to transplant should not be affected by geography[3].

Adoption of MELD score and donation service areas

The Mayo transjugular intrahepatic portosystemic shunt (TIPS) model was originally developed in 2000 as a scoring system to predict three-month mortality in patients with cirrhosis who underwent a TIPS procedure[4]. A year later this scoring system was shown to also be a reliable predictor of three-month mortality in patients with cirrhosis and became known as the MELD score[5]. The MELD score incorporated serum bilirubin, serum creatinine, international normalized ratio (INR) for prothrombin time, and etiology of liver disease. However, etiology of liver disease was

shown to have minimal impact on outcomes and was later removed from the scoring system[6].

The Final Rule led to the Organ Procurement and Transplant Network to implement the MELD score to prioritize patients awaiting deceased donor liver transplantation using only three objective lab values in its calculation—serum bilirubin, serum creatinine, and INR. In February 2002, donor liver allocation based on MELD score was implemented in the United States. The use of the MELD score led to more transplants for sicker patients and reduced waitlist mortality without reducing post-transplant survival[7]. However, distribution of donor livers prioritized patients within the local donation service area (DSA), followed by the UNOS region, and finally the nation. For example, if an organ became available, it was prioritized to the patient with the highest MELD score within that DSA. If the liver was not accepted by a transplant center within that DSA, it would be offered within the UNOS region, and then nationally. However, the differences in population size and demographics within DSAs and UNOS regions gradually led to significant geographic disparities in the MELD score at time of transplant, and therefore access to liver transplantation[7].

Policy changes to liver allocation and distribution since 2002

Since 2002, numerous changes to the system of liver allocation and distribution have been made with the goal of decreasing waitlist mortality and minimizing geographic variability in median MELD score at time of transplant without worsening post-transplant outcomes (Figure 1). Liver allocation refers to how waitlisted patients are prioritized by medical urgency based on the MELD score while liver distribution refers to the system by which donor livers are matched to patients on the waitlist based on geographic units. Each of these will be discussed below.

CHANGES IN LIVER ALLOCATION AND DISTRIBUTION IN THE UNITED STATES

Incorporation of serum sodium level (MELD-Na)

Multiple studies have shown that hyponatremia is an independent predictor of mortality in patients with cirrhosis[8-10]. Hyponatremia has also been shown to be a predictor of hepatorenal syndrome occurrence which is also associated with increased mortality[11]. In 2008, Kim *et al*[12] showed that adding serum sodium to the MELD score was a better predictor of mortality than MELD alone, making the argument that serum sodium should be added to the MELD score model[12]. The incorporation of serum sodium into the MELD score calculation was eventually adopted by UNOS in 2016. Studies evaluating the effectiveness of the MELD-Na score have shown the MELD-Na to be a more accurate predictor of 90-d mortality and that using the MELD-Na for liver allocation leads to a decrease in waitlist mortality[12-14].

Regional share 15

In 2005, Merion *et al*[15] showed mortality risk reduction in patients transplanted with a MELD score of 18 or greater with an increasing mortality reduction as the MELD score increased. But they also showed increased mortality in patients transplanted with a MELD score less than 14 compared to candidates who remained on the waitlist [15]. Due to these findings, the Regional Share 15 policy was implemented, which called for an organ to first be offered within the local DSA to patients with a MELD greater than 15 and then regionally before being offered locally to patients with a MELD less than 15.

Regional share for Status 1

Patients listed as Status 1 for liver transplantation are critically ill with acute liver failure and have a life expectancy of 7 d or less without transplantation. Under Regional Share for Status 1, patients listed as Status 1 would receive priority for transplant ahead of all other patients listed within an entire UNOS region. This policy change was implemented in December 2010 and was found to significantly increase the probability of transplantation within 7 d of listing as status 1 without negatively impacting waitlist mortality for non-status 1 patients in the same region[16].

Regional share 35 and national share 15

In 2012, it was shown that patients with a MELD score ^{3}35 had a waitlist mortality similar to patients listed with acute liver failure status 1, but only status 1 patients

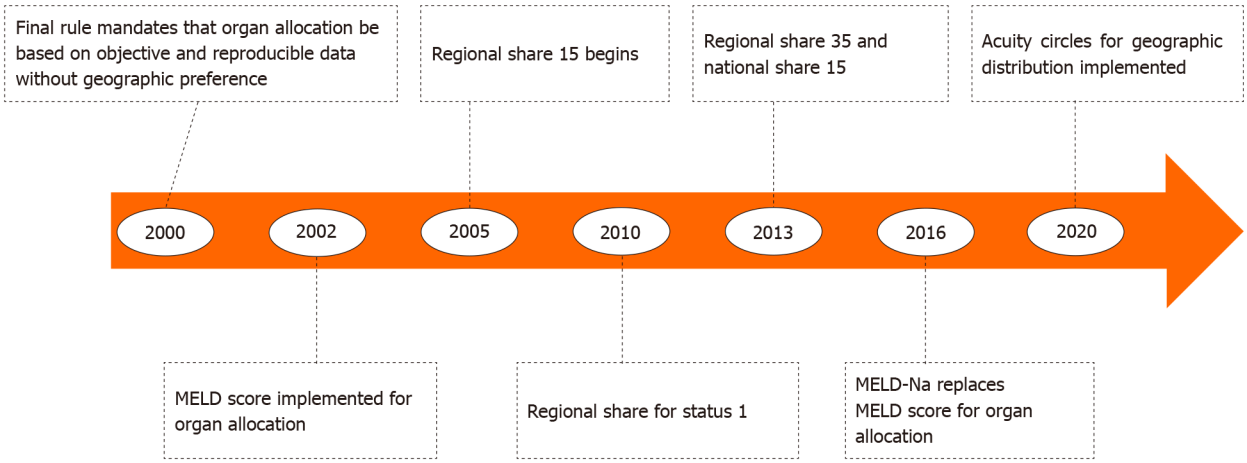

Figure 1 History of changes in organ allocation policy in the United States. MELD: Model for end-stage liver disease.

were eligible for regional sharing[17]. This lead to the Regional Share 35 and the National Share 15 policy change in 2013, which called for donor livers to be offered first to patients with a MELD score ³35 Listed within a region. If the liver was not accepted by a center then the distribution sequence was as follows: offered to patients with a MELD score ³15 within the DSA, offered to patients with a MELD score ³15 within the region, offered nationally to patients with MELD score ³15, before finally being offered locally to patients with MELD scores < 15. One year later, the Regional Share 35 policy was found to have the following effects: An increase in total transplants, 30% lower waitlist mortality for patients with MELD greater than 30, a decrease in in the number of unused organs, and no worsening of early post-transplant outcomes[18]. No difference was seen nationally when comparing post-transplant survival before and after implementation of Regional Share 35, however two regions did show significantly worse post-transplant outcomes after the policy was enacted[19].

Acuity circles distribution system

Despite the adoption of policy changes for donor liver distribution in the United States such as Regional Share for Status 1, Regional Share 35, and National Share 15, significant geographic variability in access to liver transplantation remained within the local-regional-national system of organ distribution with the median MELD score at transplant varying as much as 12 points in high *vs* low MELD score regions[20]. Spurred by lawsuits involving the lung transplant allocation system which prompted calls to eliminate the use of DSAs and UNOS regions as units of organ distribution, a new liver distribution system, known as Acuity Circles, based on concentric geographic circles around the donor site hospital was accepted in 2018 and implemented in 2020[21]. Acuity circles calls for a donor liver to first be offered to patients listed Status 1 within 500 nautical miles (nm) of the donor hospital. The organ is then offered to patients with a MELD score of at least 37 within 150 miles of the donor hospital, then to patients with a MELD score of at least 37 within 250 miles, and finally to patients with a MELD score of at least 37 within 500 miles. If the organ is not accepted for any of these patients, then it is allocated to patients with decreasing MELD score thresholds of 33, then 29, then 15 in expanding geographic circles at each MELD score tier as above before being allocated nationally, until finally being offered to patients with a MELD score under 15. As with prior policy changes, the new system was implemented to further minimize geographic disparities in access to liver transplantation.

WORLDWIDE ORGAN ALLOCATION

The MELD score is still used by many countries worldwide that perform a high volume of liver transplantations yearly. The MELD score was implemented for liver allocation in the United States in 2002 by UNOS. It was followed by North Italian Transplant (2006), Eurotransplant (2006), Canada (2006) and many others[22]. In Asia, South Korea became the first country to used MELD score for organ allocation in 2016

[23]. Some countries allow for a center-specific allocation policy, although that can only be applied in areas with high organ donation rates such as Scandinavia, Spain and Portugal[22,24].

Other countries have tried to combine recipient needs with donor availability. In 2007, France began using the French Liver Allocation Score which uses objective data of the recipient like MELD score, but additionally uses other data points such as donor-recipient distance and waiting time[24,25]. The United Kingdom began using a new allocation model in 2018 that aims to give urgent cases priority—the transplant benefit score uses donor and recipient parameters to determine optimal match[24].

LIMITATIONS OF THE MELD AND MELD-NA SCORE

The system of awarding MELD exceptions as described in the preceding section is helpful to account for conditions not addressed by the MELD calculation, however there are inherent limitations to the MELD model itself which will be discussed below.

Renal function assessment

The MELD score incorporates renal function into its calculation by using the serum creatinine value. However, patients with advanced cirrhosis often have significant muscle wasting which can lead to a "normal" creatinine level that underestimates the severity of their renal dysfunction[26,27]. Differences in muscle mass between men and women also leads to a disadvantage in organ allocation for women--their lower muscle mass leads to a lower creatinine level for equivalent renal function, leading to a lower MELD score[28,29]. Serum creatinine levels can also vary day-to-day in patients with ascites undergoing diuresis or paracentesis, and this variance is unlikely to actually reflect a true change in mortality risk[27]. Differences in the calculation of serum creatinine have also been shown to depend on the assay used by each laboratory[30].

The serum creatinine value in the MELD calculation also has a lower limit of 1 mg/dL and upper limit of 4 mg/dL, both of which have been called into question. The lower limit is in place to avoid negative values after logarithmic transformation in the MELD calculation[31], but this would assume that mortality risk is constant for all values below 1 mg/dL. The upper limit boundary was created so as to not raise the MELD score due to intrinsic kidney disease, however there is evidence that patients with a creatinine level greater than 4 mg/dL have a significantly higher mortality than those with a lower creatinine level[32].

Acute-on-chronic liver failure

Acute-on-chronic liver failure (ACLF) has been identified as a separate clinical entity from acute liver failure and acute decompensated cirrhosis and defined as "a syndrome in patients with chronic liver disease with or without cirrhosis, which is characterized by acute hepatic decompensation, organ failures, and a 28-d mortality greater than 15%[33,34]." The prevalence of ACLF is rising in the United States, particularly in the elderly[35,36]. ACLF is graded according to concurrent organ failures—ACLF grade 1 (ACLF-1) is single organ failure, ACLF grade 2 (ACLF-2) includes patients with two organ failures, and ACLF grade 3 (ACLF-3) includes patients with 3 organ failures or more[34]. ACLF-3 has a mortality without liver transplantation of 80% at 28 d and greater than 90% at one year[37].

The MELD score has been shown to be accurate for assessing mortality risk in decompensated cirrhosis, but ACLF presents a distinct entity with increased systemic inflammation and development of organ failures[37] and so the mortality risk of these patients is not completely demonstrated within their calculated MELD score. A study of the UNOS database showed that patients with ACLF-3 and MELD-Na score less than 25 had greater waitlist mortality than those without ACLF and a MELD-Na score greater than 35[38]. A recent study from the same group showed that ACLF-3 has a higher risk of waitlist mortality or delisting within 14 d compared to patients listed as status 1a, independent of their MELD score, however status 1a patients with acute liver failure have the highest chance of obtaining a liver transplant under the current organ allocation system[39]. The same study also found a rising 21-d mortality rate in patients with ACLF-3 compared to an unchanged mortality rate among status 1a listed patients[39]. A separate study from the UNOS database further demonstrated that utilization of MELD based regional sharing did not improve waitlist mortality among patients with ACLF-3[40].

Changing epidemiology of liver disease

MELD score was adopted as an accurate, objective, and reproducible tool to assess 90-d mortality risk in patients listed for liver transplant. Godfrey *et al*[41] looked to assess the predictive power of MELD score in assessing mortality risk since its adoption for organ allocation, finding that the MELD score's concordance with 90-d mortality was decreasing from 0.80 in 2003 to 0.70 in 2015[41]. The authors also found that the concordance of MELD score with mortality was lower in alcohol-related liver disease and non-alcoholic fatty liver disease while higher in patients with hepatitis C virus (HCV) related cirrhosis[41]. Given the shift from HCV-related cirrhosis to alcohol and nonalcoholic steato hepatitis-related cirrhosis as the leading indications for liver transplantation in the United States, these changes may be magnified in the years ahead. In addition to the changing epidemiology of liver disease, the emergence of ACLF as a distinct clinical entity, and the increasing reliance on MELD score exceptions, further studies are needed to determine if a MELD-based system can continue to be the most accurate, objective system for liver allocation.

ALTERNATIVES TO MELD SCORE ALLOCATION

Alternative scoring models have been proposed to the MELD score, as well as alterations to the calculation of the MELD score itself (Table 1). These alternative scoring systems attempt to address some of the issues with the MELD score that were addressed in the preceding section.

MELD-glomerular filtration rate assessment in liver disease

This scoring system aims to replace serum creatinine as a measure of renal function with a new calculation for glomerular filtration rate (GFR). The GFR assessment in liver disease (GRAIL) uses objective variables (creatinine, blood urea nitrogen, age, gender, race, and albumin) to better estimate renal function in patients awaiting liver transplantation[42]. GRAIL was developed by examining all adult patients with liver disease that underwent admission measurements of GFR using iothalamate clearance from 1985 to 2015[42]. Retrospective analysis showed that MELD-GRAIL-Na had the greatest difference compared to MELD-Na at increased disease severity—for a score ^{3}32 (observed 90 d mortality of 0.68), MELD-GRAIL-Na predicted mortality was 0.67 compared to MELD-Na predicted mortality of 0.51[43]. This scoring system would have resulted in a reclassified status for 16% of patients on the waitlist in 2015[43].

MELD-lactate

The MELD-lactate score incorporates serum lactate into the MELD calculation. This scoring model was developed by examining all patients with chronic liver disease in two health care systems in Texas from 2010-2015[44]. MELD-Lactate was shown to be a better predictor of in-hospital mortality compared to MELD and MELD-Na [area under the curve (AUC) 0.789 *vs* 0.776 *vs* 0.760; $P < 0.001$], with a more pronounced change in patients with a MELD < 15 (MELD-Lactate AUC 0.763 *vs* 0.674 for MELD) [45]. The MELD-lactate was also a better in-hospital mortality predictor when infection was the reason for hospitalization, however its performance was no different from MELD-Na in other situations[45].

MELD-plus

The MELD-Plus score uses the MELD-Na score along with additional variables found within the electronic medical record. This was developed by examining all cirrhosis related admission from 1992-2010 at Massachusetts General Hospital and Brigham and Women's Hospital and evaluating variables including demographic information, comorbidities using diagnosis codes, standard laboratory values, and current medication use[46]. Further analysis found that nine variables were the most effective predictors of 90 d mortality (bilirubin, INR, creatinine, Na, albumin, total cholesterol, white blood cell, age, and length of stay) and these were used to calculate the MELD-Plus score. A retrospective analysis showed the MELD-plus had improved 90 d mortality prediction compared to MELD-Na following a hospital admission [0.78 (95%CI: 0.75-0.81) *vs* 0.70 (95%CI: 0.66-0.73)][46].

ACLF

Patients with ACLF are defined by multi-organ failure and have increased mortality that is underestimated by the MELD score[47]. Scoring systems that may better predict

Table 1 Alternatives to the model for end-stage liver disease and model for end-stage liver disease-Na score

Test	Description	Comparison to MELD score	Ref.
MELD-GRAIL	Creatinine replaced with GRAIL	Improved 90-d mortality predictor in patients with severe disease (MELD-Na > 32), however similar to MELD-Na in patient with lesser disease severity	Asrani *et al*[42, 43], 2019
MELD-Lactate	Addition of lactate	Better predictor of in-hospital mortality when MELD < 15 or when infection is cause of hospitalization. Similar to MELD-Na in non-infectious admissions	Sarmast *et al* [44], 2020 Mahmud *et al* [45], 2021
MELD-Plus	Addition of albumin, total cholesterol, WBC count, age, and length of stay	Improved 90-d mortality predictor compared to MELD-Na, however can only be used after a hospital admission	Kartoun *et al* [46], 2017
CLIF-C ACLF	Score determined by six different organ systems failures, age and WBC count	Improved predictor of 28-d mortality compared to MELD-Na in patients with ACLF. However, only applicable for ACLF and not generalizable for decompensated cirrhosis	Jalan *et al*[51], 2014 Engelmann *et al* [52], 2018 Ramzan *et al* [53], 2020

GRAIL: Glomerular filtration rate assessment in liver disease; WBC: White blood cell; MELD: Model for end-stage liver disease; ACLF: Acute-on-chronic liver failure; CLIF: Chronic liver failure.

the mortality rate of these patients compared to MELD are being studied. The chronic liver failure–sequential organ failure assessment (CLIF-SOFA) score is a modification to the SOFA score which is used to predict outcomes in ICU level patients[48]. CLIF-SOFA includes sub scores (0 to 4) for each of its six organ components (liver, renal, neurologic, coagulation, circulation, respiratory) with higher scores indicating increased organ disease severity[49]. However, a meta-analysis showed MELD-Na to have a superior AUC compared to CLIF-SOFA for three month mortality in patients with ACLF[50].

A simplified scoring system with the same six organ components became known as the CLIF organ failure (CLIF-OF) score[37]. Further analysis showed that in addition to the CLIF-OF score, age and white cell count were also independently associated with mortality and these were combined with the CLIF-OF score to create the CLIF-C ACLF score[51]. The CLIF-C ACLF score was shown to be the most accurate predictor of 28-d mortality compared to CLIF-OF and MELD for ACLF patients (AUC 0.8 *vs* 0.75 *vs* 0.68, respectively)[52]. Another recent study found CLIF-C ACLF score ³70 at 48 h predicted mortality more accurately than MELD score[53]. These scoring systems may be superior to MELD-Na for liver allocation in patients with ACLF.

FUTURE DIRECTIONS

The number of patients awaiting liver transplantation continues to grow and outpace the amount of available organs, necessitating a fair and equitable organ allocation system. Since the creation of the MELD score in 2002, there have been many policy changes and alternatives systems proposed, however there still remains regional disparities. The recent implementation of acuity circles to address geographic distribution will need to be studied and assessed in the coming years. The success of this model will guide policy decision makers in the coming years.

MELD remains the standard scoring system to define disease severity and determine priority for transplantation, however many alternative scoring options have been discussed in this review as well but none have improved enough on the current standard to necessitate a change. Some countries have begun to explore systems that match recipient factors with donor factors to increase utilization of available organs, but more analyzation and assessment of efficacy and improvement will be needed prior to global implementation.

CONCLUSION

Liver transplant organ allocation models and policy have been changing dynamically

since the release of the Final Rule in 2000. These changes have led to improvements in liver organ utilization and making transplantation more equitable and fair for all patients, but many limitations and areas for improvement remain. Assessment of recent and past policy changes will be needed to continue to guide future direction for a more equitable liver allocation system.

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MINIREVIEWS

Antibiotic prophylaxis in patients with cirrhosis: Current evidence for clinical practice

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Abstract

Patients with cirrhosis show an increased susceptibility to infection due to disease-related immune-dysfunction. Bacterial infection therefore represents a common, often detrimental event in patients with advanced liver disease, since it can worsen portal hypertension and impair the function of hepatic and extra-hepatic organs. Among pharmacological strategies to prevent infection, antibiotic prophylaxis remains the first-choice, especially in high-risk groups, such as patients with acute variceal bleeding, low ascitic fluid proteins, and prior episodes of spontaneous bacterial peritonitis. Nevertheless, antibiotic prophylaxis has to deal with the changing bacterial epidemiology in cirrhosis, with increased rates of gram-positive bacteria and multidrug resistant rods, warnings about quinolones-related side effects, and low prescription adherence. Short-term antibiotic prophylaxis is applied in many other settings during hospitalization, such as before interventional or surgical procedures, but often without knowledge of local bacterial epidemiology and without strict adherence to antimicrobial stewardship. This paper offers a detailed overview on the application of antibiotic prophylaxis in cirrhosis, according to the current evidence.

Key Words: Cirrhosis; Quinolones; Spontaneous bacterial peritonitis; Liver transplantation; Trans-jugular intrahepatic portosystemic shunt; Variceal bleeding

Core Tip: Antibiotic prophylaxis represents a cornerstone for the management of several complications of decompensated cirrhosis, as spontaneous bacterial peritonitis

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and variceal bleeding. Short-term antibiotic prophylaxis is often applied in many other settings during hospitalization of patients with cirrhosis, such as before interventional or surgical procedures, but often without knowledge of local bacterial epidemiology and without strict adherence to antimicrobial stewardship.

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INTRODUCTION

Progress has been made on the pathogenetic and prognostic role of bacterial infection (BI) in many clinical settings of liver cirrhosis. Bacterial translocation from the intestinal lumen is now considered key factor for the development and worsening of portal hypertension[1]. Moreover, cirrhotic patients, especially at advanced disease stages, experience an impaired immune-surveillance, with reduced response to pathogens and a contemporary "exhausted" systemic inflammation[2]. Both the high susceptibility to BI and the exaggerated systemic response trigger hepatic and extra-hepatic organs dysfunction, favoring the development of acute-on-chronic liver failure [3], and a sudden worsening of portal hypertension. Therefore, it is not unusual that an episode of BI impairs the natural course of the disease, increasing morbidity, mortality, and the risk of drop-out from the liver transplantation (LT) waiting list[4-6].

The development of aggressive, tailored strategies against BI has become a cornerstone in several fields of hepatology. It has been demonstrated that every hour of inappropriate antibiotic use was associated with 1.9 higher odds of death in patients with cirrhosis and septic shock[7]. Therefore, a timely, adequate antibiotic stewardship, defined as the optimal selection, dosage, and duration of antimicrobial treatment, saves lives.

To date, among pharmacological options, antibiotic prophylaxis appears the most effective preventive measure[8]. Indeed, its wise use has improved prognosis in many settings, such as spontaneous bacterial peritonitis (SBP) or acute variceal bleeding (AVB), becoming standard of care[9].

Nevertheless, the wide and prolonged use of systemic antibiotics (not only for prophylaxis) has brought lights and shadows in cirrhosis. Indeed, there has been the spread of multidrug resistant (MDR) bacteria, a huge healthcare problem that involves many fields of medicine with significant heterogeneity and prevalence across countries and centers, but exerting a highly negative prognostic impact in the setting of decompensated cirrhosis[10]. Moreover, *Clostridioides difficile* infection has been increasingly seen in cirrhotic patients, with prolonged hospitalization and higher in-hospital mortality when compared with non-cirrhotic patients with similar burden of comorbidities[11-13]. Moreover, the onset of such infection raises an already known intestinal dysbiosis, whose prevalence aligns with the severity of liver dysfunction. This may increase the risk of a refractory infection or impair the effectiveness of several treatments, as fecal microbiota transplantation[14].

Several other issues, such as the optimal length of prophylaxis, the preferable antibiotic class to use, and potential drug-drug interactions, remain still unexplored areas. These factors may explain the relatively low adherence to antibiotic prophylaxis in some fields. In a recent survey from France[15], almost all physicians prescribed antibiotics during AVB or after an episode of SBP (97.7% and 94.8%, respectively), but 1 out of 4 did not adhere to primary prophylaxis of SBP, without significant differences between workplaces (general *vs* university hospitals). In a recently published paper from the United States, investigating potential harmful prescriptions in patients with cirrhosis[16], nearly half (48.0%) of the patients with prior SBP filled an antibiotic prescription for secondary prophylaxis, but only 8.8% consistently filled this prescription.

Apart from these areas, antibiotic prophylaxis may be applied in many other settings during hospitalization of patients with cirrhosis, such as before interventional or surgical procedures. Therefore, this paper offers a detailed overview on the

application of antibiotic prophylaxis in cirrhosis, according to current evidence.

SEARCH METHODS

PubMed/Medline until December 2020 was searched in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses[17] to identify all relevant medical literature included under the following search text terms: ("cirrhosis" OR "liver cirrhosis") AND ("antibiotic prophylaxis" OR "prophylaxis") for each of the following items: SBP, variceal bleeding, gastric varices, radiofrequency ablation (RFA), trans arterial chemoembolization, endoscopic retrograde cholangiopancreatography, LT, acute liver failure, and alcoholic hepatitis. Only studies involving patients over 18 years of age and in the English language were included. In addition, a full manual search was performed of all relevant review articles and the retrieved original studies.

SBP

According to current guidelines[9,18], primary prophylaxis should start in patients with Child–Pugh score ≥ 9 and serum bilirubin level ≥ 3 mg/dL, impaired renal function or hyponatremia, and ascitic fluid protein lower than 15 g/dL, in view of previous randomized controlled trials (RCTs)[19-21]. A meta-analysis published in 2012 on three studies confirmed the beneficial role of primary prophylaxis in preventing SBP but not in reducing mortality[22]. Recently, an updated Cochrane meta-analysis did not show any gain in survival, in either primary or secondary prophylaxis[23], but the studies were at high risk of bias. Meta-analysis further clarified that, currently, no antibiotic seemed to be superior to others[23,24].

Moreau *et al*[25] investigated the role of norfloxacin in Child-Pugh class C cirrhotic patients. In this RCT, 291 patients (95% without prior SBP) were included independently of ascitic fluid protein level and then randomized to norfloxacin (400 mg/d administered for 6 mo) *vs* placebo. The primary endpoint (*i.e.* 6-mo survival) was not different between cohorts, neither was the incidence of SBP. When LT was considered as a competing risk of death or survival, patients given norfloxacin and having low ascitic fluid proteins displayed a significantly better outcome (cumulative 6-mo probability of death: 15.5% *vs* 24.8%, $P = 0.045$). Notably, patients on norfloxacin therapy were also at lower risk of developing BI, *gram-negative* BI, and MDR infections during therapy. That said, in clinical practice, primary prophylaxis seems to be reasonable for high-risk patients (*i.e.* those with low ascitic fluid proteins and advanced disease), especially if they are waiting for LT.

The rationale behind secondary prophylaxis is the high recurrence rate in patients who recover from SBP (69% within a year)[26]. In a seminal RCT, Ginés *et al*[27] demonstrated that norfloxacin (400 mg/d) decreased SBP recurrence to 20%[27]. As a consequence, current guidelines recommend secondary prophylaxis with norfloxacin (400 mg/d) until death or LT after the first episode of SBP[9,18]. Although the previously reported meta-analysis did not strongly support this measure, due to heterogeneity across studies and a high risk of bias[23], secondary prophylaxis is routinely adopted worldwide.

Nevertheless, clouds are still on the horizon, as well as grey areas in this field. First, it has been questioned whether fluoroquinolones, widely investigated in such patients due to their potential ability in reducing the translocation of *gram-negative* bacteria from the gut lumen, still remain the drugs of choice. Indeed, there has been a changing epidemiology of BI in cirrhosis from *gram-negative* to *gram-positive* rods (especially in hospitalized patients), with increasing prevalence of *Enterococci*. Therefore, quinolones effectiveness after hospital-acquired SBP or after MDR-related SBP appears unclear. Moreover, warnings about their metabolic and cardiovascular side effects were added to previously known effects on joints and nervous system. Apart from trimethoprim-sulfamethoxazole, which has been proposed as a possible second-line drug, or first-line choice in quinolones-intolerant patients[28], no effective alternatives have been available between systemic antibiotics; head-to-head comparisons between quinolones and other drug classes, even in specific settings, are urgently needed. The use of other molecules such as rifaximin, which is poorly absorbed in the gastrointestinal tract with high intraluminal levels and already used for prophylaxis of hepatic encephalopathy, is a promising alternative[29] and warrants further investigation through dedicated trials. Moreover, there is some concern about the possible increase in MDR organisms after long-term antibiotic use, but this has not been confirmed in recent studies[25,30].

Lastly, adherence to life-long therapy represents a major issue, as mentioned above. A recent multicenter RCT demonstrated non-inferiority of prophylaxis with ciprofloxacin 750 mg once a week when compared with norfloxacin 400 mg/d in terms of SBP occurrence in a relatively small group of patients with low ascitic fluid protein and previous history of SBP[31]. If these results can be confirmed, without determining increased incidence of MDR rods, this new antibiotic schedule may be of help in clinical practice. In summary, patients with cirrhosis at highest risk of SBP development may require primary antibiotic prophylaxis, especially when awaiting LT. Secondary prophylaxis is recommended in view of stronger supporting evidence. Until now, quinolones remain the drugs of choice.

VARICEAL BLEEDING

The beneficial role of antibiotic prophylaxis has been widely demonstrated in patients with decompensated cirrhosis and AVB. The rationale behind antibiotic prophylaxis is that a relevant percentage of bleeding episodes can be due to infection-related worsening of portal hypertension and coagulopathy. Moreover, infection is a causative factor in early variceal rebleeding[32]. A meta-analysis of 12 RCTs, including 1241 patients, confirmed the beneficial role of antibiotic prophylaxis in terms of overall mortality, mortality from BIs, and overall incidence of BIs[33].

Two major issues have to be addressed in the AVB setting. First, whether one class of antibiotics could be considered more effective than the others. A RCT conducted by Fernández *et al*[34] showed that patients who received norfloxacin had a higher rate of BI than those receiving cephalosporin, quinolone resistance being a major cause of infection breakthrough in these patients. The abovementioned meta-analysis[33] did not show any superiority of a specific class of antibiotics over the others, since these were all superior to the placebo; nevertheless, the beneficial effect seemed to be more pronounced in trials using cephalosporins (relative risk: 0.16, 95% confidence interval: 0.05-0.48), followed by quinolones (relative risk: 0.27, 95% confidence interval: 0.18-0.39). Therefore, current Guidelines recommend the use of intravenous (i.v.) cephalosporins (*i.e.* ceftriaxone 1 gr/d) as the best prophylactic therapy in AVB[35,36]. In clinical practice, the choice also has to take into account local epidemiology, setting of bleeding (*i.e.* out- *vs* in-hospital bleeding), and patient's individual features [previous antibiotic therapy; previous known infections or colonization(s)].

Second, the need for universal prophylaxis. Data from a propensity-matched cohort of 381 patients with AVB[37] showed that Child-Pugh A patients had a negligible risk of infection (2% *vs* 1%) and mortality (2.5% *vs* 0.4%), regardless of prophylaxis. The risk of infection rose in Child-Pugh class B patients, being significantly different in those receiving prophylaxis (6% *vs* 14%), even if mortality did not change (5% *vs* 7%). Finally, antibiotics significantly reduced both BI (19% *vs* 39%) and mortality (35% *vs* 62%) in Child-Pugh C patients. Therefore, current guidelines advocate prospective studies to assess properly the effectiveness of antibiotic prophylaxis in compensated patients[35].

In the setting of elective variceal band ligation, antibiotic use is less common. The rationale behind prophylaxis is the risk of bacteremia, which occurs in 3%-6% of cases, but it becomes clinically relevant only in a minority. A recently published systematic review and meta-analysis investigated this topic including 1001 procedures in 587 patients from 19 studies[38]. Overall, the frequency of bacteremia was 17% and 6% after sclerosis and band ligation, respectively. Comparing elective *vs* emergency procedures, the authors showed a significant difference for sclerosis (13% *vs* 22.5%) but not for band ligation (7.6% *vs* 3.2%). In summary, data do not currently provide strong recommendations about routine antibiotic prophylaxis for elective variceal therapy[35,39]. Few data are available on the effectiveness of antibiotic prophylaxis for elective fundal variceal obturation with cyanoacrylate. A study from China[40] showed that sepsis occurred with a relatively low frequency (0.64%), whereas the risk was four-fold higher in the emergency setting. A further prospective RCT from China, including 107 patients undergoing elective cyanoacrylate obturation, showed that 53 who received cefotiam 2 gr i.v. before endoscopy experienced a lower incidence of post-operative complications, even if differences on infectious complications were not exhaustively reported[41]. Finally, a small study from Thailand compared cyanoacrylate injection in urgent *vs* elective setting, showing a negligible rate of peri/post-procedural infectious episodes in the former group (0% *vs* 20%)[42].

In summary, antibiotic prophylaxis remains a cornerstone for decompensated cirrhosis with AVB. According to available data, its use may be not routinely used in

the non-urgent setting.

INTERVENTIONAL PROCEDURES

Trans jugular intrahepatic portosystemic shunt (TIPS) has been increasingly adopted in patients with cirrhosis, especially for the treatment of refractory ascites and variceal bleeding. Sepsis or bacteremia are quite common complications of TIPS placement, occurring in 2%-10% of cases[43,44]. Stent infection (*i.e.* endotipsitis) is a rare condition, caused by either *gram-positive* or *gram-negative* bacteria and can occur early (*i.e.* within 3 mo) after stent placement, or in a later period[45,46]. A single-center randomized study on 105 patients showed a non-significant reduction of post-interventional infections (20% *vs* 14%) after prophylactic administration of cephalosporin (cefotiam, 2 g i.v.). At multivariate analysis, multiple stenting, maintenance of central venous line, but not severity of underlying liver disease, had a significant impact on post-TIPS infection[47]. The same group further demonstrated that different antibiotic dosages for prophylaxis (single dose of ceftriaxone, 1 gr *vs* 2 gr i.v.) were not associated with different outcomes in terms of post-procedural infections in 82 patients undergoing elective TIPS (2.6% BI occurrence within 1 wk, in both groups)[48]. That said, current guidelines do not suggest the routine use of antibiotic prophylaxis for TIPS placement[49,50], mainly because strong evidence for this is still lacking[51]. Nevertheless, this must be weighed against the risk of serious post-procedural septic events. Therefore, antibiotic prophylaxis may be considered at least for expected technically difficult procedures or in patients with previous biliary interventions.

Considering endotipsitis, there is no evidence for adopting long-term prophylaxis given the rarity of the condition and the absence of robust microbiological data. Lastly, it has been proposed that antibiotic prophylaxis may be considered in patients having a diagnosis of a thrombosed TIPS, before invasive procedures (*e.g.*, gastrointestinal endoscopy), but larger studies are needed to properly assess this[46].

Endoscopic retrograde cholangiopancreatography (ERCP) is a commonly used procedure for many benign and malignant diseases of the biliary tract. A systematic review of nine RCTs showed that antibiotic prophylaxis reduced bacteremia in patients undergoing elective ERCP, but in the subgroup of patients with uncomplicated ERCP, the effect of antibiotics was less pronounced[52]. Therefore, American guidelines recommend antibiotic prophylaxis for prevention of cholangitis in cases of biliary duct obstruction and incomplete drainage[53]. Endoscopic procedures in patients with primary sclerosing cholangitis fall in this special group, due to multiple strictures and frequent prevalence of bacteriobilia, therefore antibiotic prophylaxis is recommended[54,55].

RFA and trans-arterial chemoembolization (TACE) are interventional procedures for the treatment of hepatocellular carcinoma. RFA has been classified as a clean procedure in such patients, not requiring routine antibiotic administration[56]. The incidence of post-procedural abscess is equal to 0.8%, according to available case series [57,58].

Thermal ablation determines heat-induced coagulative necrosis of the tumor. Therefore, bacterial superinfection may be a quite common complication, due to bacterial colonization of the necrotic area; moreover, thermal injury can connect biliary ducts with the ablation zone, creating a route for contamination from enteric bacteria in patients with underlying altered biliary anatomy (*e.g.*, choledocho-jejunostomy, prior endoscopic sphincterotomy). Current evidence therefore suggests that antibiotic prophylaxis may be used in such patients[59-63].

The rationale of TACE is to reduce arterial feeding to a malignant nodule, adding local chemotherapy, such as doxorubicin. A recent retrospective, single-center study from the United States analyzing the outcome of 171 patients who underwent 253 TACE without antibiotic prophylaxis[64] reported no infectious complications. A meta-analysis on four studies reported no significant difference between patients undergoing antibiotic prophylaxis and patients without[65], but interventional techniques were not homogeneous across studies and some endpoints (*e.g.*, post-procedural fever) may unmask inflammatory response rather than true infectious complications. Local instillation of antibiotic particles during interventional procedures has recently been proposed[66] but requires further investigations.

Yttrium^{90} embolization is a relatively novel interventional technique for the treatment of hepatocellular carcinoma or liver metastases. Few data are currently available about antibiotic prophylaxis in this setting, also in view of heterogeneous patients' characteristics, such as presence or absence of cirrhosis. A recently published

survey from 45 European centers confirmed different strategies regarding antibiotic prophylaxis, which was routinely adopted in 8% of cases[67]. However, as for chemoembolization, patients with a history of biliary endoscopic or surgical interventions seemed to be those who may receive antibiotic prophylaxis[68].

In summary, antibiotic prophylaxis is not routinely recommended for elective interventional procedures in patients with cirrhosis. It should be carefully considered in high-risk patients, such as those with bilio-enteric anastomosis, whereas it should be routinely adopted in patients with primary sclerosing cholangitis undergoing ERCP.

LT

Infection remains a major cause of morbidity and mortality in liver transplant recipients, with a significant burden on short-term post-operative graft and patient survival. Length of surgery, prior transplant or abdominal surgery, severity of liver disease at time of transplantation, and post-operative complications represent the most important risk factors for post-LT surgical site infection (SSI). The pathogens most commonly associated with early SSIs are *Escherichia coli, Klebsiella, Enterobacter, Acinetobacter*, but also *Enterococci*[69,70].

Theoretically, the main role of pre-operative prophylaxis would be to prevent SSI. Although a Cochrane meta-analysis, after including only one RCT (at high risk of bias), concluded that benefits and harms of prophylactic regimens were difficult to assess[71]; antibiotic prophylaxis has been widely used before LT, being justified by high infection rates (even during ongoing prophylaxis) and complexity of surgery.

Data on the type and length of peri-operative LT prophylaxis are scant. In a survey from 61 European LT centers, Vandecasteele *et al*[72] reported that the type of antibiotic prophylaxis was heterogeneously chosen among centers. An extended spectrum antibiotic regimen was reported in the majority of cases (73%) for elective LT. Notably, 25% centers reported a change in prophylactic schedule (in terms of drug class and length) for the sickest candidates (*i.e.* those with acute-on-chronic liver failure). The survey further demonstrated that one-third of centers used to change antibiotic prophylaxis in the presence of LT for candidates with acute liver failure (ALF).

Current American guidelines recommend the use of piperacillin–tazobactam, or cefotaxime plus ampicillin as routine prophylaxis during LT[73], considering cefuroxime, metronidazole, clindamycin, or quinolones as important alternatives in candidates with allergy to B-lactams. Notably, the guidelines highlight correct timing of prophylaxis (60 min before surgical incision for most antibiotics) and the need to repeat the dose in cases of prolonged surgery and suggest against the routine use of vancomycin, since it may increase the risk of post-transplant MDR rods. Pre-transplant surveillance for ruling-out colonization(s), as well as updates on local bacterial epidemiology, represent further important measures for tailoring prophylaxis to prevent antibiotic failure and reduce MDR development[74,75]. The length of antibiotic prophylaxis remains debated, with heterogeneous courses ranging from 24 h to 5 d. Recently, a RCT from the United States compared short-course (*i.e.* intraoperative doses) and 72-h extended course in 97 adult LT recipients[76]. The authors did not find any difference in prevalence of SSI (19% *vs* 27%) or overall infection (35% *vs* 37%) between groups, providing evidence in favor of a shorter antibiotic schedule. Larger studies are warranted to confirm properly these hypotheses. Recently, antibiotics have been investigated as factors potentially changing post-surgical ischemia-reperfusion injury. In mice, antibiotics prior to LT reduced the gut microbiota, decreasing the inflammatory response and promoting homeostatic responses[77]. These data were confirmed in a retrospective group of LT recipients, confirming that pretreatment with antibiotics was associated with improved hepatocellular function and a decreased incidence of early allograft dysfunction. Further data are needed to confirm properly the effectiveness of antibiotic therapy in LT recipients, beyond its preventive role against SSI.

SPECIAL CONDITIONS

Severe alcoholic hepatitis

Patients with severe alcoholic hepatitis (sAH) are prone to develop infection due to their severe state of immunosuppression[78]. BI accounts for nearly 80% of overall

invasive infections, although growing attention has been paid to fungal infection, especially Aspergillosis. The prevalence of BI at hospital admission and during hospitalization is up to 30% and 60%, respectively[79,80]. Urinary tract and airways are the most common infectious sites in such a cohort, the latter being highly prevalent after corticosteroid treatment, probably due to an increasing need for mechanical ventilation and intensive care management.

Corticosteroid therapy has been proven effective in improving short-term survival in sAH and currently represents the first-choice medical therapy.

Given the high prevalence of BI at baseline, and the theoretical immunosuppressive role of corticosteroids, several studies investigated whether they would increase infectious risk, and whether infection occurring during corticosteroid therapy would significantly impair survival[81]. A study on a large cohort of patients with sAH confirmed an increasing rate of BI during corticosteroid treatment (23% *vs* 12% at baseline)[82], but the actual role of corticosteroids was difficult to ascertain. Considering prognosis, a landmark study from France[79] demonstrated that the probability of being infected after/during corticosteroids reduced the survival benefit given by medical therapy. A further meta-analysis on 12 studies involving 1062 patients did not show a higher short-term risk of death for infection in those receiving corticosteroids, when compared with those receiving a placebo[83].

That said, antibiotic prophylaxis has been proposed in such a setting. Vergis *et al*[82] demonstrated that an infection occurring prior to corticosteroid introduction has a more favorable course if the antibiotic is continued also during steroid therapy. Moreover, the use of prophylactic antibiotics (prescribed in 45% of cases) was associated with a lower risk of death than that in patients who did not receive prophylactic antibiotics (13% *vs* 52%)[82]. Summarizing the available data, infection is highly prevalent in patients with sAH, both in those receiving steroids and not. The impact of steroids as a potential risk factor for infection is currently debated and not supported by robust data. An ongoing clinical trial (NCT02281929) assessing the prophylactic role of amoxicillin-clavulanic acid will probably clarify this point.

ALF

In a similar fashion to sAH and acute-on-chronic liver failure, ALF is characterized by a severe state of immunosuppression. Moreover, the rapidly evolving scenario of ALF, including the changing neurological status and need for circulatory support and mechanical ventilation, makes diagnosis of BI even more difficult. The prevalence of BI is nearly 30%-34%, according to recent studies[84,85]. Severity of the underlying condition and presence of cerebral edema seem to be associated with infection development. Occurrence of infection is obviously associated with worse outcome in ALF, since it may further derange hepatic and extra-hepatic organ(s) failure and may delay or contra-indicate LT. Recently, a retrospective analysis of a large United States cohort by Karvellas *et al*[86] did not show any significant improvement with administration of antibiotic prophylaxis in 600 patients with ALF, if compared with the 951 patients who did not receive antibiotics. Indeed, there was no significant difference in the probability of having bloodstream infection based on receiving prophylaxis (12.8%) or not (15.7% $P = 0.12$). Notably, the timing of prophylaxis was not homogeneous, nor were the clinical characteristics between cohorts, such as type of prophylaxis (47% extended spectrum beta-lactam, 39% vancomycin, 27% fluoroquinolones, and 20% third and fourth generation cephalosporins). Other strategies, such as selective bowel decontamination, did not show any significant benefit either [87]. In summary, current guidelines say that, even the routine use of prophylactic antibiotics does not increase survival in such patients, a strict surveillance for infection should be provided in order to start antibiotic therapy as early as possible[88,89]. Prophylaxis should be considered in cases where illness progression is considered likely, as in those with worsening encephalopathy, signs of systemic inflammation, or awaiting LT[90,91]. The choice of antibiotic class is even more debated, probably due to heterogeneous epidemiology across studies and the relevant number of culture-negative infections. That said, the high prevalence of pneumonia[87], as well as the presence of indwelling catheters and invasive procedures should be taken into account.

Table 1 Current recommendations and uncertainties regarding antibiotic prophylaxis in patients with cirrhosis

Procedure/clinical setting	Antibiotic prophylaxis	Areas of uncertainties
Spontaneous bacterial peritonitis	Primary prophylaxis recommended in decompensated patients with low ascitic fluid proteins. Secondary prophylaxis recommended	Second-line antibiotics. Quinolone resistance. Rifaximin. Secondary prophylaxis after MDR infection
Variceal bleeding	Prophylaxis recommended in acute bleeding from esophageal/gastric variceal bleeding	Prophylaxis in compensated (*e.g.*, Child-Pugh A) patients having acute variceal bleeding. Prophylaxis in elective endoscopic therapy of gastric/esophageal varices
Endoscopic retrograde cholangiopancreatography	Routine prophylaxis not recommended. Prophylaxis is recommended in patients with incomplete drainage and in those with primary sclerosing cholangitis	
Transjugular intrahepatic portosystemic shunt	Prophylaxis should be considered in difficult procedures	Prophylaxis in patients with thrombosed transjugular intrahepatic portosystemic shunt undergoing invasive procedures
Radiofrequency ablation. Trans-arterial chemoembolization. Radioembolization	Routine prophylaxis not recommended. Advisable in patients with prior interventions on biliary tree	Intra-procedural antibiotic instillation
Liver transplantation	Routine prophylaxis is recommended	Length of prophylaxis
Severe alcoholic hepatitis receiving steroids	Prophylaxis would be preferable	Length of prophylaxis, antibiotic class
Acute liver failure	Prophylaxis is advisable in high-risk patients, or those waiting for liver transplant	Antibiotic class

CONCLUSION

BI represents a common complication in patients with cirrhosis due to disease-related immune dysfunction. In this setting, antibiotic prophylaxis plays a major role, especially in high-risk patients. Type and length of prophylaxis are supported by low quality data in several fields of hepatology and LT (Table 1) and are currently heterogeneously adopted across centers. Since unnecessary prophylaxis or prolonged schedules may increase the risk of anaphylaxis and development of MDR rods, a wise adherence to current recommendations and a rigorous application of antibiotic stewardship are of utmost importance. Other important remarks should be offered to the reader. First, this paper does not include prophylaxis against invasive fungal infection, which is another serious complication in cirrhosis, having an increasing prevalence and a dreadful outcome[92]. Second, although we have focused on systemic antibiotic prophylaxis, growing evidence on non-antibiotic prophylaxis against BI in cirrhosis has to be mentioned. The role of rifaximin, a nonabsorbable antibiotic, has been largely demonstrated for patients with prior episodes of hepatic encephalopathy. Other emerging selective gut decontamination modalities, including prebiotics and probiotics, and fecal microbiota transplant are in the pipeline[93]. Future studies are therefore warranted to investigate whether these modifications to gut microbiota will reduce the occurrence of BI (especially SBP), acting as prophylactic strategies. Moreover, the preventive role of non-selective beta blockers and albumin has to be robustly confirmed, according to underlying liver function and setting[94,95].

Finally, we strongly encourage an updated review of local bacterial epidemiology in clinical practice, and a strong liaison with infectious disease specialists, pharmacologists, microbiologists, and epidemiologists, in order to use tailored prophylaxis regimens, because the right prevention works better than a cure.

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MINIREVIEWS

Kidney transplant from donors with hepatitis B: A challenging treatment option

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Abstract

Utilizing kidneys from donors with hepatitis B is one way to alleviate the current organ shortage situation. However, the risk of hepatitis B virus (HBV) transmission remains a challenge that undermines the chance of organs being used. This is particularly true with hepatitis B surface antigen (HBsAg) positive donors despite the comparable long-term outcomes when compared with standard donors. To reduce the risk of HBV transmission, a comprehensive approach is needed. This includes assessment of donor risk, optimal allocation to the proper recipient, appropriate immunosuppressive regimen, optimizing the prophylactic therapy, and post-transplant monitoring. This review provides an overview of current evidence of kidney transplants from donors with HBsAg positivity and outlines the challenge of this treatment. The topics include donor risk assessment by adopting the nucleic acid test coupled with HBV DNA as the HBV screening, optimal recipient selection, importance of hepatitis B immunity, role of nucleos(t)ide analogues, and hepatitis B immunoglobulin. A summary of reported long-term outcomes after kidney transplantation and proposed criteria to utilize kidneys from this group of donors was also defined and discussed.

Key Words: Hepatitis B virus; Organ donor; Recipient allocation; Kidney transplant; Transmission; Long term outcomes

Core Tip: Low-risk hepatitis B surface antigen (HBsAg) positive kidney donor, defined by a negative test of hepatitis B virus (HBV) DNA being allocated to immune-recipients with anti-HBs at least 10 mIU/mL is a key factor in overcoming the risk of HBV transmission. The risk may be further eliminated with optimal nucleos(t)ide analog prophylaxis. Blood tests for HBV DNA, HBs Ag, and liver function tests

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should be routinely monitored after transplantation and when there is a change of immunosuppression. The excellent long-term outcomes being reported suggested that the outcomes of this treatment option are promising. This will lead to broader use of organs with positive HBsAg.

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INTRODUCTION

Kidney transplantation (KT) is the preferred treatment for patients with end-stage kidney disease (ESKD). It is associated with reduced mortality and improved quality of life when compared to dialysis therapy[1]. However, the number of ESKD patients awaiting KT far exceeds the number of organ donations globally and leads to a problem of organ shortage. This major barrier has led to a prolonged waiting time and subsequently excess mortality of patients in the waiting list pool[2]. There are several proposed rationales to solve the problem of organ shortage[3]. One possible solution is to expand the donor pool by utilizing "extended donor criteria organs". Such organs include those from donors with hepatitis B virus (HBV) infection.

The prevalence of chronic HBV infection varies greatly by geographical region, ranging from 0.4% to 1.6% in the region of the Americas, 1.2% to 2.6% in Europe, 1.5% to 4.0% in Southeast Asia, 2.6% to 4.3% in the Eastern Mediterranean, 5.1 to 7.6 % in the Western Pacific, and 4.6% to 8.5% in Africa[4]. Discarding all kidneys from donors with markers of HBV infections may substantially harm the donor pool in endemic areas since the prevalence in donors is similar to that of the general population. Thus, one challenge is determining the optimal use of kidneys from such donors. The best utilization may involve allocating such kidneys to transplant candidates at low risk of acquiring a donor-transmitted hepatitis B infection. Prophylactic therapy and appropriate monitoring will further eliminate the risk of HBV transmission.

According to current guidelines, there is an increasing trend of accepting non-liver organs from total hepatitis B core antibody-positive [anti-HBc (+)] donors to be used in any recipient regardless of HBV immune status without prophylaxis due to the negligible risk of de novo infection. However, utilizing kidneys from donors with positive hepatitis B surface antigen (HBsAg) [HBsAg (+)] remains controversial, and it is generally suggested that such organs be discarded[5-7]. In this review, we aim to summarize the current evidence regarding the use kidneys from HBsAg (+) donors with an emphasis on the risk of HBV transmission, liver related morbidities, and the outcomes of KT.

SCREENING TEST FOR HBV INFECTION IN ORGAN DONORS

Screening for HBV infection usually relies on a panel of serologic tests. The test for HBsAg is widely distributed. However, it can fail to detect disease during a 35-44 d window period after inoculation or occult infection defined as detectable viral DNA in absence of HBsAg[8]. Another importance serologic screening test for previous HBV exposure is anti-HBc. In acute hepatitis B infection, immunoglobulin M (IgM) antibody to hepatitis B core antigen (IgM anti-HBc) becomes positive after 4 wk to 6 wk of exposure indicating recent infection and active viral replication whereas total hepatitis B core antibody (anti-HBc) appear at the onset of symptoms and persists for life. Hepatitis B e antigen (HBeAg) and hepatitis B e antibody (anti-HBe) are additional tests to identify viral replicative activity as HBeAg positivity which indicates active viral replication (*i.e.*, usually a viral load > 10000 IU/mL). In contrast, anti-HBe positivity indicates the presence of the non-replication phase (*i.e.*, a viral load < 10000 IU/mL). Lastly, hepatitis B antibody (anti-HBs) is a marker of immune status due to either naturally- or vaccine-acquired immunity[9].

In the situation of deceased kidney donation, HBs Ag and anti-HBc are generally accepted as cost-effective screening tools. The results should be integrated with additional essential information of the donors to assess the risk of donor-derived infection as previously described[10-12]. Some transplant centers in endemic areas routinely add on anti-HBe and HBeAg to the donor screening platform as biomarkers of high viral replication and infectivity activity relating to a high viral burden[13-15]. However, serologic testing alone still has limitations due to the long window period and the lack of sensitivity to detect occult infections, raising concerns over risk misclassification[16,17]. In clinical practice, isolated anti-HBc is commonly observed. This may occur in several clinical settings. First, the early window period of acute hepatitis B. Second, a resolved HBV infection with waning of anti-HBs titer. Third, a false positive anti-HBc. This setting is commonly found in an area with a low prevalence of HBV infection. Fourth, an occult chronic HBV infection with low viremia and undetectable HBsAg. The latter can occur with a poor test quality or when there is a mutation of HBsAg[18,19].

To improve the sensitivity of screening tests, the nucleic acid test (NAT), which is usually in the form of an HIV/HCV/HBV multiplex, has been proposed as an optional donor screening test. This test is advantageous, because it shortens the windows period to 20-22 d compared to 35-44 d by conventional serology[8]. Although NAT seems a promising solution, obstacles to its implementation include whether it is cost-effective in a particular healthcare setting, the logistic challenges, the long turn-around times (*i.e.*, as much as 8 h), the technical proficiency required, and the reliability of an in-house developed test[8,20]. In low prevalence settings, such as the United States , the concern is that the benefit may not outweigh the disadvantage that can lead to loss of organ donor, and have suggested that routine use of NAT screening was unnecessary[8]. However, a look-back study demonstrated adding NAT to routine screening by serologic testing enhanced the physician's confidence in using organ with discordant results [*i.e.*, anti-HBc(+)/NAT(-)], and adding NAT led to a gain in overall organ utilization after policy implementation[21]. Currently, this test is gradually becoming accepted in national policies in several countries. For example, the US Public Health Service 2020 guideline revision suggests performing NAT for HIV, HBV, and HCV in organ donors in all donor transplants[22]. While guidelines in the Transplantation Society of Australia and New Zealand suggests performing NAT in donors with HBsAg positivity, anti-HBc positivity, or HBsAg and anti-HBc negativity with increasing behavioral risk for HBV infection[6]. However, the decision to use NAT in individuals depends on the context of each setting or country. For practical purposes, we suggest that all serologic tests for HBV (HBsAg, anti-HBc, HBeAg, anti-HBe) as well as other essential infectious markers are done at the donor hospitals. In parallel, a universal NAT test for HBV (usually in combination with HIV and HCV) should be conducted at the central or regional organ allocation center and the result should come back before or at the time of organ retrieval.

RISK OF HBV TRANSMISSION AND INFECTION AFTER KT

Donor factors and the role of HBV DNA

The risk of donor-transmitted HBV infection is lower in kidney transplant recipients compared with liver transplant recipients with similar serologic marker positivity[23]. Specific HBV receptor recognition may play important roles in this hepatotropism phenomenon[24]. The demonstration of persistent HBV viral genome in the liver and peripheral blood mononuclear cells of patients with acute and chronic HBV infection after the clearance of HBsAg in the blood has led to an awareness of possible HBV reactivation in the immunocompromised host. This notion was supported by previous studies that showed the presence of HBV covalently closed circular DNA and total DNA in the serum of patients with negative HBsAg[25,26].

Important behavioral risk factors to acquire HBV (and other coincidental infections such as HIV and HCV) should be carefully reviewed when assessing the risk of HBV transmission from the donors. Patients who have strong risk factors for HBV/HCV/HIV combination should be tested for HBsAg, HBV NAT, and then HBV DNA by a test with the highest sensitivity and specificity. A previous study had suggested a test with a lower detection limit of less than < 0.1 ng/mL for HBsAg and 10 IU/mL for HBV DNA[27]. Donors with HBV infections are generally categorized into two groups according to their serologic status. The first donor group is the anti-HBc positive group in which the rate of transmission appears to be negligible according to the recipient's protective immunity status. The overall seroconversion rate was 3.24% (mostly anti-

HBc seroconversion). HBsAg seroconversion rate from this study was shown to be 0.28% with no symptoms of hepatitis and no excess mortality[28]. The second donor group is the HBsAg positive group where the HBV transmission remains a challenging problem[5]. In the current era, interesting information regarding the use of kidneys from HBsAg (+) donors is increasing. Previously, it was generally believed to discard the use of these kidneys. However, several recent studies and guidelines suggested that kidneys from HBsAg (+) donors can be carefully considered to be transplanted to appropriate recipients after careful consideration of the risk and benefit with informed consent[5,29]. The role of NAT in reducing the window period of serological test in combination with a careful evaluation of the donor behavioral risk factors has been increasingly emphasized[30]. KT from living HBsAg (+) donors can be donated to anti-HBs (+) recipients with protection who have no abnormalities of liver function test, no history of liver disease within the previous 28 days, and who are not living in the area of possible mutation strain of HBV[31].

It is important to note that fulminant hepatitis B infection had been reported in a naïve recipient who received kidneys from donors with HBsAg (+)/HBeAg (+) donors [32]. Since this report, HBeAg and anti-HBe were routinely checked in HBsAg (+) donors to ensure a low infectivity rate of HBV before performing KT[14,15,33]. Use of antiviral medications to treat HBV add benefit to the treatment plan to use organs from HBsAg (+) donors. Unlike liver transplantation, KT from this type of donor can be associated with a functional cure of HBV. The functional cure was defined by a state of sustained loss of HBsAg with or without anti-HBs seroconversion which was usually associated with good clinical outcomes[34]. A recent study performed 83 living KTs from HBsAg (+) donors to HBsAg (-) recipients. Before the transplant, 28% of the donor in the latter study were HBV DNA (+) and 24% of the recipients had no anti-HBs. All recipients in the latter study received hepatitis B immunoglobulin (HBIG) and antiviral medication as prophylaxis treatment. The results showed that this treatment was associated with excellent graft and patient survival without excess HBV transmission when compared with the control group[35]. In recent years, tests for HBV DNA have increasingly become popular. Several studies revealed that the prevalence of hepatitis B viremia in HBsAg (+)/HBeAg (-) donors ranged from 2.3%-28.3%[14,15,35]. Chancharoenthana *et al*[14] reported that kidney transplants from HBsAg (+)/HBV DNA (-) (< 20 IU/mL) donors to 20 immune recipients (anti-HBs > 100 mIU/mL) was safe and was not associated with any HBV viremia, hepatitis or death despite the absence of antiviral prophylaxis. The other two studies reported excellent outcomes of transplanting kidneys from HBsAg (+)/HBV DNA (-) donors to a total of 146 recipients with anti-HBs > 10 mIU/mL. Those studies have also shown excellent outcomes with no evidence of HBV transmission[36,37]. It was interesting to note that there was one out of 58 recipients of HBsAg (+)/HBV DNA (-) donor who developed HBsAg seroconversion one month after transplantation. That patient had received HBV vaccination, but with low (non-protective) anti-HBs titer (4.6 mIU/ml). However, this patient did not develop clinical evidence of hepatitis and has acquired anti-HBs seroconversion which may be due to prophylactic therapy lamivudine and HBIG in the study protocol[15].

Recipient factors and the role of protective immunity

In principle, the recipients who received kidneys from donors with hepatitis B should have protective anti-HBs. Several guidelines and studies have suggested that an anti-HBs > 10 mIU/mL was protective[5,33,36,37]. It is important to note that HBV transmission may not necessarily lead to clinical evidence of HBV infection. This was clearly shown in one study that performed transplantation of HBsAg (+) kidney to four immunized patients with an anti-HBs ranged from 63 mIU/mL to > 1000 mIU/mL. The results showed that there was no HBsAg seroconversion, although the anti-HBc IgG was positive in all 4 cases at six months despite the presence of anti-HBs positivity. This study showed evidence of HBV transmission by the kidney grafts without any clinical manifestations of HBV infection[38].

For KT, it was unclear whether a higher level of anti-HBs concentration was associated with a higher level of protection of HBV transmission as was shown in liver transplantation. Immunity to hepatitis B was crucial to prevent donor-derived infection. However, it was suggested that an anti-HBs concentration of > 10 mIU/mL was protective[39]. It was shown in studies of transplanting kidneys from anti HBc (+) donors to 50 recipients with anti-HBs > 10 mIU/mL, that there was no anti-HBc IgM or HBsAg seroconversion[40]. Tuncer *et al*[36] and Asuman *et al*[37] reported that kidney transplants from HBsAg (+) donors to 146 recipients with anti-HBs > 10 mIU/mL were not associated with any *de novo* HBV infection or active liver diseases. A study in 43 recipients of HBsAg (+)/HBV DNA (-) donor with patients with higher

anti-HBs level (> 100 mIU/mL) found that there was neither anti-HBc nor HBsAg seroconversion and there was no evidence of HBV DNAemia[14]. However, a recent study of kidney transplants from HBsAg (+) donors to 83 HBsAg (-) recipients with varying degrees of anti-HBs did not support the importance of high anti-HBs concentration[35].

There was variation in the definitions of HBV transmission *via* transplantation of non-liver organs[5]. In the setting of kidney transplants from HBsAg (-) donors to immune protective recipients (Anti-HBs > 10 mIU/mL), definitions of HBV transmission may include anti-HBc IgM seroconversion, HBsAg seroconversion, and HBV DNAemia. *De novo* HBV infection can occur as a consequence of HBV transmission with clinical evidence of acute or chronic liver disease associated with HBV.

Differences in the reported rate of HBV transmission and/or infection after kidney transplant may be related to the different targets of protective anti-HBs concentration. Subclinical infection presenting with anti-HBc seroconversion was observed with kidney transplants from both anti-HBc (+) and HBsAg (+) donors[14,15,35,41]. In addition, the need for higher levels of immunity is related to global variation in HBV genotypes. The genotype predominance by region is A in North America, B in Europe, C in Asia and Australia, and D in the middle east and central Asia[42,43]. Most commercially available HBV vaccines were developed using genotype A2. Although cross-protection against other genotypes is observed, it has been suggested that a higher antibody concentration (> 50 mIU/mL) might be required[43]. However, the immune benefit may be lost in cases of HBV antigenic variation due to mutation in the 'a' determinant region of HBsAg[43,44]. In this case, the protective effect of HBIG is also lost. One case of fulminant hepatitis B in a kidney transplant recipient with vaccine-acquired immunity and an HBV infection of the D2 genotype with an escape mutation at G145R (glycine to arginine, G145R) was reported after the recipient had received a kidney from an HBsAg (+) donor, despite the recipient having received HBIG and NA prophylaxis[45]. Although such cases are rare, they may lead to fatal complications.

MONITORING OF HBV INFECTION AFTER TRANSPLANTATION

For kidney transplant recipients, The American Association for the Study of Liver Diseases (AASDL) suggested periodic assessment of serum ALT, HBV DNA, and HBsAg during immunosuppressive therapy. Reactivation of HBV infection was defined by detectable HBV DNAemia or positive HBsAg seroconversion. In addition, hepatitis flare was defined by rising of serum ALT more than 3 times the baseline level and > 100 U/L with evidence of hepatitis B reactivation[19].

The optimal frequency of monitoring for HBV infection in a susceptible individual is still varied. The Infectious Disease Community of Practice of the American Society of Transplantation advised monitoring liver enzymes, HBsAg, and HBV DNA every 3 mo for at least 12 mo post-transplantation. Subsequent management was based on the evolution of test results over the first year[46]. In the case of naïve recipient receiving Anti-HBc (+) kidney without antiviral prophylaxis, the European guidelines recommend monitoring for HBsAg, and HBV DNA at least during the first year. Also, most of the recipients from donors with HBV infection were suggested to receive lifelong monitoring[47].

Besides, all kidney transplant recipients who have a resolved infection of HBV (defined by positive anti-HBc serology) should be aware of a possibility of HBV reactivation during a course of intensive immunosuppression particularly rituximab [48]. Kim *et al*[49] studied HBV reactivation in a cohort of 499 kidney transplant recipients. 86.6 % of those recipients were anti-HBs (+) and 29.6% received kidneys from donors with positive anti-HBc IgG. No recipients received kidneys from donors with positive HBsAg. The authors reported that the incidence rate of hepatitis B reactivation was 2% during a follow-up period of 6.7 years. HBV reactivation was observed at the median time of 2.8 years (range 1.4-11.5). A high incidence of reactivation was observed in recipients with ABO incompatibility, who received plasmapheresis, received acute rejection therapy, and received induction therapy with rituximab[49]. These findings provided evidence that HBV reactivation can occur at any time after KT. As such, HBV reactivation may be the consequence of either donor-derived infection or the resolved recipient infection.

THE ROLE OF PROPHYLAXIS THERAPY

Vaccination and revaccination protocol

Anti-HBs play a key role to minimize the risk of HBV transmission. Hepatitis B vaccination should be given to naïve recipients or previously immune recipients who have anti-HBs concentration below 10 mIU/mL[39]. Also, the KDIGO guideline suggested a concentration of Anti-HBs below 100 mIU/mL can be rapidly lowered down to a non-protective level and may require a booster dose at this step[50]. Differences in suggestions may be due to a concern that patients with chronic kidney disease may have impaired anamnestic response to viral infection. This can lead to an insufficient immune response to HBV, and suppression of memory T and B cells that may result in a low or absence of antibody titer[44]. As an antibody concentration is likely to wane over time, monitoring of anti-HBs concentration should be done at least yearly. A further booster dose of vaccine may be required. This can be prescribed by either a single-shot high dose (40 μg) or a total complete course with a follow-up level at 4-wk after a complete course of treatment[39,51]. One study found that 95% of immune recipients with waning titer can be successfully boosted with a full course of hepatitis B. However, 10% of patients might have delay response of titer up to 6 mo after treatment completion. Higher antibody concentration was observed in patients who had a shorter duration of dialysis and positive anti-HBc status[52].

A high dose of HBV vaccine was suggested to patients with ESKD who were receiving hemodialysis therapy. A protocol of three or four high-dose (40 μg) hepatitis B vaccine series with a target level of 10 mIU/mL at 4 wk post-treatment was suggested. Also, a second three doses of vaccination were suggested if the anti-HBs could not reach the desired level[51]. Similarly, the CDC recommended Recombivax™ vaccine at 0, 1, and 6 mo or Engerix B™ at 0, 1, 2, and 6 mo[53]. Despite this approach, at least 30% of hemodialysis patients were still not successfully immunized[54].

The strategies to improve vaccine efficacy may be related to the type, dose, and route of administration. Besides the use of commercially available hepatitis B vaccine derived from genotype A2, a vaccine specifically derived from common genotype in the specific geographical area will add a layer of protection. This practice has been investigated in Korea and Japan where Type-C derived vaccine (Bimmugen™) was being given. The proof of this concept will take up to a decade[43,55]. To those who were not responding to conventional vaccine protocol, a subcutaneous injection route was reported to be associated with increased responsiveness (70 by intramuscular, 74 by subcutaneous)[54]. Also, a third-generation vaccine containing pre s/s epitope vaccine has been reported to be associated with good immunogenicity and responsiveness in a healthy individual[56]. The results of this third-generation vaccine when administered to patients with ESKD are further required to fill the practice gap.

Despite a debate, there was a suggestion to keep anti-HBs concentration more than 100 mIU/mL. Reactivation after KT has been reported in patients with antibody titer less than 100 mIU/mL[57]. In another study, no anti-HBc or HBsAg seroconversion was developed in patients who had received a booster vaccine to keep levels above 100 mIU/mL[52]. Due to the low-risk nature of the interventions, KDIGO suggested re-evaluating anti-HBs annually and administering re-vaccination if anti-HBs were found to be below 10 mIU/mL[50].

Antiviral medications (nucleos(t)ide analogues) and HBIG

Another modality to prevent HBV transmission *via* kidney transplant organs was the use of antiviral medications and HBIG. HBIG provides passive immunity for a high concentration of anti-HBs that are aimed to act as neutralizing antibodies to HBV[58]. Most prescriptions of HBIG were used in combination with antiviral nucleos(t)ide analogs (NAs) that aim to prevent recurrent infection of HBV after liver transplantation. This regimen was found superior to HBIG or NA alone[59]. However, the optimal dose of HBIG to be used for kidney transplant recipients from donors with HBV was not clearly known.

NAs are a group of antiviral medications that directly suppress HBV virus replication. Lamivudine was the most popular prophylaxis agent being used globally [5]. However, its efficacy was hampered by small number of lamivudine-resistant hepatitis B. Therefore, other drugs with a high genetic barrier such as entecavir were considered as a better alternative[19]. This was especially noteworthy in selected patients who were at risk of exposure to a lamivudine-resistant strain of HBV, including those who received kidneys from the donors previously treated by lamivudine. From a meta-analysis of 12212 chronic naïve hepatitis B patients, the prevalence of lamivudine-resistant HBV was 8% in China, 0-6.6% in other Asian

regions, 0%-4.5% in South America, 1%-3% in Europe, and 0.71% in the United State [60]. The incidence of lamivudine-resistance can be increased with longer durations of exposure (as high as a fifty percent increase after 2 years)[61]. In chronic hepatitis B liver transplant recipients, high genetic barrier nucleos(t)ide analog combined with HBIG was superior to lamivudine combined with HBIG in the prevention of recurrent HBV infection (disease recurrent rate 1.0% compare to 6.1%)[62].

Serologic markers of HBV infection may have some impact on the choice to prescribe antiviral medications (NA). Anti HBs (> 10 mIU/mL) and positive recipients can receive kidney transplants from anti-HBc (+) donors without a need for prophylaxis antiviral medications due to the negligible risk of HBV transmission. In contrast, naïve recipients who received kidneys from anti-HBc (+) donors should receive lamivudine prophylaxis without HBIG for at least 1 year[5]. In the setting of HBs Ag (+) donors, recipients with protective anti-HBs (> 10 mIU/mL) were considered suitable to receive the allocation of kidney grafts. Further risk should be assessed by the result of the NAT test and HBV DNA measurement. If the result of nucleic acid for HBV was negative and HBV DNA was undetectable (by a method with a detection limit as low as 20 copies per mL), preventive strategies varied from no NA prophylaxis (in the setting of no potent induction therapy), or prescription of NA alone without HBIG. If the anti-HBs is > 100 mIU/mL, one can proceed to KT without NA prophylaxis[14]. However, if HBV DNA was not measured by a method of optimum low detection limit or the result of HBV DNA cannot be obtained due to any reason, NA may be prescribed to make the risk of HBV transmission as low as possible.

In the setting of HBsAg (+)/HBV DNA (+) donor, most authors prescribed universal NA prophylaxis with or without HBIG as a prophylaxis regimen among patients with different levels of anti-HBs concentration[14,15,35]. However, the optimal dose of HBIG in this setting was not clearly known. One important issue in this setting was the use of potent induction therapy. A study in 24 immunized recipients (mean anti-HBS 452 ± 384 mIU/mL), 89% who received induction therapy including anti-thymocyte globulin, found that three of them had detectable HBV DNAemia. This HBV DNAemia occurred although all patients received six months of lamivudine therapy. Fortunately, none of those patients developed liver failure[13]. Thus we have suggested that the use of HBsAg (+)/HBV DNA (+) donors to patients with immunized anti-HBs should be exercised with due caution as this group still carries a significant risk of de novo HBV infection particularly in the recipients who receive potent induction therapy[13].

Use of HBsAg (+)/DNA (+) donors to recipients with naïve or anti-HBs < 10 mIU/mL was the group with the highest risk being reported. A study in 20 naïve recipients who received prophylactic NA or HBIG or combination showed that the incidence of acute liver injury, anti-HBc seroconversion, and HBV DNAemia was 20 %, 10%, and 10% respectively[35]. Thus the use of this treatment option should be restricted to patients with an urgent need for KT (exhausted multiple vascular access, with ongoing uremia despite adequate hemodialysis prescription).

Another interesting issue is the use of HBsAg positive donors to recipients with HBsAg positive serology. A few studies[63-66] have reported favorable outcomes of this treatment option provided that the recipients received antiviral treatment before transplantation. Also, there is a suggestion that the recipients with positive HBsAg should have the result of liver biopsy that did not show evidence of cirrhosis. However, it should be noted that the number of patients being reported with this option was small. Additional information for this setting may be required.

Figure 1 showed the important factors associated with the risk of HBV transmission in the setting of KT from donors with HBV. Figure 2 showed a practical approach to the use of kidneys from donors with positive HBsAg.

One important use of NAs was in the setting of treatment with rituximab. This monoclonal antibody acted directly against CD 20 which can lead to impaired immunoglobulin production[67]. There was a study that showed HBV reactivation in kidney transplant recipients with resolving hepatitis B infection[48]. We believe that NA should be prescribed to kidney transplant recipients, who receive kidney allograft from donors with HBV, who have been treated with rituximab either as anti-rejection therapy or induction therapy in ABO-incompatible recipients.

LONG TERM OUTCOMES AND SURVIVAL

Regarding HBsAg (-) anti-HBc (+) donors, historic studies found that there were no

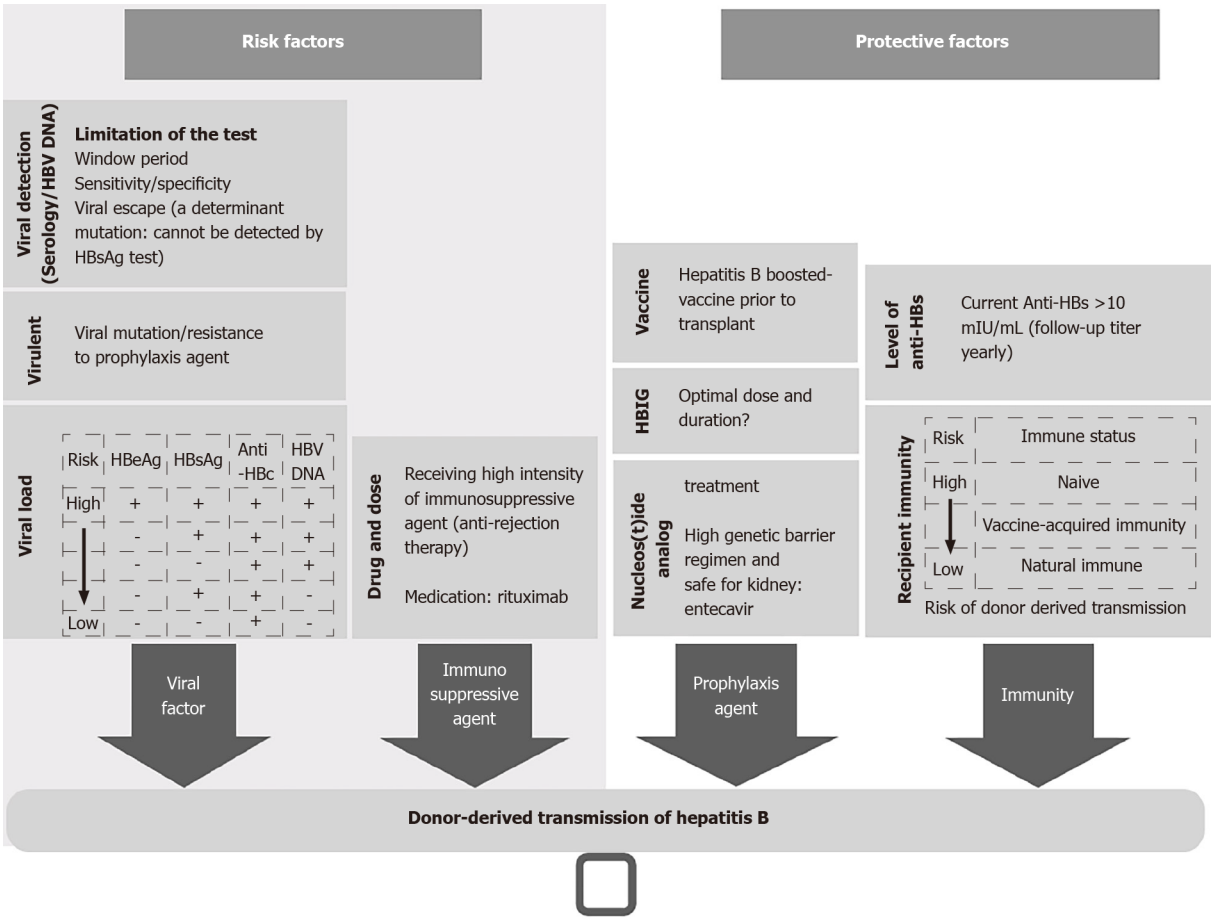

Figure 1 Risk factors of donor derived transmission of hepatitis B virus and proposed protective factors. HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; Anti-HBc: Hepatitis B core antibody; Anti-HBs: Hepatitis B surface antibody.

HBsAg seroconversion and no excess risk of morbidity and graft failure[68]. Subsequent studies that examined the outcomes in children have shown a similar result in terms of patient survival and graft survival[69]. A quantitative review of nine studies found the seroconversion rates of HBsAg, anti-HBc, anti-HBs were 4/1385, 32/1385, and 5/1385 recipients. Those numbers were considered to be very low and the authors conclude that HBsAg (-) anti-HBc (+) kidneys can be transplanted safely to patients with ESKD[28].

The amount of information on KT from HBsAg (+) donors is much less than anti-HBc (+) donors. However, the results of long-term outcomes being reported showed favorable outcomes when compared with donors with no markers of HBV with proper prophylaxis regimen[13-15,37]. Our result of HBsAg (+) donor to anti-HBs (> 10 mIU/mL) recipient reported a ten-year actuarial graft survival rate of 84.6% and patient survival rate of 92.8% (with no hepatitis and hepatoma) provided that the recipients received no induction therapy[33].

The previous report of fulminant hepatitis B infection in the setting of HBsAg (+) /HBeAg (+) donor to anti-HBs (-) recipients has been a major concern. However, our review of published articles from 2005 onwards (Supplementary Table 1) has shown there were a total of at least 412 KTs from HBsAg (+) donors to HBsAg (-) recipients. This treatment option was associated with good outcomes. First, in 20 HBsAg (+) donors to anti-HBs (-) recipients, there was 1 death from liver disease, and there were 2 HBV transmissions (2 HBsAg seroconversion). Next, in 392 HBsAg (+) donors to anti-HBs (+) recipients, there were two deaths and four HBV DNAemias. One death occurred in a patient with HBV mutation that escaped from the protective effect of anti-HBs. Another death was associated with liver failure which was reported to be due to nonadherence to lamivudine. There was one HBsAg seroconversion (with HBV DNAemia) associated with lamivudine resistance. The final three HBV DNAemias were reported from a single study. This study reported that the mean anti-HBs of the recipients was 452 ± 384 mIU/ml. However, all of the latter three patients could be successfully treated with lamivudine therapy. No excess risk of liver failure was reported[13,15,70]. It was important to note that most HBV DNAemias being observed

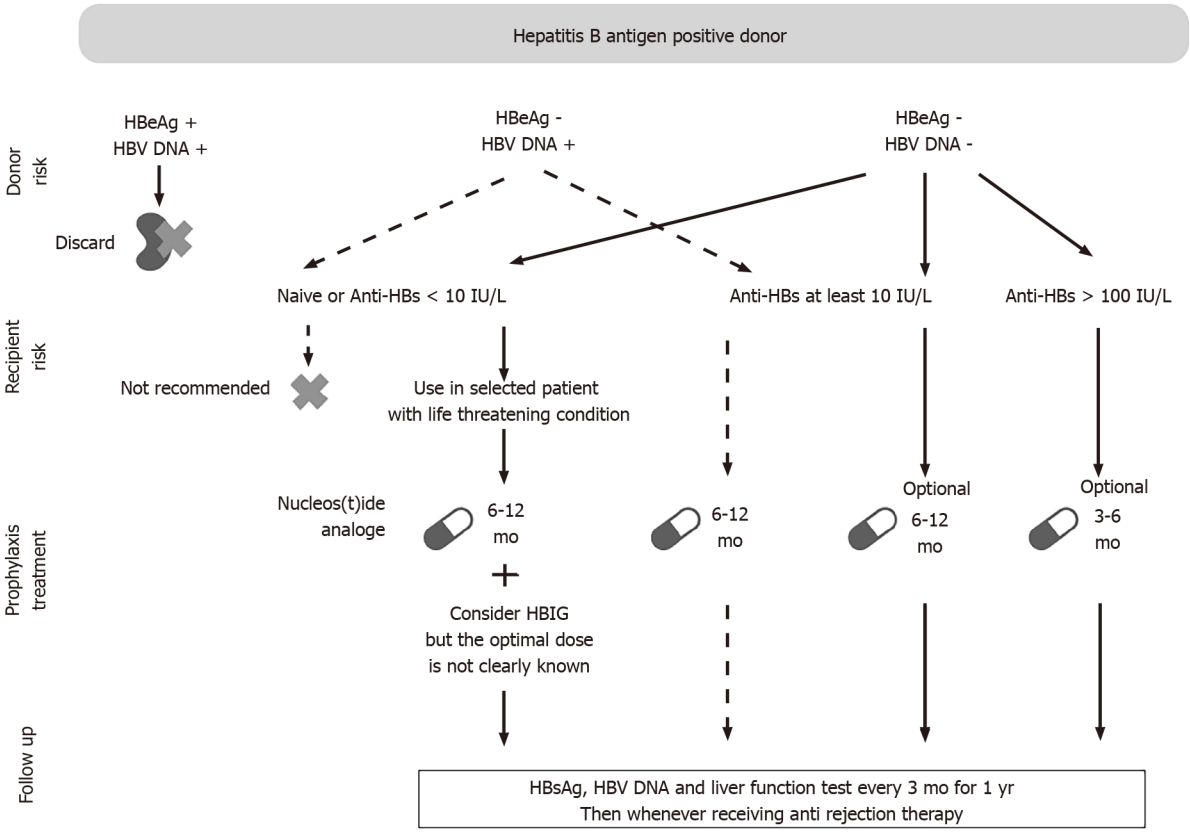

Figure 2 Proposed management for several types of donor and recipient pairs according to the results of hepatitis B virus serology test and DNA markers. HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; Anti-HBs: Hepatitis B surface antibody; HBIG: Hepatitis B immunoglobulin; HBsAg: Hepatitis B surface antigen.

were usually observed with lamivudine resistance or non-adherence. These HBV DNAemias occurred despite the presence of anti-HBs > 100 mIU/ml. These results suggested that kidney transplants from HBsAg positive donors to appropriate recipients was a cost-effective option when compared with keeping the potential recipient in the waiting list pool[71].

RISK BENEFIT OF TRANSPLANTATION AND PROPOSED CRITERIA FOR HBsAg (+) DONOR UTILIZATION

As has been mentioned earlier, organs from HBsAg (+) donors are generally suggested to be discarded[72]. However, with careful individual risk and benefit assessment, these organs may be utilized safely and serve as an alternative treatment to shorten waiting time rather than stay on a usual transplant waiting list. Shortened waiting time was also beneficial in improving 10-year graft survival in both living and deceased donor KTs[73]. Moreover, recipients can benefit from excellent graft survival without excess risk of liver disease as aforementioned[33,35].

It has long been shown and recently confirmed that kidney transplants promoted both longer life expectancy and better quality of life at a lower cost relative to staying on dialysis treatment[74,75]. In order to gain comparable survival benefit to kidney transplant, an intensive home hemodialysis has to be attained which would be a much higher effort than an in-center standard hemodialysis and this option is not feasible in some countries[76]. A recent economic study using data from USRDS showed that kidney transplants using standard donors were a cost saving procedure compared to remaining on dialysis. The same study also showed that kidney transplant using high risk donors were cost-effective[77]. All of the above studies have highlighted the benefit of expanding the donor pool by using kidneys from donors with HBsAg positivity.

Utilized kidneys from HBsAg (+) donors not only direct benefits to the potential recipients, but also the national society. However, the criteria for utilization of kidneys from donors with HBsAg positivity has not been well described. We would like to describe our proposed criteria to define three groups of potential recipients. The first group is patients with urgent need to receive KT. Urgent condition included patients with exhausted vascular access for hemodialysis, patients with ongoing uremia despite adequate dialysis prescription, and patients who cannot remain in the dialysis treatment (hemodialysis or CAPD) due to any reason. The second group is the recipients with positive HBsAg[6,30,46]. The third group is patients being registered as active waiting list who have waiting time longer than the median time to receive a kidney in each national society. The potential recipients should be discussed about the willingness to receive a kidney from donors with HBsAg positivity. They may choose not to take this opportunity and continue to wait for HBsAg negative donors. Examples of the use of kidneys with increased risk of blood borne viral infection has been previously described[78]. A short summary of prophylaxis regimen and special requirements for recipients of kidneys from HBsAg (+) donors is discussed below.

Our rationale for proposal of the third criteria is related to the following information. Data from OPTN (organ procurement and transplantation network) showed that the median time to receive a kidney for a new transplant candidate in waiting list is 4.5 years[77,79]. In US, waiting-listed patients were associated with 5%-7% increase in mortality which continues to increase in older waiting-listed patients. As reported in Matas *et al*[80], there was 2% mortality rate in those aged between 18-34 years which increased to 8% for patients over 65. Utilizing kidneys from HBV infection donors can be one strategy to shorten the recipients' waiting time. This can help to decrease the mortality rate of waiting list candidates and downsize the waiting list pool.

Due to the risk of infection transmission before undergoing KT, recipients should be fully informed and consent must be obtained from each individual. In addition, all potential recipients should be vaccinated that aim to achieve anti-HBs at least > 10 mIU/mL. The potential recipients should not have HCV coinfection nor other cause of chronic liver disease which may worsen after KT. All recipients of HBsAg (+) donors should receive anti-viral medication, especially in the situation when the result of HBV DNA cannot be obtained before actual transplantation. HBIG may be considered for recipients with non-protective anti HBsAb level and/or in the situation of unknown HBV DNAemia of the donor. A protocol for close surveillance of viral reactivation and liver disease must be implemented. For HBsAg (+) recipient candidates, they must be treated with NA and evaluated by a specialist in liver disease. Untreated patients result in a higher mortality rate, with liver-related complications[19]. The AASDL recommends further evaluation of HBV DNA, ALT and to undergo staging with biopsy or elastography to determine whether advanced fibrosis or cirrhosis is present in order to assess the need for simultaneous liver KT[22,72].

It is an ethical challenge to allocate kidneys from donors with positive HBsAg to potential recipients with anti-HBs < 10 IU/ml. In our opinion, this treatment option should be limited to recipients with urgent criteria under a careful management that includes HBIG, antiviral medication and a careful protocol. Wang *et al*[35], demonstrated the possibility of this option (see section: Antiviral medications). However, these transplants should be performed by experienced teams.

CHALLENGING PERSPECTIVE

KT from donors with HBsAg (+) donors is not a risk-free procedure. A careful allocation to appropriate recipients can be successfully performed. NAT for HBV is now accepted to be a useful screening test. The result of a sensitive HBV DNA test is of prime importance in the organ allocation and the design of the prophylactic protocol. The rate of HBV transmission from this treatment option was reported to be low and manageable. HBV reactivation can occur in resolved HBV infection. Thus, a regular monitoring schedule for HBV is an essential part of post-transplant care. Differentiation between donor-derived HBV infection and reactivation of recipient strain HBV infection may be difficult. We believe that the use of kidney organs from donors with HBV infection in the area where the national organ donation rate is less than the rate of endemic HBV infection is a better alternative than discarding the organs.

CONCLUSION

Within this era of several newer antiviral medications, the presence of positive HBsAg in potential organ donors should not preclude the use of kidney organs. Several additional steps and experienced transplant teams are specifically required to prepare waiting list candidates who are willing to receive a kidney from such donors. These steps should be regularly assessed for each individual during his or her registration as active waiting list to receive KT from deceased donors. However, the criteria that we have described in this review, can also be applied to patients who are planning to receive living (related) KT as well.

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MINIREVIEWS

Unpacking the challenge of gastric varices: A review on indication, timing and modality of therapy

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Abstract

Upper gastrointestinal bleeding from oesophageal or gastric varices is an important medical condition in patients with portal hypertension. Despite the emergence of a number of novel endoscopic and radiologic therapies for oesophagogastric varices, controversy exists regarding the indication, timing and modality of therapy. The aim of this review is to provide a concise and practical evidence-based overview of these issues.

Key Words: Upper gastrointestinal bleeding; Portal hypertension; Gastric varices; Variceal band ligation; Variceal obliteration; Sclerotherapy; Transjugular intrahepatic porto-systemic shunt; Balloon-occlusion retrograde transvenous obliteration

Core Tip: Gastric varices are an uncommon source of bleeding in patients with portal hypertension. Although evidence supports acute bleeding treatment and secondary prophylaxis using interventional endoscopy or radiology, there is still lack of data to support primary prophylaxis for all patients. If treatment is required, both interventional endoscopy and radiological approaches should be considered. Interventional endoscopy using endoscopic ultrasound-guided combination coil and cyanoacrylate obliteration appears to be the optimal approach based on the current literature.

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INTRODUCTION

Incidence

The incidence of gastric varices (GV) is 15%-20% from endoscopic epidemiological studies of portal hypertension[1,2]. Unlike oesophageal varices that tend to be present in the lamina propria mucosae and superficial submucosa, GV lie deep in the submucosa and as such can be difficult to differentiate from prominent gastric rugae with standard endoscopy. Endoscopic ultrasonography studies have demonstrated that a proportion of GV are undiagnosed on standard diagnostic endoscopy[3,4]. However, this may not be clinically significant, as the size of the varix is one of the characteristics that predict risk of haemorrhage, and larger GV are less likely to remain undetected by standard endoscopy.

Both GV and oesophageal varices develop as a consequence of portal hypertension. Portal hypertension may lead to reversal of flow through the portal circulation, with two common outlets - *via* the coronary (gastric) vein to the right and left gastric veins, and *via* the splenic vein to the short and posterior gastric veins[5]. The former supply the distal oesophagus and cardia of the stomach where transmitted pressures and increased flow lead to formation of oesophageal and cardio-oesophageal varices. The latter supply the fundus whereby increased pressures and flow through this system leads to the formation of fundal varices. In a haemodynamic study of oesophageal and and GV by Watanabe *et al*[5], 78% of patients with portal hypertension had the majority of collateral flow through the left and right gastric veins, likely accounting for the difference in incidence between oesophageal and GV.

In the same study, GV were demonstrated to bleed at lower portal pressures than oesophageal varices, largely due to the higher prevalence of gastro-renal shunts in those with GV. These shunts decompress the portal system. This finding has since been confirmed in further studies[6,7].

GV CLASSIFICATION

Sarin and Kumar[8] seminal paper on the anatomical classification of GV from 1989 remains the most widely accepted method for describing GV. They are divided into two groups, with further sub-classification (Figure 1): (1) Gastroesophageal varices (GOV) – are continuation of oesophageal varices that extend beyond the gastroesophageal junction. These are divided into: (a) Type 1 (GOV1) – those that extend along the lesser curve of the stomach. These account for 75% of all GV[2]; (b) Type 2 (GOV2) – those that extend along the greater curve of the stomach into the fundus; (2) Isolated GV (IGV) – occur in the absence of oesophageal varices and are sub-classified into: (a) Type 1 (IGV1) – located in the fundus and do not extend to the cardia. They are also called fundal varices; (b) Type 2 (IGV2) – can occur anywhere in the stomach (*i.e.*, body, antrum, pylorus). These are rare, occurring in < 5% of those with GV.

The use of this classification system has been shown to predict risk of bleeding and guides management. GOV1 varices behave similarly to oesophageal varices, and so the treatment paradigm for prophylaxis and acute variceal haemorrhage is the same for oesophageal varices. IGV1 and GOV2 varices are more difficult to control when they bleed compared with GOV1 varices and portend a poorer prognosis[2].

An alternate classification, published by Hashizume *et al*[9], is a more detailed examination of GV describing the form (tortuous, nodular or tumorous), location (anterior, posterior, lesser curve or greater curve of cardia, or fundic), and colour (red or white) of the varix (Figure 2). Similar to classification systems for oesophageal varices, this classification is aimed at stratifying patients at highest risk of bleeding. In a stepwise logistic regression analysis, those with varices in the anterior or greater curve of the cardia, nodular appearance (*i.e.*, larger size), or red colour spot had the highest predicted risk for bleeding[9]. In another study, which focused on patients with fundic varices, increased size and presence of a red spot increased risk of

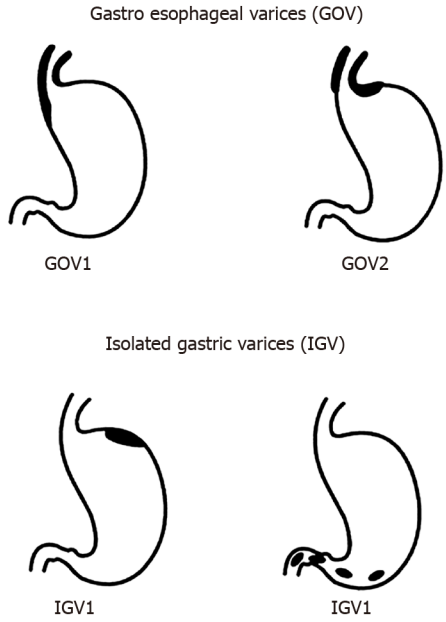

Figure 1 Classification of gastric varices according to Sarin *et al*[2]. Citation: Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: A long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992; 16: 1343-1349. Copyright © The Authors 1992. Published by John Wiley and Sons.

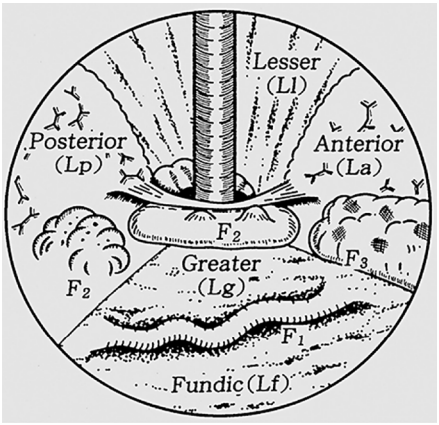

Figure 2 Classification of gastric varices according to Hashizume *et al*[9]. Citation: Hashizume M, Kitano S, Yamaga H, Koyanagi N, Sugimachi K. Endoscopic classification of gastric varices. *Gastrointestinal Endoscopy* 1990; 36: 276-280. Copyright © The Authors 1990. Published by Elsevier.

haemorrhage[10]. Advanced liver disease, as determined by the Child-Turcotte-Pugh classification, was an additional risk factor for bleeding[10]. Other classification systems exist[11], however are used less frequently than those described by Sarin and Kumar[8], and Hashizume *et al*[9].

ACUTE GASTRIC VARICEAL HAEMORRHAGE

Bleeding from GV is considered definite if there is active spurting or oozing from the varix or an adherent clot or fibrin plug on the varix. GV bleeding should be considered the cause of upper gastrointestinal bleeding when a GV without high-risk stigmata is present in the absence of oesophageal varices or an alternate source of bleeding[12].

Pre-endoscopic management

Pre-endoscopic management follows that for oesophageal variceal bleeding, namely use of splanchnic vasoconstrictors (*i.e.*, terlipressin or octreotide) to reduce portal pressures, prophylactic antibiotics (*e.g.*, ceftriaxone), and a restrictive transfusion protocol[13,14]. The same medical treatment is instituted in patients with a presumed

diagnosis of variceal haemorrhage with known portal hypertension who present with symptoms of upper gastrointestinal bleeding.

Endoscopic management

As outlined above, GOV1 varices are considered an extension of oesophageal varices and so at the time of haemorrhage should be treated in the same manner as bleeding oesophageal varices [*i.e.*, endoscopic variceal band ligation (EVBL), Figure 3][2,12-14]. One small prospective randomized controlled trial (RCT) reported numerically higher haemostasis and lower re-bleeding rates in the subset of patients with GOV1 haemorrhage treated with endoscopic variceal obturation (EVO) rather than EVBL [15], although this did not reach statistical significance. Both treatments may be considered equally efficacious for GOV1 varices.

Current guidelines support the use of cyanoacrylate injection – either as *N*-butyl-2-cyanoacrylate (*e.g.*, Histoacryl®) or 2-octyl-cyanoacrylate (*e.g.*, Dermabond) – for acutely bleeding fundic varices (GOV2 and IGV1), in a procedure termed EVO[13,14]. Cyanoacrylate is a tissue adhesive that rapidly polymerizes upon contact with water/blood, leading to a change in the liquid composition to one of a hard brittle acrylic plastic. Majority evidence for its use stems from uncontrolled retrospective and prospective studies[16], with one RCT demonstrating a statistically non-significant increased haemostasis rate when compared to alcohol-based sclerotherapy (89% *vs* 62%)[17]. Haemostasis rates for cyanoacrylate glue injection are 80%-100%, with re-bleeding rates of 10%-60%[16]. Complications are rare, with fever and pain being the most common, while the most feared is embolization of the glue into systemic beds that can lead to ischaemia in those tissues (*e.g.*, stroke, myocardial infarction, splenic infarction, pulmonary embolus).

Thrombin injection has been utilized as an alternative to cyanoacrylate for EVO for almost three decades; however, like cyanoacrylate, evidence for its use is taken from small, uncontrolled studies[16]. It appears safe, with few adverse procedure-related outcomes, and haemostasis and re-bleeding rates similar to cyanoacrylate.

Sclerotherapy, the injection of a sclerosant agent into the varix, has gone out of favour for the treatment of gastric variceal haemorrhage due to unacceptably high re-bleeding rates of up to 90%-100%[16]. This is often due to ulceration at the point of injection resulting from the high volume of sclerosant required to obliterate GV, with a large amount of sclerosant flowing away from the variceal bed *via* co-existent gastro-renal shunts that occur with high prevalence in patients with GV[16]. Adverse events include fever, and retrosternal and abdominal pain.

IGV-2 varices are rare; hence little evidence exists as to the optimal endoscopic management. In general, it is accepted that they should be treated according to GOV2/IGV1 varices with EVO.

Salvage therapy

Balloon tamponade with Sengstaken-Blakemore, Minnesota or Linton-Nachlas tubes can be utilized in patients with bleeding from GOV1, GOV2 and IGV1 varices. They will not be effective for IGV2 varices, given the ectopic location of the culprit lesion. The Linton-Nachlas tube may be preferred in gastric variceal haemorrhage if available, as the gastric balloon has greater volume capacity[12].

Transjugular intrahepatic portosystemic shunt (TIPS) (Figure 4) is an effective salvage therapy for patients with endoscopically-uncontrollable bleeding oesophageal varices, however its utility in refractory gastric variceal haemorrhage is less clear[12]. Although haemostasis rates exceed 90%, re-bleeding is reported to occur in 15%-30% [18-20] and concerns remain over post-TIPS encephalopathy, which can be recalcitrant to standard medical therapy and necessitate revision of the TIPS. Several hypotheses have been proposed to explain the risk of re-bleeding[21,22]; 'Proximity' theory – feeding vessels to GV lie further away from a TIPS shunt than feeding vessels to oesophageal varices, hence the shunt is less effective in decompressing GV; 'Throughput' theory – gastro-renal shunts that occur in high frequency in association with bleeding GV compete with the TIPS for portal flow and can continue to feed the gastric variceal bed; 'Recruitment' theory – development of new feeder vessels after proximal embolization of a GV.

In retrospective comparison studies, Mahadeva *et al*[23] found TIPS to be more effective in preventing re-bleeding when compared with EVO in acute gastric variceal haemorrhage, whilst Procaccini *et al*[24] found no difference between the two modalities.

Balloon-occlusion retrograde transvenous obliteration (BRTO) and its modifications (coil-assisted or plug-assisted retrograde transvenous obliteration) aim to sclerose a varix without treating portal hypertension. BRTO is often reserved for use in patients

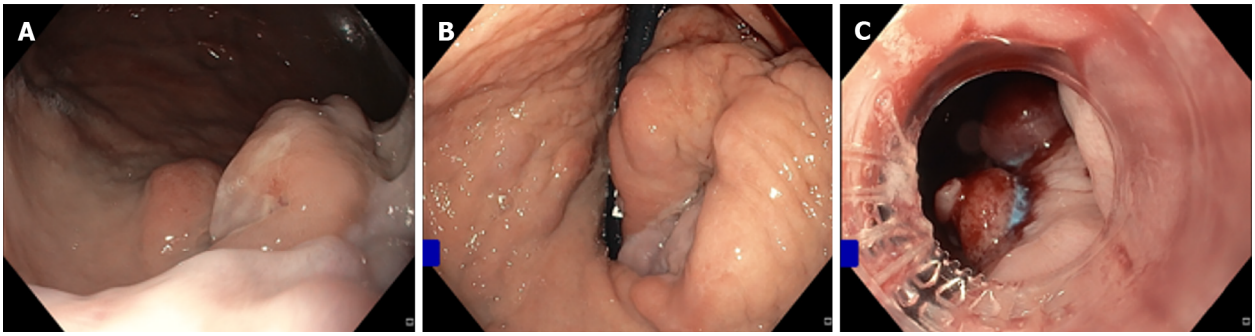

Figure 3 Endoscopic variceal banding of gastroesophageal varices 1. A: Pre-banding forward view of varix; B: Pre-banding retroflexed view of varix; C: Immediately post-banding of varix.

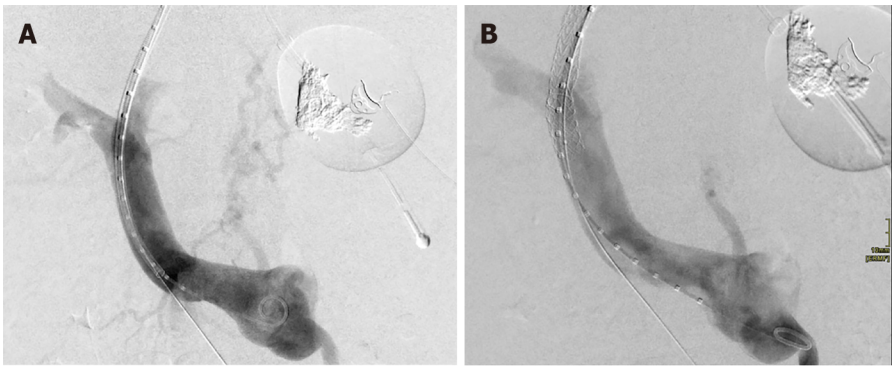

Figure 4 Transjugular intrahepatic portosystemic shunt decompressing gastric varix. A: Pre-transjugular intrahepatic portosystemic shunt (TIPS) with contrast toward gastric variceal bed; B: Post-TIPS with no contrast flow toward gastric variceal bed.

with anatomy not amenable for TIPS or where TIPS is contraindicated (*i.e.*, past history of hepatic encephalopathy or advanced synthetic liver dysfunction), and is reliant on the presence of a gastro-renal shunt for technical feasibility. Similar to TIPS, it is highly effective in achieving haemostasis with success rates > 90%[21,25]. A meta-analysis of uncontrolled studies reported a clinical success rate of 97%, defined as no GV recurrence or re-bleed of acutely bleeding GV or no bleed in the case of at-risk GV that have never-bled[26]. The main sclerosant used for BRTO in reported studies was ethalonamine oleate, in 94% of cases, and the most common side effect was haematuria, occurring in 70%[26]. Given ethalonamine oleate is a known cause of haemolysis, the common occurrence of haematuria is somewhat expected from consequent haemoglobinuria. The antidote for this is parenteral administration of haptoglobin. Although this review by Park *et al*[26] included patients who underwent BRTO for acute treatment of variceal haemorrhage, primary prophylaxis and secondary prophylaxis, a breakdown of indication was not provided and subgroup analysis for this purpose not available. Another, more recently published meta-analysis[27] found that there was no significant difference in immediate haemostasis rates between the two procedures, but a higher re-bleeding rate post-TIPS [relative risk (RR) 2.61, 95% confidence interval (CI) 1.75–3.90, $P < 0.01$], higher post-procedural hepatic encephalopathy rate post-TIPS (RR 16.11, 95%CI: 7.13–36.37, $P < 0.01$), statistically non-significant higher rate of ascites in the BRTO group and statistically non-significant worsening in Child-Pugh status in those who received TIPS. Apart from a small pilot study out of Seoul, Korea[28] that randomly assigned 14 patients with acutely bleeding GV to up-front TIPS or BRTO, there have not been any head-to-head RCTs to ascertain the difference in safety and efficacy between these procedures in patients with acutely bleeding GV. A disadvantage of BRTO is that it can lead to the development or worsening of non-GV (oesophageal or ectopic) as portal blood flow is diverted through alternate pathways, or exacerbation or new development of ascites due to raised portal pressures. This is not an issue post-TIPS, which effectively decompresses the portal system.

SECONDARY PROPHYLAXIS

Non-selective beta-blockers

No controlled study has demonstrated efficacy of non-selective beta-blockers (NSBB) for secondary prophylaxis following gastric variceal bleeding. In a RCT by Mishra *et al* [29], EVO was far more effective in preventing re-bleeding than propranolol, with a relative risk reduction of 80% and absolute risk reduction of 35%. Hung *et al*[30] and Chen *et al*[31] explored the adjunct use of propranolol or carvedilol, respectively, to 3-4 weekly EVO alone following gastric variceal haemorrhage in an RCT setting, albeit with no placebo arm. Neither found a difference in gastric variceal re-bleeding rates between the two groups. Of note is that both studies were conducted in the same institution with similar inclusion and exclusion criteria, except the more recent study by Chen *et al*[31] included all patients with any form of gastric variceal bleeding, whilst Hung *et al*[30] only included patients with fundic variceal haemorrhage (GOV2 or IGV1). The study by Chen *et al*[31] did demonstrate a significant reduction in all-cause upper gastrointestinal re-bleeding in the group assigned to carvedilol (28% *vs* 48%, $P = 0.03$), driven by a reduction in bleeding from portal hypertensive gastropathy, and oesophageal and gastric ulcers. However, the authors also reported on a higher incidence of adverse events in the carvedilol group (53% *vs* 15%, $P < 0.001$), due to more frequent dizziness and exertional dyspnoea. Despite this, no patient in the carvedilol group discontinued therapy. The lack of efficacy with NSBB following gastric variceal haemorrhage is postulated to be due to the fact that GVs bleed at lower portal pressures, with NSBB having little effect on preventing flow of blood to the culprit variceal bed *via* co-existent gastro-renal shunt[30,31].

Endoscopic therapy

Although endoscopic ultrasound (EUS) guided injection of cyanoacrylate reduces embolic complication rates, as a result of reduced volume of cyanoacrylate injected, its use during acute gastric variceal haemorrhage is limited in most centres due to access to endoscopists with expertise in EUS. However, it is an emerging therapy for secondary prophylaxis. A two-part observational comparative study by Lee *et al*[32] compared fortnightly EUS-guided injection of cyanoacrylate in patients presenting with acute bleeding from any type of GV with "on demand" therapy, whereby standard endoscopy and injection of cyanoacrylate was only undertaken at the time of re-bleeding. A significant reduction in re-bleeding was demonstrated in the active endoscopic treatment group (35% *vs* 70%, $P = 0.0006$). There was no impact on mortality, likely due to the small number of patients in the study. In a similar cohort trial design, Bick *et al*[33] found that there was a lower gastric variceal and all-cause upper gastrointestinal re-bleeding rate (9% *vs* 24%, $P = 0.045$ and 19% *vs* 50%, $P < 0.001$, respectively) in those managed with EUS-guided cyanoacrylate injection compared with standard endoscopy guided injection. It is important to note that the standard endoscopy cohort had a higher mean MELD (17 *vs* 13, $P = 0.004$) and lower incidence of IGV1 varices (8% *vs* 47%), with the latter likely accounted for by the greater sensitive of EUS for the detection of GV.

A novel endoscopic method that is gaining popularity globally is EUS-guided coiling of GV, which involves injection of metal embolization micro-coils coated with synthetic stainless steel-fibres, leading to turbulent blood flow and intravariceal clot formation to obliterate the varix[34]. This can be combined with injection of cyanoacrylate glue (Figure 5), in a procedure that aims to prevent systemic embolization of the cyanoacrylate, as the coils may provide a scaffold for polymerization, as well as requiring less volume of glue injection as a result of precise delivery into the target tributary[35]. The additional benefit of EUS over standard endoscopy is the ability for immediate post-treatment Doppler evaluation of the variceal bed and its afferent tributaries, to ensure complete obliteration[34,35]. In a retrospective, multicentre study by Romero-Castro *et al*[36] comparing outcomes of 30 patients who underwent EUS-guided coil ($n = 11$) with those who underwent EUS-guided cyanoacrylate injection ($n = 19$) into GVs that had previously bled ($n = 23$) or never bled ($n = 7$), both methods were highly effective in obliterating the varices (96.7% cumulatively) without a difference in re-bleeding rate. The cyanoacrylate group required more sessions to achieve obliteration (29 sessions *vs* 14 sessions, $P = 0.29$) and had lesser proportion of patients achieving variceal obliteration after a single endoscopic session (18% *vs* 82%), whilst also having a higher reported adverse event rate (58% *vs* 9%, $P < 0.01$). However, the majority of adverse events were asymptomatic pulmonary emboli detected on routine computed tomography (CT) of the chest of patients post-procedure, with no difference noted in the symptomatic adverse event rate between

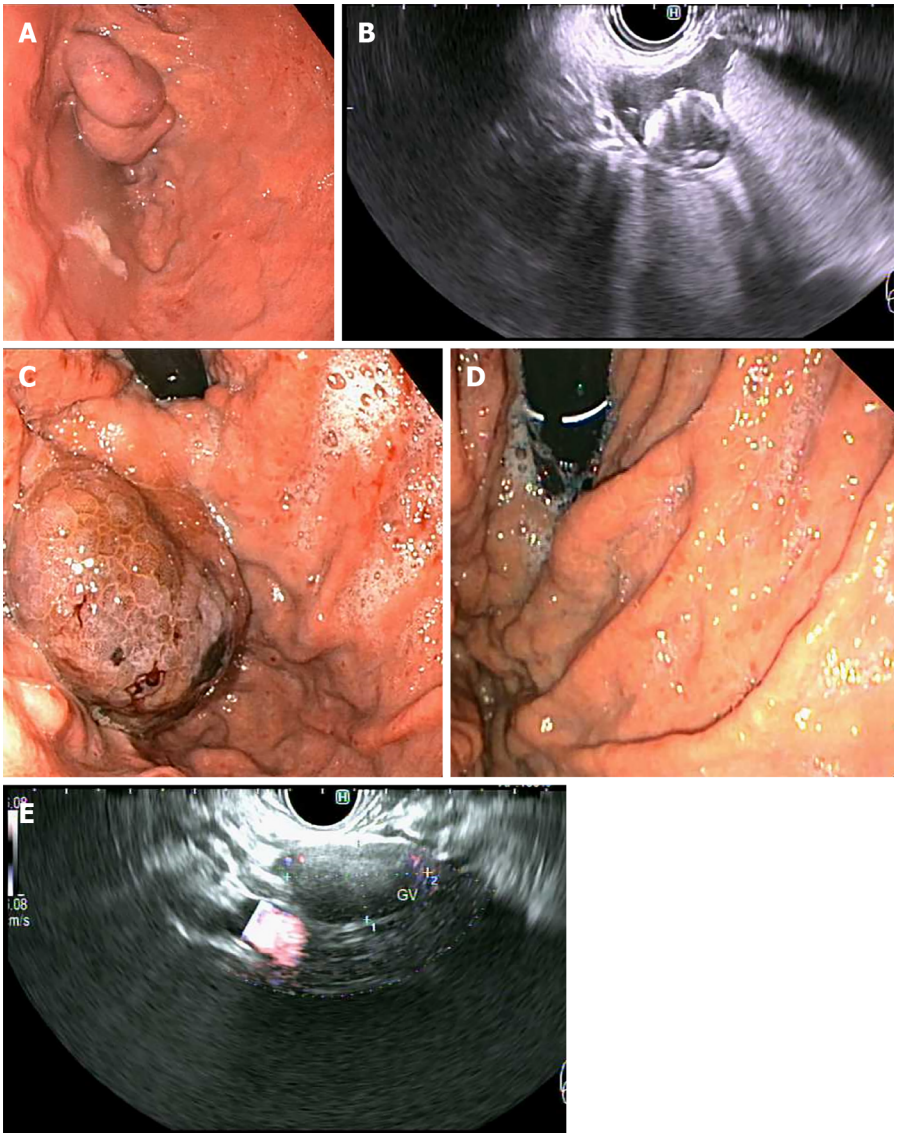

Figure 5 Primary prophylaxis of isolated gastric varices 1 with five 0.18 10 mm micronester coils in combination 1 mL cyanoacrylate glue. A: Pre-treatment endoscopic appearance; B: Endoscopic ultrasound (EUS) appearance immediately post-deployment of coils; C: Endoscopic appearance 1-mo post-treatment; D: Complete obliteration 4-mo post-treatment; E: EUS appearance of varix with no Doppler flow 4-mo post-treatment.

groups. It is also noteworthy that a statistically significant higher proportion of patients with bleeding varices and Child-Pugh C status cirrhosis were represented within the cyanoacrylate group in this study.

Binmoeller *et al*[37] were the first to publish on the efficacy and safety of combined EUS-guided coil and cyanoacrylate injection for GV, predominantly in patients who had recovered from an acute gastric variceal haemorrhage (n = 28/30). The same group reported on a more extensive patient cohort (n = 152) some years later, with high obliteration rate (93%) at follow-up endoscopy, low re-bleeding rate (16%, with 50% re-bleeding events non-variceal in origin), and few procedure-related adverse events (7%; 4/9 patients with abdominal pain, 1/9 patients with pulmonary embolus) [38]. Of note, 26% of patients in this study underwent treatment as primary prophylaxis, somewhat unique in the GV treatment evidence base. A single randomized trial has been performed evaluating combination coiling and cyanoacrylate injection with coiling alone, reporting a higher variceal disappearance rate on immediate post-procedure endoscopy (87% *vs* 13%, P < 0.001), and lower re-bleeding rate (3.3% *vs* 20%, P = 0.04), variceal reappearance rate on follow-up endoscopy at 3-mo (13% *vs* 47%, P < 0.001), and re-intervention rate (17% *vs* 40%, P = 0.045) in the arm allocated to combination therapy[39]. The cumulative mortality rate of 28% from this study despite relatively preserved liver function in participants (90% Child Pugh A, median MELD 9.5 at enrolment) is of concern and somewhat unexplained, particularly given 10/17 patients died from uncontrolled haemorrhage and 9/10 of these were variceal in

nature.

Interventional radiology

Only a single RCT has evaluated EVO with up-front TIPS for secondary prophylaxis of gastric variceal haemorrhage[40], and revealed a 71% relative risk reduction over 3 years in gastric variceal re-bleeding rate in the TIPS arm, albeit with 26% of TIPS patients suffering from hepatic encephalopathy. This study pre-dates the era of EUS-guided coils and very few patients in this study had IGV1 varices. TIPS may be an attractive option in patients with concurrent ascites and/or presence of other non-GV, but less so in those with a history of prior encephalopathy or advanced synthetic liver dysfunction.

A single prospective, non-randomized study[41] and two retrospective, observational studies[42,43] have demonstrated a lower re-bleeding rate in patients treated with BRTO rather than EVO for secondary prophylaxis of variceal haemorrhage (3%-15% *vs* 22%-71%). They each had differing inclusion criteria, with the prospective study including patients with GOV1, GOV2 and IGV1 varices, whilst the two retrospective studies both excluded patients with GOV1 varices, and one only included patients with IGV1 varices[42].

Contemporary case series have begun exploring the feasibility and safety of combined interventional radiological procedures, namely TIPS with balloon-occluded transvenous obliteration (whether in an antegrade or retrograde fashion)[44-46]. Purported benefits from retrospective audits of combined procedures are reduced re-bleeding and post-procedure encephalopathy rates, stable or improved liver function, and prevention or improvement of ascites. Finally, percutaneous transhepatic obliteration is an alternate route to obliteration of a gastric varix in those without a gastro-renal shunt and who may have contraindication to TIPS[47].

Given the wide array of therapeutic options available are reliant on specific anatomical features, such as feeding vessels into the variceal bed or presence of a gastro-renal shunt, appropriate imaging of the portomesenteric circulation with CT should be attained in patients with GV to allow the most anatomically suitable intervention to be chosen.

PRIMARY PROPHYLAXIS

Whilst there is a modest evidence-base for secondary prophylactic measures for bleeding GV, there is a paucity of data examining the role of primary prophylaxis. Few trials have recruited patients with the intention to treat GV prior to bleeding, and those that have[36,38,39] have done so in low numbers which prevents any meaningful subgroup analysis.

One RCT by Mishra *et al*[48] randomized patients with never-bled GOV2 or IGV1 ≥ 10 mm in size to cyanoacrylate injection, propranolol or no therapy in a 1:1:1 ratio. This demonstrated a significant reduction in GV bleeding in those treated with cyanoacrylate compared to those with propranolol or no therapy (10% *vs* 38% *vs* 53%, $P = 0.003$), as well as a significant reduction in bleed-related mortality between those receiving endoscopic therapy and those who received no specific therapy (0% *vs* 20%, $P = 0.025$). There was no statistical difference in overall mortality between the groups (7% *vs* 17% *vs* 26%, $P = 0.113$), nor therapy-related complications (3% *vs* 3% *vs* 7%, $P = 1.0$). This suggests endoscopic cyanoacrylate therapy could be recommended in patients with GV larger than 10mm in size, and NSBB therapy considered in those with contraindication to, or declining, cyanoacrylate injection.

In subgroup analysis of another study by Bhat *et al*[38], 93% of patients undergoing combined EUS-guided coiling with cyanoacrylate for primary prophylaxis had no GV bleeding over a mean follow-up time of 449 d.

To date, there are no head-to-head trials comparing endoscopic therapy with radiologic interventions for primary prophylaxis, nor any specific trials to compare various endoscopic therapies (coil *vs* cyanoacrylate or combination therapy *vs* monotherapy).

CONCLUSION

Future directions

The majority of evidence for the treatment of GV stems from retrospective studies, and

so there is a need for further prospective and randomized trials to better guide management. In particular, there is a paucity of data on primary prophylaxis of GV, the risk of treating small (< 10 mm) or low-risk GV, and on the optimal approach to secondary prophylaxis (endoscopic, radiologic or combined) since the advent of EUS-based combination therapy. Furthermore, little is known regarding the ideal timeframe for surveillance of GV, whether treated or untreated.

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MINIREVIEWS

Pathogenesis of autoimmune hepatitis

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Abstract

Autoimmune hepatitis (AIH) is a chronic progressive liver disease whose etiology and pathogenesis are not yet clear. It is currently believed that the occurrence of AIH is closely related to genetic susceptibility and immune abnormalities, and other factors such as environment, viral infection and drugs that may cause immune dysfunction. This article reviews the pathogenesis of AIH and describes the latest research results in the past 5 years.

Key Words: Autoimmune hepatitis; Genetic susceptibility; environmental factors; Immunomodulation; Drug-induced liver injury; Intestinal microbes

Core Tip: Autoimmune hepatitis (AIH) has no specific clinical manifestations. AIH patients often require steroid hormones plus immunosuppressive maintenance therapy. Long-term medication may cause various adverse reactions, complications, and relapse after drug withdrawal, which imposes a heavy burden on patient's health and quality of life. Although the exact pathogenesis of AIH is still unclear, there are multiple theories, and continuous in-depth research on its pathogenesis has led to development in treatment of AIH. Genetic susceptibility, environmental factors (viruses, parasites, pets, *etc.*), immune system, drugs and biological agents, pregnancy and liver transplantation have been reported to be associated with AIH.

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INTRODUCTION

Autoimmune hepatitis (AIH) is more common in female patients. There are no specific clinical symptoms in the early stage. Serology mainly manifests as hypergammaglobulinemia and multiple autoantibodies. Histologically, a large number of plasma cells infiltrate the portal area and involve the surrounding liver parenchyma to form interface hepatitis. AIH was first proposed in 1950. Because of the similar clinical manifestations and autoantibodies between this disease and systemic lupus erythematosus, it was originally called lupus-like hepatitis. After 10 years, it was discovered that this disease had obvious differences in clinical manifestations and autoantibodies from systemic lupus erythematosus, and autoimmune liver disease and autoimmune chronic active hepatitis are collectively referred to as AIH[1]. AIH has a global distribution and can occur in men or women of any age and race. The age of onset is bimodal. The peak onset is in adolescence and middle age, especially menopausal women. At present, the clinical treatment of AIH is unsatisfactory, and with the increase of morbidity, it imposes a heavy burden on health and quality of life. Although the exact pathogenesis of AIH is still unclear, there are many theories, and the continuous in-depth research on its pathogenesis has led to development in treatment of AIH. This article summarizes recent progress of research into the pathogenesis of AIH.

GENETIC PREDISPOSITION

AIH is a polygenic disease. HLA class II DRB1 alleles are associated with AIH in different populations (Table 1). HLA-DRB1*13:01 and *03:01 alleles are related to AIH type I. In South America, AIH is mainly related to HLA-DRB1*1301 alleles, while HLA-DRB1*0301-negative type I AIH is mostly related to HLA-DRB1*0401[1,2], and in Japan it is related to HLA-DRB1*0405, *0401, *0802 and *0803. It may be that the amino acid sequence in the binding region of HLA-II molecules of different races differs slightly[3]. The high frequency of HLA-DRB3*0101 and HLA- DQB1*0201 haploid is also related to type I AIH. In South America, HLA-DQ2 is a risk factor for AIH, and HLA-DR5 and DQ3 are protective factors for this population[4]. HLA-DRB1 *0405, HLA-DRB1*1301, HLA-DQB1*02 and HLA-DQB1*0603 are the main risk factors for the onset of AIH, while HLA-DRB1*1302 and DQB1*0301 are protective factors. These HLA molecules have P1, P4, and P6 pockets. The physicochemical acquaintances and differences of the key amino acids encoded by the peptide-binding grooves illustrate their influence on the development of disease. In Europe and Japan, HLA-DRB1*1501 is also a protective factor[3]. HLA-DRB1*0701, *0301, and *0201 alleles are associated with AIH type II. Patients with HLA-DRB1*0701 have rapid disease progression and poor prognosis. The genetic susceptibility and severity of disease in British and Brazilian type II AIH patients are related to HLA-DRB1*0301 alleles[1-3]. Gene mutations other than HLA are also related to AIH susceptibility or progression: Fas-670a/g and Fas-1377g/a polymorphisms[5], VDR[6], and GATA-2[7] are closely related to the onset of AIH. The high-affinity combination of y1 and -1993 c alleles inhibits expression of tbx21, which may inhibit the occurrence of AIH I by inhibiting the type 1 immune response[8]. The haplotypes of the rs7582694-c and rs7574865-t alleles in the stat4 allele are related to the increased risk of AIH I, while the rs2476601 in the ptpn22 allele is related to reduced risk of AIH I[9]. The CTLA-4 molecule is a key regulator of lymphocyte response, and ctla4a/a is a protective genotype of Tunisian patients, and the Ctla4 gene +49 polymorphism is related to AIH susceptibility. Ctla4 gene mutations may lead to changes in the structure of CTLA-4 protein, leading to onset of AIH[10]. a20 encoded by Tnfaip3 is an inhibitor of the nuclear factor (NF)-kB signaling pathway and a susceptibility gene for autoimmune diseases. The harmful mutations of tnfaip3 and drb1 alleles may be independently related to type I AIH, and are related to AIH and liver cirrhosis in Japan[1]. GATA2 encodes a transcription factor for hematopoietic cells, and mutations may be manifested as a reduction in monocytes, lack of dendritic cells and B cells, bone

Table 1 Susceptibility genes of autoimmune hepatitis

Type of AIH	Susceptibility genes or alleles (protective alleles are in bold)	Country	Ref.
AIH I	DRB1*03:01, DRB1*04:01, **DRB1*15:01**	European, North American	Higuchi *et al*[1], 2021
			Higuchi *et al*[2], 2019
	DRB1*04:01, DRB1*04:05, **DRB1*13:02**, **DRB1*15:01**, DRB1*0802, DRB1*0803	Japanese	Higuchi *et al*[1], 2021
			Higuchi *et al*[2], 2019
	DRB1*0404, DRB1*0405, DRB1*1301, **DRB1*1302**	Latin American	Duarte-Rey *et al*[4], 2009
	DQB1*02, DQB1*0603, **DQB1*0301**, **DR5**, **DQ3**, DQ2	Latin American	Duarte-Rey *et al*[4], 2009
	Fas-670a/g	New Zealand, China, United States, Japan	Yan *et al*[5], 2020
	GATA-2	European, Caucasian ancestry	Webb *et al*[7], 2016
	TBX21-1993C	China	Sun *et al*[8], 2017
	STAT4 (rs7582694-c, rs7574865-t), **Ptpn22-rs2476601**	China, Japan	Li *et al*[9], 2017
	CTLA4	European, Japanese	Chaouali *et al*[10], 2018
	SH2B3, VDR, FAS-1377g/a, TNFAIP3	Japanese	Ngu *et al*[3], 2017
			Yan *et al*[5], 2020
			Kempinska-Podhorodecka *et al*[6], 2020
			McReynolds *et al*[11], 2018
	SH2B3, CARD10	Netherlands	Motawi *et al*[13], 2019
	MIF-173gc	United States, Japan	Alsayed *et al*[14], 2020
AIH II	DRB1*0701, DRB1*0201	European	Ngu *et al*[3], 2017
			Duarte-Rey *et al*[4], 2009
	DRB1*0301	British and Brazilian	Ngu *et al*[3], 2017
	DQB1*0201	Latin American	Duarte-Rey *et al*[4], 2009

AIH: Autoimmune hepatitis.

marrow dysplasia and immunodeficiency, which are related to the pathogenesis of AIH[7,11]. HLA-DRB15 is significantly correlated with increased levels of interleukin (IL)-8. IL-6, IL-8 and tumor necrosis factor (TNF)-α may be biomarkers of AIH activity. *HLA* gene expression may play a role in the production of cytokines, and enable earlier diagnosis and better treatment[12]. Recent studies have reported that AIH I in Dutch adults is associated with mutations in the MHC region, and identified sh2b3 and card10 mutations as possible risk factors. These findings support the complex genetic basis of AIH pathogenesis and indicate partial inheritance. Susceptibility overlaps with other immune-mediated liver diseases. However, in the Japanese population, there is no connection between the card10 rs6000782 variant and AIH[13]. The Mif-173 gc polymorphism is associated with the severity of AIH in children, and may help predict the increase in serum alanine aminotransferase (ALT) levels in the early stage of onset and necrotizing inflammation/fibrosis after immunosuppressive treatment[14]. TIPE2 has a protective effect on AIH. The expression of TIPE2 in mice with AIH is significantly reduced, while the serum ALT and aspartate aminotransferase (AST) levels of TIPE2-deficient mice are significantly increased, the release of pro-inflammatory cytokines is increased, and hepatitis is more serious. It is suggested that TIPE2 alleviates liver dysfunction after AIH and inhibits harmful inflammatory immune responses, so it can be used as a new drug for the treatment of AIH[15]. Immunogenetic factors can affect the clinical manifestations of AIH in ethnic groups[3]. The prognosis of AIH patients in Asians is poor. The indigenous Alaskan population has acute jaundice hepatitis, while the Spanish ethnic group is prone to cirrhosis. HLA-DRB1*0301/*0401 also has a significant impact on the clinical manifestations of AIH. DRB1*0301-positive patients are younger and more ill. They have a poor response to

glucocorticoid treatment and are prone to relapse. It is more common to die of liver failure, and the probability of liver transplantation is high. Patients who are positive for HLA-DRB1*0401 are generally elderly women, who are relatively mildly ill, often accompanied by other autoimmune diseases, and hormone therapy is effective.

ENVIRONMENTAL FACTORS

Peptides of some viruses and hepatocyte antigens can cross-react

Since immune cross-reaction is not seen until a long time after virus infection, it is difficult to find the basis for viral infection. Common viruses include hepatitis viruses, measles virus, cytomegalovirus, Epstein–Barr virus, and varicella–zoster virus, and the most evidence is related to hepatitis viruses[16,17]. There is no difference between hepatitis E virus (HEV) seroprevalence rate in AIH patients in Catalonia and the general population. In patients with acute AIH, higher gammaglobulin levels and antibody titers, and higher HEV seropositivity indicate that there is a cross-reaction between HEV and liver antigens[17]. HEV infection may induce onset of AIH and affect its therapeutic response[16,17]. During acute HEV infection, AIH needs to be ruled out. Similarly, before diagnosis of AIH, acute HEV infection should be excluded. Immunization may also cause AIH, and influenza vaccination may trigger the development of AIH[18].

Vitamin D

Vitamin D has immunoregulatory, anti-inflammatory, antioxidative and antifibrotic effects, which may affect the occurrence and outcome of immune-mediated diseases. Macrophages and dendritic cells produce 1,25-dihydroxyvitamin D in the microenvironment, which can inhibit proliferation of immune cells, promote distribution of anti-inflammatory cytokines, expand regulatory T cells (Tregs), enhance the effect of glucocorticoids, increase production of glutathione, and inhibit hepatic stellate cells. Vitamin D deficiency usually exists in patients with immune-mediated liver disease and non-liver disease, and is related to the histological severity of AIH, advanced liver fibrosis, the ineffectiveness of conventional glucocorticoid therapy, and the need for liver transplantation[19]. Another study found that genetic variants of VDR genes (TaqI-rs731236, BsmI-rs1544410 and ApaI-rs7975232) can affect the susceptibility of individuals to chronic autoimmune liver diseases (such as AIH and primary biliary cholangitis, and affect quality of life[6].

Intestinal microenvironment and intestinal barrier

Intestinal barrier dysfunction and bacterial translocation can initiate autoimmune responses in AIH. Intestinal leakage in AIH patients is related to abnormal intestinal microbes. Damage to the intestinal barrier can cause pathogenic bacteria and their products such as lipopolysaccharide and DNA-containing unmethylated CpG to enter the liver. These gut-derived toxins may promote the signaling pathways related to liver inflammation through the abnormal activation of the innate immune system, such as activating NF-kB, inducing activation of macrophages and releasing various pathogenic inflammatory cytokines, leading to occurrence of AIH[20-22]. Because AIH patients have impaired integrity of intestinal tight junctions, they also have intestinal flora imbalance, characterized by decrease of bifidobacteria, and changes in fecal microbes of specific diseases have been found. AIH patients may have bacterial flora migration, and intestinal barrier dysfunction and bacterial translocation are related to disease severity/increased activity[21]. Study of the changes in the composition and function of the intestinal microbiome in AIH, using the intestinal microbiota as a non-invasive biomarker, can be used to assess disease activity[22]. These results indicate that the intestinal flora provides new diagnostic methods and therapeutic targets in AIH.

Alcohol, pets and parasites

Alcohol exposure can affect the function of dendritic cells, reduce antigen presentation, and thereby inhibit the immune response. Studies have pointed out that antibiotics are an independent risk factor for the occurrence of AIH. Wood heating of households is an independent protective factor for prevention of AIH[23]. Close contact with pets (especially cats) is a risk factor for autoimmune liver disease. This finding indicates that an unknown substance (*i.e.*, toxin/microorganism) is involved in the triggering of these diseases[24]. Parasite studies have shown that soluble liver

antigen/liver pancreas (SLA/LP) protein is a highly specific diagnostic marker for AIH. The immunodominant regions of SLA/LP and rickettsial surface antigen ps120 are structurally similar, and may drive the autoimmune response mediated by CD4+ T lymphocytes[25].

DRUG OR BIOLOGICAL AGENT INDUCTION OF AIH

Drug-induced AIH (DIAIH) occurs in patients who have not previously been diagnosed with AIH or are susceptible to AIH. Many drugs can induce AIH, including nitrofurantoin, minocycline, hydralazine, methyldopa, indomethacin, diclofenac, atorvastatin, Tienilic acid, interferon, TNF-α, and some Chinese herbal medicines. The occurrence of DIAIH is related to gender, age, drug dose, genetic polymorphism, and drugs. Its pathogenesis is related to autoantibodies against proteins expressed in liver cells, and results from the reaction of unstable drug metabolites with cellular components. In particular, proteins in the P450 cytochrome system are considered neoantigens[26,27]. DIAIH is different from other forms of hepatotoxicity in which autoantibodies are usually negative. DIAIH has antinuclear antibodies, elevated anti-smooth muscle antibodies or gammaglobulin, and/or a specific HLA haplotype[26-28]. The difference in the incidence of DIAIH among countries may be due to population differences and the heterogeneity of the drug supply. Nitrofurantoin and minocycline are the main causes of DIAIH. Among cases of hepatotoxicity with nitrofurantoin and minocycline, DIAIH accounts for 82% and 73%, respectively. The incidence of AIH induced by methyldopa is 55%, and 43% for hydralazine. A prospective study of the Drug-induced Liver Injury Network (DILIN) showed that nitrofurantoin and nonsteroidal anti-inflammatory drugs accounted for 84% of DIAIH cases, and nitrofurantoin cases were as high as 67%[28,29]. Biological agents (*e.g.*, infliximab/adalimumab) have recently begun to constitute a cause of DIAIH, appearing in the early stage of drug withdrawal (as early as 2 mo), accompanied by short-term immunity inhibition, but there are no records of recurrence[30,31]. Diagnosis of DIAIH and AIH is difficult to distinguish. The response of DIAIH to hormone therapy is similar to that of AIH, but DIAIH has good prognosis. After discontinuation of immunosuppressive therapy, no patients have relapsed or progressed to cirrhosis or required liver transplantation. AIH has a higher degree of fibrosis than DIAIH has, and relapse can occur after drug discontinuation, with later progress to liver cirrhosis or even liver transplantation. More importantly, compared with AIH, patients with DIAIH have higher serum ALT and AST levels, more severe lobular inflammation, and higher frequency of necrosis, the number of CD4 + Foxp3 + CD25 +/- Tregs in hepatic lobules is higher, but there is no significant difference in the frequency of peripheral blood CD4+ Foxp3+ CD25+/- Tregs between DIAIH and AIH [30]. An increasing number of studies have shown that drugs have some effect on AIH, but the specific pathogenesis needs further research.

ABNORMAL AUTOIMMUNE REGULATORY MECHANISM

It is currently believed that the immune response of AIH is likely initiated by the presentation of autoantigens to uncommitted naive CD4+ helper T (Th0) cells. CD4+ Th0 cells are activated in the antigen presentation process in the presence of appropriate co-stimulatory signals, and differentiate into different helper T cell populations according to the cytokine environment to which they are exposed. Th0 cells in the presence of IL-12 differentiate into Th1 cells, differentiate into Th2 in the presence of IL-4, and differentiate into Tregs or Th17 cells in the presence of TGF-β[32,33]. Tregs and Th17 cells play an important role in the occurrence and development of immune-mediated hepatitis. Tregs include two subgroups, CD4+ CD25+ and CD8+. The former is the main factor in maintaining immune tolerance. The surface of Tregs can express IL-2 receptor, glucocorticoid-induced TNF receptor, Foxp3, CTLA-4, and chemokine receptors 4, 6, 7, 8 and 10. CD4+ CD25+ Foxp3+ Tregs inhibitory effector cells play an important role in maintaining cell homeostasis[34-36]. AIH patients have low expression of F0xp3 in peripheral blood, decreased Tregs, and decreased ability to regulate CD4+ and CD8+ effector T cell proliferation. Th17/Th22 cells in AIH peripheral circulation and liver are increased; interferon-γ, IL-17 and IL-22 levels increase; IL-17 increases release of inflammatory factors such as TNF-α and IL-6, and induces an immune inflammatory response. The imbalance between Tregs and Th1 and Th17/Th22 cells, activated macrophages, complement and natural killer cell

activation may all participate in the pathogenesis of AIH[33-36]. The IL-1 family has a proinflammatory function, and IL-33 is a ligand for receptors of IL-1 receptor-related protein ST2 (IL1RL1/ST2) and IL-1 receptor accessory protein (IL-1RaP). The interaction of IL-33 with these receptors triggers the signaling pathways related to MyD88 and NF-κB. The interaction between IL-33 and IL1RL1/ST2 receptors regulates Th2 response, and serves as an important part of the Th1/Th17-mediated response and inflammation induced by innate immunity[37]. IL-33 and its soluble receptor ST2 play a vital role in the pathogenesis and severity of type I AIH, and may be a new target for the treatment of AIH[37,38].

PREGNANCY AND LIVER TRANSPLANTION

Patients with a past history of AIH during pregnancy have an increased risk of recurrence of AIH. The maternal immune system expands through Foxp3+ Tregs during pregnancy and guides Th2 transformation to maintain immune tolerance and immune response in the fetus to protect against invasive organisms. However, this immunotolerant state returns to Th1 dominance, leading to AIH[39,40]. Therefore, patients with elevated transaminase or immunoglobulin G (IgG) levels during pregnancy or postpartum should be alert to the possibility of secondary AIH. AIH can appear or recur after liver transplantation, and is called *de novo* AIH or recurrent AIH. AIH may occur in patients undergoing liver transplantation due to different diseases. *De novo* AIH after transplantation may be caused by an immune response to an allogeneic antigen that triggers an autoimmune response[41,42]. Recurrent AIH is associated with elevated liver enzymes and IgG before liver transplantation, lymphoplasmacytic infiltration and steroid deficiency after liver transplantation[43,44]. Although the prognosis after liver transplantation is good, AIH may still occur/relapse after transplantation, with an estimated 1-year recurrence rate of 8%–12% and 5-year recurrence rate of 36%–68%[40]. The pathogenesis of recurrent or *de novo* AIH after liver transplantation is unclear, and may be related to factors such as transplanted organs and immunosuppressive drug treatment. Early rapid diagnosis can avoid strong rejection and possible secondary liver transplantation[41-43].

SUMMARY AND OUTLOOK

AIH has no specific clinical manifestations. AIH patients often require steroid hormones plus immunosuppressive maintenance therapy. Long-term medication may lead to various adverse reactions, complications, and relapse after drug withdrawal, which imposes a heavy burden on patient's health and quality of life. The etiology of AIH has not yet been fully clarified.

CONCLUSION

Genetic susceptibility, environmental factors (viruses, parasites, pets, *etc.*), immune system, drugs and biological agents, pregnancy and liver transplantation have been reported to be associated with AIH. The pathogenesis of AIH still needs further research.

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MINIREVIEWS

Current state of endohepatology: Diagnosis and treatment of portal hypertension and its complications with endoscopic ultrasound

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Abstract

The diagnosis and management of cirrhosis and portal hypertension (PH) with its complications including variceal hemorrhage, ascites, and hepatic encephalopathy continues to evolve. Although there are established "standards of care" in liver biopsy and measurement of PH, gastric varices remain an area without a universally accepted therapeutic approach. The concept of "Endo Hepatology" has been used to describe of the applications of endoscopic ultrasound (EUS) to these challenges. EUS-liver biopsy (EUS-LB) offers an alternative to percutaneous and transjuglar liver biopsy without compromising safety or efficacy, and with added advantages including the potential to reduce sampling error by allowing biopsies in both hepatic lobes. Furthermore, EUS-LB can be performed during the same procedure as EUS-guided portal pressure gradient (PPG) measurements, allowing for the collection of valuable diagnostic and prognostic data. EUS-guided PPG measurements provide an appealing alternative to the transjugular approach, with proposed advantages including the ability to directly measure portal vein pressure. In addition, EUS-guided treatment of gastric varices (GV) offers several possible advantages to current therapies. EUS-guided treatment of GV allows detailed assessment of the vascular anatomy, similar efficacy and safety to current therapies, and allows the evaluation of treatment effect through doppler ultrasound visualization. The appropriate selection of patients for these procedures is paramount to ensuring generation of useful clinical data and patient safety.

Key Words: Portal hypertension; Endoscopic ultrasound; Liver biopsy; Gastric varices

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Core Tip: In this review we familiarize the reader to salient aspects of endoscopic ultrasound (EUS)-guided hepatic interventions including liver biopsy, portal pressure measurements, and treatment of gastric varices, and outline the data supporting their use. We highlight the potential advantages and disadvantages of EUS guided interventions compared to the current standards of care, and propose clinical scenarios in which EUS guided interventions may be favored over the current standard of care.

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INTRODUCTION

Chronic liver disease (CLD) continues to represent a substantial healthcare burden, with an estimated 1.5 billion persons affected worldwide. Since 2000 there has been a 13% increase in incidence of CLD and cirrhosis, in addition to increasing prevalence and mortality of cirrhosis in the United States. Moreover, the epidemiology of CLD is shifting from viral hepatitis to an increasing prevalence of liver disease caused by metabolic syndrome and alcohol misuse[1].

Accompanying the increase in cirrhosis is the development of portal hypertension (PH); resulting in the majority of its complications including ascites, variceal hemorrhage, and encephalopathy. Clinically, cirrhosis is often dichotomized into compensated (absence of portal hypertensive complications) and decompensated (presence of portal hypertensive complications), with decompensated cirrhosis portending a poor prognosis[2].

A diagnosis of PH typically requires invasive testing to measure the gradient between the hepatic sinusoids and the hepatic vein (which is the outflow tract of the liver), termed the hepatic venous pressure gradient (HVPG) (Figure 1). PH is present if HVPG > 5 mmHg, with clinically significant PH (CSPH) defined as > 10 mmHg associated with the development of clinical complications (hence its designation) including variceal hemorrhage and ascites. HVPG is an independent prognostic variable, with a 3% increase in mortality risk for each 1 mmHg gradient increase[3].

Accompanying the increasing burden of CLD has been the need for safe, accurate, and cost-effective diagnostic modalities to appropriately classify patients requiring additional therapeutic interventions. Classically liver biopsy; percutaneous liver biopsy (PC-LB) and transjugular liver biopsy (TJ-LB) was utilized to assess the etiology and severity (fibrosis stage) of liver disease by histology. Additionally, invasive measurement of the HVPG *via* the transjugular venous route in interventional radiology (IR) could be utilized to obtain additional prognostic data in appropriate circumstances. Noninvasive modalities, such as elastography or serologic markers, have been developed as alternatives to liver biopsy[4].

The concept of "Endo-hepatology" was introduced in 2012 as an area of integration or overlap of endoscopic procedures within the practice of Hepatology[5]. In this review we focus on two diagnostic modalities including endoscopic ultrasound (EUS) guided liver biopsy (EUS-LB) and EUS-guided measurement of PH, and one therapeutic application; EUS-guided management of gastric varices (GV).

Hepatologists should have a fundamental understanding of the similarities and differences in techniques between current clinical standards of practice and EUS-guided modalities, while also recognizing opportunities to appropriately implement EUS-guided diagnostics and therapeutics into their practice. An in depth review of EUS anatomy, devices, and techniques is outside the purview of this review.

LIVER BIOPSY

Once considered the cornerstone in the evaluation and management of liver disease, the role and modalities of liver biopsy has evolved substantially over the past decade.

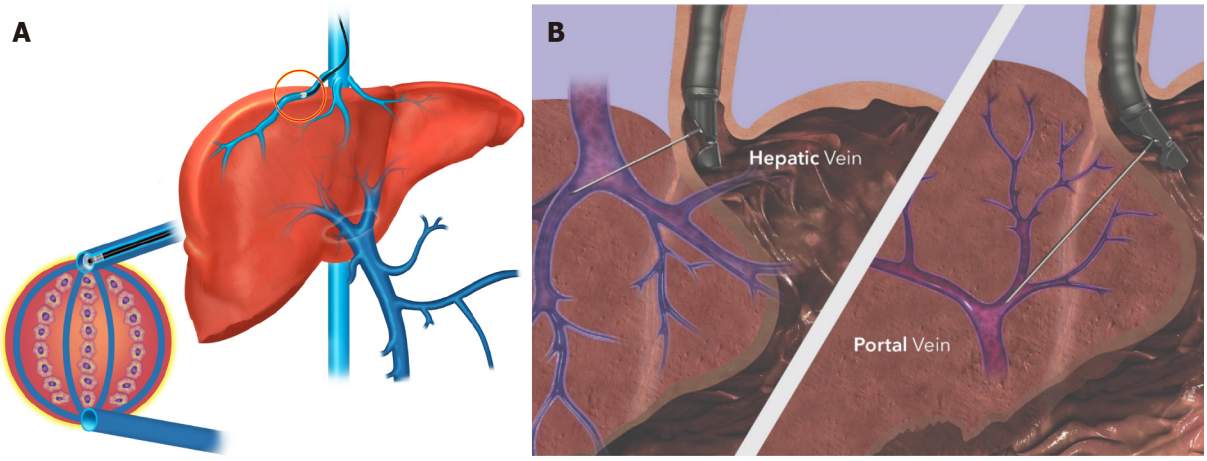

Figure 1 Comparison of modalities for measuring portal hypertension. A: Methods for obtaining hepatic venous pressure gradient measurement *via* the transjugular approach. Placement of catheter into right hepatic vein for measurement of free hepatic venous pressure, followed by balloon or "wedged" occlusion (inset) to measure wedged hepatic venous pressure, indirectly measuring the portal vein pressure *via* the sinusoids; B: Portal pressure gradient measurement *via* endoscopic ultrasound. The hepatic vein (left panel) and portal vein (right panel) are both directly accessed with transgastric needle puncture. Permission for use granted by Cook Medical, Bloomington, Indiana.

The evolution of noninvasive testing coupled with concerns regarding the cost and risk of liver biopsy has brought into question the exact role of liver biopsy in the early 21st century[4]. At present, liver biopsy is still considered appropriate for establishing diagnosis, evaluating stage of liver disease (fibrosis), and directing management decisions[6].

Traditionally, liver biopsy has been performed through percutaneous, transjugular, or surgical approaches. At present, image-guided liver biopsy ("real time" or marking) has become the de facto standard of care in most centers, replacing the palpation/percussion guided technique[7]. Because the diagnosis, grading, and staging of liver disease is dependent upon adequate sample size, it is recommended that the length of the sample is at least 2-3 cm and 16-gauge in caliber (or wider), ideally with ≥ 11 portal tracts for evaluation[6]. Complications related to liver biopsy include pain (30%-50% patients)[8], serious bleeding (0.6%)[9], injury to other organs (0.08%)[10], and rarely death (0.1%)[6].

Since its first description in 2007, publications describing experience with EUS-LB have continued proliferate[11]. Proposed advantages to EUS-LB include more precise localization and characterization of the target tissue, ability to biopsy both lobes of the liver, decreased invasiveness, improved patient tolerance, decreased recovery time, and decreased complications[12]. Acknowledged disadvantages include increased technical difficulty and higher cost compared to other available methods (Table 1).

A single center retrospective study compared the safety and efficacy of "standard of care" [PC-LB (n = 287) & TJ-LB (n = 91)] to EUS-LB (n = 135). There were no statistically significant differences between modalities in regards to rates of adverse events, technical success rate, and diagnostic adequacy. Notably, the number of complete portal tracts for analysis and mean specimen length (two metrics for assessing specimen adequacy) were higher in the EUS-LB group compared to PC-LB and TJ-LB[13]. These results support comparable safety profile and diagnostic adequacy (*i.e.*, non-inferiority) of EUS-LB to current standard of care liver biopsy modalities.

In 2019 a systematic review and meta-analysis that included eight studies with a total of 437 patients reported the efficacy and safety of EUS-LB biopsy[14]. The primary analysis focused on diagnostic yield; specifically addressing successful histologic diagnosis and frequency of insufficient histologic sample size. A second analysis described pooled rates of all adverse events. A subgroup analysis was performed regarding needle type used for biopsy [core needle *vs* fine-needle aspiration (FNA) needle]. A 19-gauge needle was used in all included studies. Indications for liver biopsy included abnormal liver tests, non-alcoholic steatohepatitis, cholestasis, primary sclerosing cholangitis, cirrhosis, and congestive heart failure.

The pooled rate of successful histologic diagnosis was 93.9% and the pooled insufficient specimen rate was 10.1%. The pooled rates of adverse events and bleeding were 2.3%, and 1.2%, respectively. In the subgroup analysis, the only statistically significant difference between core needle and FNA needle was obtaining insufficient specimen, which occurred in 20% of patients biopsied with core needle compared to

Table 1 Relative advantages and disadvantages of liver biopsy modalities

Modality	EUS-LB	PC-LB	TJ-LB
Advantages	Ability to obtain simultaneous bi-lobar biopsies	Familiarity	Circumvent challenging body habitus
	Circumvent challenging body habitus	Less technical expertise	Ability to perform other diagnostics simultaneously (*i.e.*, HVPG measurement)
	Improved patient tolerance	Lower cost	Fewer contraindications (*i.e.*, ascites and coagulopathy)
	Decreased recovery time		
	Ability to perform other diagnostics simultaneously (*i.e.*, PPG measurement)		
Disadvantages	Higher cost	Poorer patient tolerance	Higher cost
	Need for technical expertise	May be limited by patient body habitus	Need for technical expertise
		More prone to sampling error	More prone to sampling error

PH: Portal hypertension; TJ-LB: Transjugular liver biopsy; EUS-LB: Endoscopic ultrasound-guided liver biopsy; PPG: Portal pressure gradient; HVPG: Hepatic venous pressure gradient; PC-LB: Percutaneous liver biopsy.

4% of patients biopsied with FNA needle (P = 0.03). The authors concluded that FNA needles provide better specimens and have improved diagnostic outcomes compared to other core needle biopsies, though they acknowledged significant heterogeneity in the overall analysis.

Despites its limitations, the study by Mohan *et al*[14] provides robust data describing the performance characteristics and technical considerations (needle device choice) of EUS-LB. The safety profile of "standard of care"; (PC-LB or TJ-LB) was compared head-to-head in a propensity score matched analysis of 978 patients who underwent PC-LB compared to 489 undergoing TJ-LB. Hematomas developed in 1.2% of patients undergoing PC-LB compared to 0.2% with TJ-LB (P = 0.049). Cardiac complications occurred more frequently in TJ-LB compared to PC-LB (0.4% *vs* 0%; P = 0.045). There were no significant differences in other adverse events or complications [15].

Ultimately, multiple factors influence the choice of liver biopsy modality, and the decision should be made on a case-by-case basis (Figure 2). A seemingly pertinent use of EUS-LB, is in patients with discordant noninvasive testing in whom the goal is to exclude cirrhosis and/or PH, as direct measurements of portal pressures can also be performed simultaneously and biopsies from both lobes can be obtained. With discordant noninvasive testing, accurate fibrosis staging by liver biopsy is paramount. Indeed, it has been demonstrated in patients with NAFLD, biopsies performed on the same day characterized 35% of patients with advanced fibrosis on one sample, while the other sample from the same day did not suggests significant fibrosis[16]. This discordance is of profound significance and directly influences clinical decision-making. As PC-LB and TJ-LB typically sample one hepatic lobe, obtaining "bilobar" biopsies by EUS-LB provides a potential advantage to minimize the risk of misclassifying fibrosis stage.

MEASUREMENT OF PH

Although invasive and considered the gold standard in assessment of PH, HVPG is in fact an indirect method of measurement[17]. Calculation of the HVPG includes measuring the free hepatic venous pressure (FHVP) and wedged hepatic venous pressure (WHVP; typically wedged pressure in the right hepatic vein). The transduced wedged hepatic venous pressure estimates sinusoidal pressure. The difference between the WHVP and FHVP is the estimated portosystemic gradient[18]. Conceptually, this is analogous to Swan-Ganz catheterization in the pulmonary artery.

In the absence of fibrosis/nodules (*i.e.* cirrhosis), the pressure equalizes throughout the interconnected sinusoidal network, and results in minimal gradient (*i.e.*, normal; up to 4 mmHg). Thus, it does not provide useful information regarding prehepatic or presinusoidal PH (*i.e.*, non-cirrhotic causes of PH). In the presence of cirrhosis, the

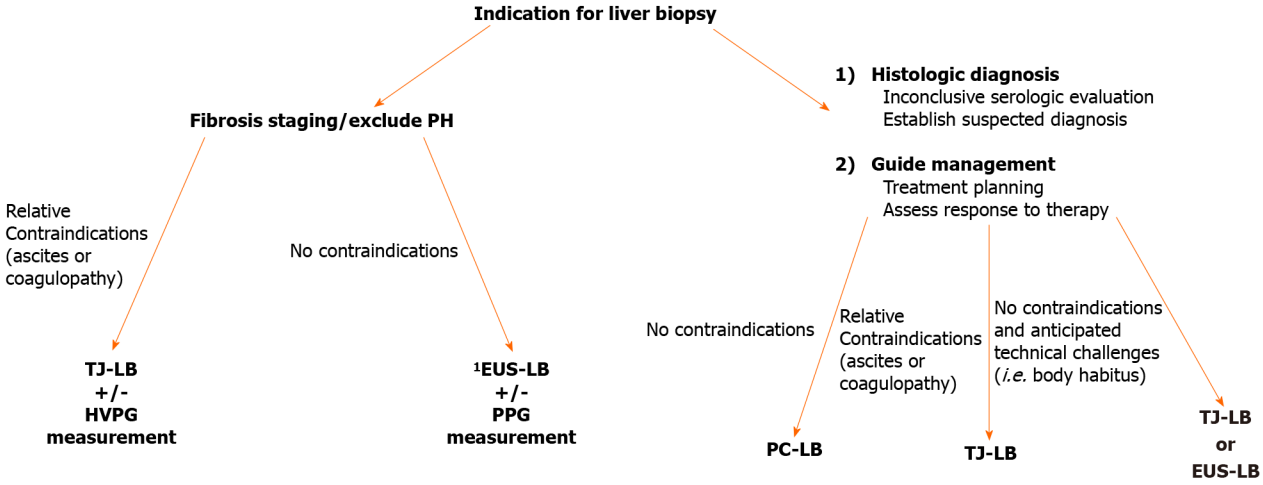

Figure 2 Proposed algorithm for choosing suitable modality for liver biopsy. [1]Allows endoscopic exam for evidence of portal hypertension (*i.e.*, varices/PHG), high-resolution endoscopic ultrasound images of liver contours/parenchyma, endoscopic "palpation" of the liver, bi-lobar biopsies, and direct measure of portal pressure gradient. PH: Portal hypertension; TJ-LB: Transjugular liver biopsy; EUS-LB: endoscopic ultrasound-guided liver biopsy; PPG: Portal pressure gradient; HVPG: Hepatic venous pressure gradient; PC-LB: Percutaneous liver biopsy.

WHVP is an accurate surrogate for portal vein pressure, allowing calculation of the gradient by the equation: WHVP-FHVP = HVPG. As previously outlined, HVPG has significant prognostic value in predicting poor outcomes in patients with PH[3].

In comparison, EUS-guided portal pressure gradient (PPG) measurements employ a direct sampling technique. Thus, the direct measurement of the portal vein pressure could be considered the gold standard because it is not an estimate of sinusoidal pressure as is WHVP. The difference in the mean measurement of these pressures is termed the PPG which is analogous to the HVPG, with the caveat that direct portal vein measurement also allows for the assessment of prehepatic/presinusoidal PH; a limitation of the transjugular approach.

In 2016, Huang *et al*[19] published their experience in a porcine animal model with a novel EUS-guided system which included a manometer attached to a 25-gauge FNA needle for directly measuring pressures in the hepatic and portal veins. The purpose of this animal study was to assess clinical feasibility and assess correlation with the standard of care; HVPG measurement through transjugular approach[19].

In a pilot study, 28 patients between the age of 18-75 years with a history of liver disease or suspected cirrhosis underwent EUS-PPG measurements utilizing the technique and equipment in the animal study. The portal vein and hepatic vein were targeted *via* a transgastric–transduodenal approach (IVC was substituted for hepatic vein when not technically feasible). Feasibility was defined as the technical success of obtaining pertinent measurements. Safety was assessed by postprocedural interview and telephone call 48 h following procedure. As correlation to the standard of care (transjugular HVPG) was obtained in animal studies, clinical parameters of PH were evaluated in each patient. Exclusion criteria included pregnancy, international normalized ratio (INR) > 1.5, platelet count < 50000, active GI bleeding, and post sinusoidal PH[20].

Technical success rate of EUS-PPG measurement was 100% without any adverse events. PPG measurements had excellent correlation with clinical parameters of PH. Mean PPG in patients with varices was 14.37 mmHg, compared to 4.26 mmHg in patients without varices (P = 0.0002); which is consistent with criteria that gradients ≥ 10 mmHg (*i.e.*, CSPH) are associated with the development of varices. The authors concluded that EUS-PPG measurement was a safe and feasible alternative to currently available diagnostics[20].

There are obvious limitations of this pilot study which may limit widespread generalizability of this technique. The exclusion of patients with INR > 1.5 and inclusion of only 4 patients with INR > 1.2 (especially with the knowledge that INR is a poor predictor of procedural bleeding risk in patients with cirrhosis) is a major limitation of this small pilot study[21].

Results of this pilot study ultimately led to the Food and Drug Administration approval of the EchoTip Insight portosystemic pressure gradient measurement system (Cook Medical, Winston-Salem, NC, United States) in 2019 (Figure 1). Following approval, multiple centers have begun utilizing this method. Registry data are eagerly

anticipated to assess the feasibility, utility, and safety profile of this method outside the realm of small pilot study/clinical trials.

One of the challenges facing any new technology, including EUS-PPG measurement is identifying the appropriate clinical application. Despite the useful prognostic information it provides, in current clinical practice, obtaining the HVPG is not considered standard of care in many areas due to its invasiveness, cost, and limited availability[2]. With the exception of Transjugular intrahepatic portosystemic shunt (TIPS) and TJ-LB in the authors' experience, HVPG measurements are not routinely obtained.

A potential role of EUS–PPG measurements in current practice would be to supplant the transjugular approach for HVPG/biopsy, and reserve the latter approach for patients undergoing TIPS and in those with more severe coagulopathy. Furthermore, the additional evidence gleaned during the endoscopic evaluation (*i.e.*, presence/absence of varices or portal hypertensive gastropathy) would have treatment implications. Whether the combination of EUS-PPG measurements (with or without simultaneous liver biopsy) can be routinely incorporated during evaluation of patients with cirrhosis remains to be seen.

TREATMENT OF GV

There is significant heterogeneity in the location, vascular anatomy, bleeding risk, and response to treatment of GV. The Sarin classification has been the most commonly used for risk stratification and management, however it is limited to describing endoscopic anatomy, and does not necessarily reflect the underlying vascular anatomy of GV; which has significant treatment implications[22,23].

A proposed algorithm for the treatment of acute GV bleeding suggests utilizing variceal band ligation for treatment of gastroesophageal varices (GOV) 1 (*i.e.*, treat as esophageal varices), while utilizing injection therapies (*i.e.*, tissue adhesives such as cyanoacrylate) in the management of GOV2 and isolated gastric varices 1 (IGV1) (together known as "cardiofundal varics")[24]. At present, therapeutic options for treatment of GV hemorrhage include endoscopic injection of tissue adhesives (*via* EGD or EUS), TIPS, and balloon-occluded retrograde transvenous obliteration) (BRTO). It has been suggested that EUS-guided therapy of GV is superior to endoscopic injection as it decreases the rate of rebleeding[25].

In 2000, Lee *et al*[26] published their results of a prospective study utilizing cyanoacrylate and lipiodol injection in the management of bleeding GV[26]. In this study 38% of patients had GOV2 and 27% patients had IGV1. After initial bleeding was controlled, 47 patients received "on demand" therapy if bleeding recurred, while 54 patients underwent biweekly EUS with injection until obliteration of varices was confirmed. Although early rebleeding rates (defined ≤ 48 h) were similar between both groups, the recurrence of late bleeding (> 48 h) was significantly reduced in the repeat injection group (18.5% *vs* 44.7%, $P = 0.0053$).

A randomized trial evaluated prevention of first GV bleed (primary prophylaxis) [27]. In a study of 89 patients with large (≥ 10 mm) GOV2 and IGV1, patients were randomized to endoscopic cyanoacrylate glue injection, nonselective beta blocker (NSBB), and observation. Overall, cyanoacrylate injection was associated with lower bleeding rates (10%) than NSBB (38%), and observation (53%). Survival was similar in the cyanoacrylate (93%), and NSBB group (83%), but higher compared to the observation group (74%). Of note, only 15% of patients in the study had IGV1. This study formed the basis for recommendation of NSBB for primary prophylaxis of GV hemorrhage in GOV2 and IGV1.

The management of active hemorrhage from GV remains a significant clinical challenge. A meta-analysis comparing cyanoacrylate glue injection to endoscopic band ligation demonstrated similar results for initial hemostasis, but favored cyanoacrylate injection for prevention of rebleeding[28]. Limitations of this meta-analysis included variable quality of evidence, and heterogeneity in type of varices treated.

The addition of endovascular coils to cyanoacrylate glue injection has been proposed to reduce the risk of systemic embolization, a rare but potentially fatal complication[29,30]. A single center retrospective study of 152 patients specifically addressed the use of coil injection and cyanoacrylate glue in patients with cardiofundal varices; 94% of whom had IGV1. Over a 6-year period, 5% of patients treated had active hemorrhage, while 69% had evidence of recent bleeding (*i.e.*, treatment constituted secondary prophylaxis). Technical success rate was 99%. Follow-up EUS examinations were available for 100/152 patients. Complete obliteration of varices

Table 2 Comparison of endoscopic ultrasound-guided treatment modalities for gastric varices; combination therapy *vs* monotherapy [31]

Treatment	CYA+ coil (combination therapy)	CYA alone	Coil alone	*P* value (combination *vs* CYA alone/combination *vs* coil alone)
Outcome rate (%)				
Technical success	100	97	99	< 0.001/< 0.001
Clinical success	98	96	90	< 0.001/< 0.001
Adverse event	10	21	3	< 0.001/0.057
Adverse event	14	30	17	< 0.001/1.00
Re-intervention	15	26	25	< 0.001/0.047

CYA: Cyanoacrylate.

based on Doppler was confirmed in 93%, and bleeding from obliterated varices occurred in 3% of patients. The authors concluded that combination of therapy with cyanoacrylate and coil embolization is highly effective for hemostasis and active bleeding, and for primary and secondary prophylaxis with minimal adverse effects.

A systematic review and meta-analysis compared combination therapy (cyanoacrylate + coils) to monotherapy with (cyanoacrylate alone *vs* coil alone or non-cyanoacrylate treatment)[31]. Eleven studies were included (n = 536) which included 2 randomized control trials, one prospective study, and 8 retrospective studies. Measured outcomes included technical success, clinical success, adverse events, and rate of rebleeding/or intervention. Subgroup analysis compared 3 treatment cohorts; EUS- guided cyanoacrylate injection/EUS-guided coil embolization + cyanoacrylate injection/EUS-guided coil injection alone) (Table 2).

Overall technical success of EUS-guided therapies was 100%, clinical success was 97%, and adverse events were 14%. In the subgroup analysis, combination therapy resulted in better technical success (100%) and clinical success (98%) compared to monotherapy with cyanoacrylate alone (97% and 96%, respectively) or coil embolization alone (99% and 90%, respectively). Combination therapy also resulted in lower adverse event rates (10%) compared to monotherapy with cyanoacrylate alone (21%), and coil embolization alone (3%). The authors concluded that EUS-guided treatment is safe and effective, and that combination therapies should be the preferred strategy for management of GV.

Based upon current treatment algorithms, and understanding the limitations of currently available data, EUS-guided treatment for GV should be reserved for cardiofundal varices. The main advantages of this approach include acute hemostasis and prevention of rebleeding. Furthermore, the use of EUS allows delineation of the vascular anatomy of the variceal complex, which can enable precise delivery of therapy into the varix lumen or afferent vessel (potentially decreasing the risk of embolization) and allow confirmation of vessel obliteration *via* Doppler examination [32-34]. Cyanoacrylate is off-label for the treatment of GV hemorrhage in the United States, so its use should be limited to centers with appropriately trained endoscopists and experience[2,35].

CONCLUSION

EUS-guided interventions for the diagnosis and management of PH and its complications have evolved from a novel innovation into a useful clinical tool with a growing evidence-base supporting its role.

Available data suggests that EUS-LB results in comparable diagnostic adequacy (*i.e.*, tissue specimen) to currently available options with similar low rates of adverse events [14]. Measurements of PPG correlate with HVPG measurements and have a similar safety profile[19,20]. An additional benefit is the direct measurement of the portal vein pressure, allowing diagnosis of prehepatic/presinusoidal PH that is not obtained during HVPG measurements as well as the ability to perform liver biopsy. EUS-treatment for GV bleeding may be more effective than current endoscopic therapies, and offers several potential advantages[25,31].

EUS-guided interventions have demonstrated similar efficacy and safety to current standards of care, and should be viewed as a complement (not a replacement) to current diagnostic and therapeutic modalities. A multidisciplinary approach between Hepatologists and EUS-trained endoscopists is vital to ensure appropriate patient selection, ensure accurate and useful data are generated from diagnostic procedures, and that maximal therapeutic benefit is derived from EUS-guided treatments.

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MINIREVIEWS

Solid pseudopapillary neoplasm of the pancreas

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Abstract

Solid pseudopapillary neoplasms are rare. This article reviews the clinical and pathologic features of solid pseudopapillary neoplasm of the pancreas, including the epidemiology, cytology, molecular pathology, differential diagnosis, treatment, and prognosis. Solid pseudopapillary neoplasms are low-grade malignant tumours of the pancreas characterized by poorly cohesive epithelial cells with solid and pseudopapillary patterns. Solid pseudopapillary neoplasms occur predominantly in young women. Although solid pseudopapillary neoplasms can occur throughout the pancreas, they arise slightly more frequently in the tail of the pancreas. The aetiology is unknown. Extremely rare cases have been reported in the setting of familial adenomatous polyposis. There are no symptoms unique to solid pseudopapillary neoplasms, however, the most common symptom is abdominal pain or discomfort. The features of solid pseudopapillary neoplasms on computed tomography imaging are indicative of the pathologic changes within the tumour. Typically, well-demarcated masses with variably solid and cystic appearances. Microscopically, these tumours are composed of epithelial cells forming solid and pseudopapillary structures, frequently undergoing haemorrhagic cystic degeneration. Typically, these tumours express nuclear and/or cytoplasmic β-catenin. Almost all solid pseudopapillary neoplasms harbour mutations in exon 3 of *CTNNB1*, the gene encoding β-catenin. The overall prognosis is excellent, and most patients are cured by complete surgical resection.

Key Words: Cancer of pancreas; Pancreatic neoplasms; Solid pseudopapillary neoplasm of the pancreas; Non-ductal pancreatic tumours; Pancreas

Core Tip: Solid pseudopapillary neoplasms are low-grade malignant tumours that mimic other solid cellular neoplasms of the pancreas. This article summarizes the

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INTRODUCTION

First described by Frantz in 1959[1], solid pseudopapillary neoplasms are low-grade malignant tumours composed of poorly cohesive uniform epithelial cells forming solid and pseudopapillary structures[2]. Several names have been used to describe these tumours including solid cystic tumour, papillary cystic tumour, solid and papillary epithelial neoplasm, papillary cystic carcinoma, Hamoudi's tumour, and Frantz's tumour[3-5]. Solid pseudopapillary neoplasms are rare tumours of uncertain histogenesis. In certain cases, distinguishing between solid pseudopapillary neoplasms and other solid cellular neoplasms of the pancreas may pose a diagnostic dilemma.

This article reviews state-of-the-art knowledge on the clinical and pathologic features of solid pseudopapillary neoplasm of the pancreas, including the epidemiology, cytology, and molecular pathology, and also provides the differential diagnosis, treatment, and prognosis.

EPIDEMIOLOGY

Solid pseudopapillary neoplasms are exceptionally rare. They account for approximately 0.9%-2.7% of all exocrine pancreatic neoplasms and 5% of cystic pancreatic neoplasms[2,3]. Although these tumours occur in a wide age range from 2 to 85 years [3], the mean age at presentation is 28.5 years[5]. They occur predominantly in young women with a female-male ratio of 9.8:1[3]. There is no known ethnic predilection. An increased number of cases have been reported in the literature since 2000, most likely because of rising awareness of these tumours and advances in imaging and other diagnostic techniques[5].

AETIOLOGY

The aetiology is currently unknown. Although rare cases have been reported in the setting of familial adenomatous polyposis[6,7], there are no well-established risk factors for solid pseudopapillary neoplasms. There is no association with functional endocrine syndromes[2].

CLINICAL FEATURES

The clinical symptoms are non-specific. A large number of patients are asymptomatic (38.1%)[5], however most patients are symptomatic, with the most common presenting symptom being abdominal pain or discomfort[3,5,8]. Other symptoms include abdominal mass, weight loss, jaundice, anorexia, fever, fatigue, abdominal discomfort, nausea, and vomiting[3,5,8]. Rarely, patients may present with spontaneous[9,10] or traumatic[11] rupture of the tumour leading to haemoperitoneum.

These tumours may involve any portion of the pancreas but are slightly more common in the tail of the pancreas[2,3,5,12]. Rarely, these tumours can arise in extra pancreatic sites including the omentum[13], mesentery[14], retroperitoneum[15], ovary [16], stomach, and duodenum[17].

Distant metastases occur in 7.7% of cases and lymph node metastases occur in approximately 1.6% of cases[5]. Other sites of metastases include the lung[18], small and large bowel mesentery, liver, and peritoneum[3,5,12,19]. Occasionally, these tumours directly infiltrate adjacent structures including the portal vein, duodenum, and spleen[2,3,5].

IMAGING

Solid pseudopapillary neoplasms on computed tomography (CT) imaging show features reflective of the pathologic changes within the tumour. Usually, well-demarcated large heterogeneous masses with variably solid and cystic appearances on CT. Enhancing solid areas are mostly peripheral, with cystic areas tending to be centrally located. Peripheral or central stippled calcifications may be identified in the tumour[20,21].

MRI shows a well-defined mass with heterogeneous signal intensity on T1- and T2-weighted images indicative of the variably solid and cystic nature of the tumour. High signal intensity on T1-weighted images correspond to areas of haemorrhagic necrosis or debris[21,22]. The signal intensity of these areas is variable on T2-weighted images because of the presence of multiple degradation products of haemoglobin. The solid component of the tumour may show iso- to low signal intensity on T1-weighted images and slightly high signal intensity on T2-weighted images[21,22].

CYTOLOGY

Although endoscopic ultrasound-guided fine needle aspiration is operator dependent, it is a well-tolerated minimally invasive procedure that has become the method of choice for the diagnosis of solid and cystic pancreatic neoplasms. The sensitivity for malignant cytology is 85% and the specificity is about 98%[23].

Typically, these smears are very cellular, with neoplastic cells forming loose papillary clusters with central fibrovascular cores. The neoplastic cells are uniform with nuclear indentations. There are multinucleated giant cells, foamy macrophages, and haemorrhagic debris in the background[24,25].

PATHOLOGY

Grossly, solid pseudopapillary neoplasms are round solitary masses with fibrous pseudocapsule. Multicentric tumours are exceptionally rare[26]. They are large tumours ranging from 0.5 cm to 25 cm (mean, 10 cm)[2]. These tumours are typically solid with varying proportion of cystic degeneration. They have a well-demarcated fleshy cut surface with haemorrhagic and necrotic areas[27]. In rare cases, extension into adjacent structures may occur[2].

Microscopically, solid pseudopapillary neoplasms are composed of poorly cohesive epithelial cells forming solid and pseudopapillary structures (Figure 1A and B). The pseudopapillae are formed by epithelial cells loosely arranged around hyalinised stroma that contains thin-walled blood vessels (Figure 1A and B). The neoplastic cells are small and monomorphic. The cytoplasm of the neoplastic cells is eosinophilic or clear, and usually lacks mucin. The nuclei are round to oval and may show grooves, indentations, and clefts. The nuclei have fine chromatin pattern and absent or inconspicuous nucleoli. Mitotic figures are infrequent.

Although not specific, the presence of hyaline globules is a characteristic feature of solid pseudopapillary neoplasms. These globules are diastase-resistant, periodic acid-Schiff (PASD)-positive eosinophilic cytoplasmic inclusions (Figure 1C), corresponding to α-1-antitrypsin granules[2,27]. Most tumours contain foamy histiocytes (Figure 1D), cholesterol clefts, and foreign body giant cells (Figure 1E). Calcifications may be present. Perineural infiltration and vascular invasion is uncommon[28]. Rarely, undifferentiated carcinoma component may be seen[19].

Solid pseudopapillary neoplasms usually express nuclear and/or cytoplasmic β-catenin (Figure 1F). They are also positive for a wide range of antibodies including CD56 (Figure 1G), vimentin (Figure 1H), CD10 (Figure 1I), α-1-antitrypsin, α-1-antichymotrypsin, cyclin D1 (Figure 1J), CD99, claudin 5, claudin 7, and progesterone receptors[2,12,27]. Immunoreactivity for E-cadherin depends on the antibodies used.

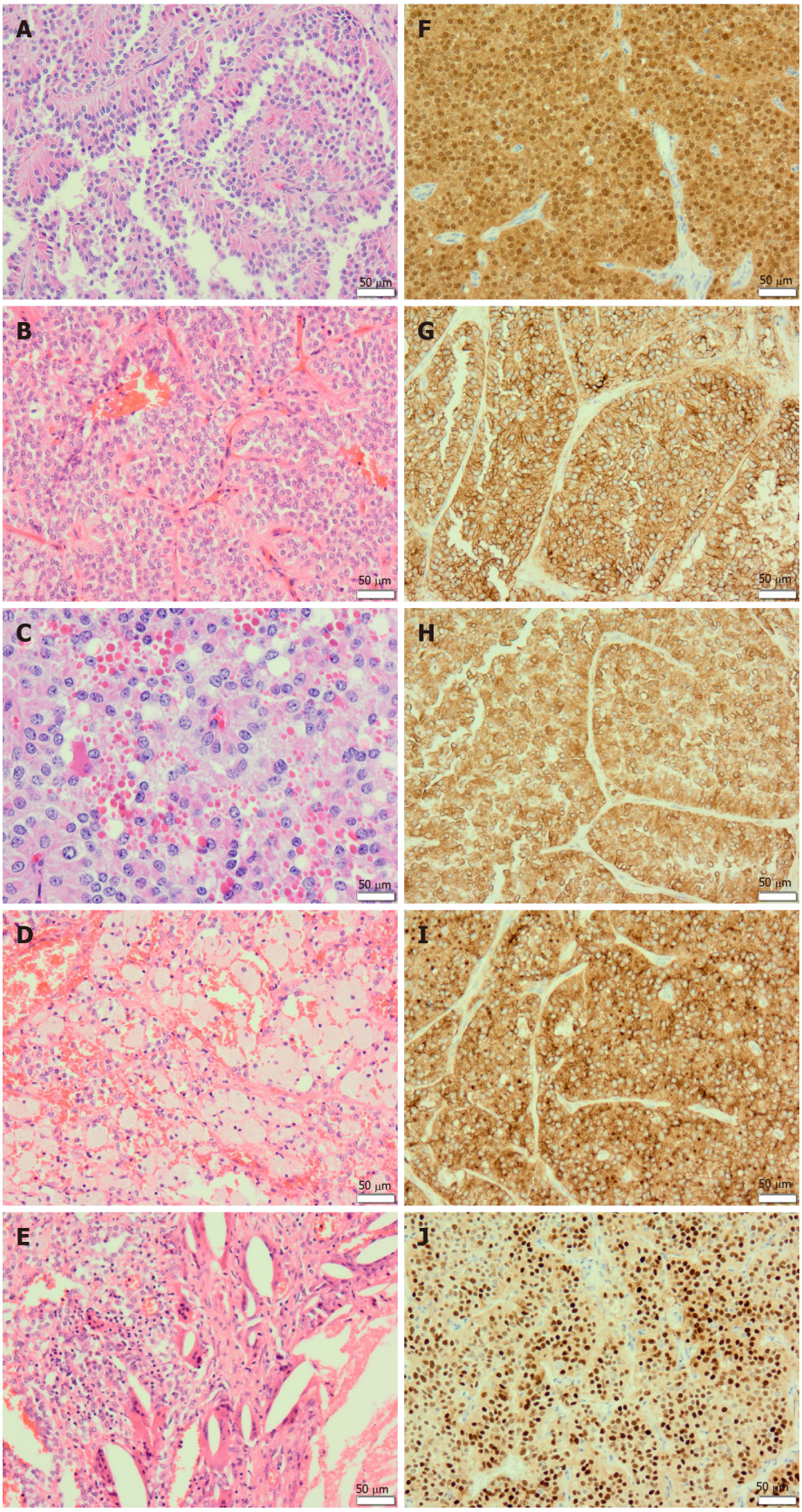

Figure 1 Solid pseudopapillary neoplasm of the pancreas. A: The tumour shows pseudopapillae formed by poorly cohesive cells arranged around hyalinized fibrovascular stalks (200 ×); B: The tumour consists of cells forming solid and pseudopapillary structures (200 ×); C: Solid pseudopapillary neoplasm of the pancreas shows characteristic eosinophilic cytoplasmic hyaline globules (400 ×); D: An example showing foamy histiocytes (200 ×); E: These are cholesterol clefts surrounded by foreign body giant cells (200 ×); F: The tumour shows nuclear and cytoplasmic expression of β-catenin (200 ×); G: The tumour shows immunolabelling

for CD56 (200 ×); H: The tumour is positive for vimentin (200 ×); I: The tumour shows immunolabelling for CD10 (200 ×); J: Solid pseudopapillary neoplasm of the pancreas shows nuclear positivity for cyclin D1 (200 ×).

Antibodies to the intracellular domain of E-cadherin shows an abnormal cytoplasmic/nuclear expression while antibodies to the extracellular domain of the protein shows complete loss of expression[28].

Solid pseudopapillary neoplasms may be focally positive for synaptophysin and neurone-specific enolase. However, these tumours are negative for chromogranin A, trypsin, chymotrypsin, lipase, oestrogen receptors, and BCL10[2,27,28].

MOLECULAR PATHOLOGY

Solid pseudopapillary neoplasms harbour mutations in exon 3 of *CTNNB1*, the gene encoding β-catenin[2,27,28]. They lack the molecular alterations that have been described in pancreatic ductal adenocarcinoma such as KRAS, TP53, SMAD4/DPC4, and CDKN2A[27,28].

B-catenin maintains cell-cell adhesion and regulates gene transcription in the canonical Wnt (β-catenin dependent) signalling pathway[29,30]. β-catenin is regulated by the β-catenin destruction complex composed of proteins including adenomatous polyposis coli, axin, protein phosphatase 2A, glycogen synthase kinase 3, and casein kinase-1[29,30]. In the absence of Wnt signalling, the β-catenin destruction complex targets β-catenin for ubiquitin-mediated proteasomal degradation. However, in the presence of Wnt signalling, the β-catenin destruction complex is inactivated, preventing β-catenin degradation. This leads to β-catenin accumulation in the cytoplasm and eventual translocation into the nucleus, where it acts as a co-transcriptional activator of lymphoid enhancer binding factor/T cell factor (LEF/TCF) family of transcription factors. Activated LEF/TCF family of transcription factors upregulates the expression of a variety of target genes involved in diverse cell functions such as cell proliferation, differentiation, and epithelial-mesenchymal transition. The *CTNNB1* mutations observed in solid pseudopapillary neoplasms and other cancers lead to constitutive activation of the Wnt/β-catenin pathway and abnormal stabilization of cytoplasmic β-catenin[29,30].

Gene expression studies have identified solid pseudopapillary neoplasm-specific mRNA and microRNA expression profiles distinct from other pancreatic tumours[31]. Pathway enrichment analysis of differentially expressed genes in solid pseudopapillary neoplasms has shown that in addition to Wnt/β-catenin signalling pathway, Hedgehog and androgen receptor signaling pathways are also activated in these tumours[31].

Proteomic analyses of solid pseudopapillary neoplasms have confirmed that proteins involved in Wnt/β-catenin signaling (CTNNB1 and DKK4) and proteins that bind directly to β-catenin (FUS, hnRNPM, BGN, NONO, YWHAZ, DDX5, SELENBP1, and FN1) are upregulated in these tumours[32]. Furthermore, 9 proteins involved in metabolism including SLC25A13, GPI, PGK1, HK1, ENO2, PDHB, ALDH7A1, PKM2, and DLD are overexpressed in solid pseudopapillary neoplasms[32].

DIFFERENTIAL DIAGNOSIS

Distinguishing solid pseudopapillary neoplasm of the pancreas from the more common pancreatic ductal adenocarcinoma is not diagnostically challenging. The differential diagnosis of solid pseudopapillary neoplasms include pancreatoblastoma, acinar cell carcinoma and pancreatic neuroendocrine tumour.

Pancreatoblastoma is a malignant epithelial tumour composed of neoplastic cells showing predominantly acinar differentiation with characteristic squamoid nests. Although pancreatoblastomas frequently occur in childhood, they can be seen in adults[33,34,35]. Pancreatoblastomas exhibit malignant behaviour with local infiltration of adjacent structures and distant metastasis at the time of diagnosis or afterwards in the course of the disease[33,34,35]. Both pancreatoblastomas and solid pseudopapillary neoplasms are solid cellular tumours of the pancreas. The features that favour a diagnosis of pancreatoblastomas include predominant acinar units, squamoid nests, prominent central nucleoli, granular eosinophilic cytoplasm containing DPAS-positive zymogen granules, and immunolabelling for trypsin,

chymotrypsin, BCL10, and lipase[2,33,35].

Acinar cell carcinomas are malignant neoplasms of the pancreas characterized by acinar differentiation but without squamoid nests. Unlike solid pseudopapillary neoplasms, acinar cell carcinomas frequently occur in men, lack pseudopapillary structures, and express trypsin, chymotrypsin, lipase, and BCL10. Acinar cell carcinomas are negative for β-catenin, CD56, and CD10. The prognosis of acinar cell carcinoma is poor with a 5-year survival rate of 25%[2].

Solid pseudopapillary neoplasms with a predominant solid pattern can be confused with pancreatic neuroendocrine tumours. In addition, both tumours express synaptophysin and CD56. Typically, pancreatic neuroendocrine tumours are composed of uniform cells with round to oval nuclei. The nuclei are centrally located with characteristic salt and pepper chromatin[2,33]. Features that favour a diagnosis of solid pseudopapillary neoplasms include the presence of solid and pseudopapillary structures, foamy histiocytes, cholesterol clefts, foreign body giant cells, scattered PASD-positive hyaline globules, nuclei with indentations, and expression of nuclear and/or cytoplasmic β-catenin, CD56, CD10, and vimentin.

TREATMENT

Surgical resection is the treatment of choice for solid pseudopapillary neoplasms[3,5]. The type of operation will depend on the site and size of tumour. Common surgical procedures include distal pancreatectomy and splenectomy, spleen preserving distal pancreatectomy, central pancreatectomy, total pancreatectomy, pancreaticoduodenectomy, and pylorus-preserving pancreaticoduodenectomy[3,5]. A Cochrane systematic review comparing the effectiveness of classic Whipple procedure *vs* pylorus-preserving pancreaticoduodenectomy, showed no significant differences in overall survival, post-operative mortality, and morbidity between both procedures except for delayed gastric emptying, which significantly favoured classic Whipple procedure[36].

Although most of these tumours are treated by open surgery[5], a recent systematic review suggested that compared to a traditional open approach, minimally invasive pancreatectomy is associated with decreased intraoperative blood loss, lower blood transfusion requirements, and a shorter post-operative time to diet and hospital stay [37]. However, there were no significant differences in operating time, margin positivity, post-operative morbidity, and post-operative pancreatic fistula rates[37].

PROGNOSIS

The overall prognosis is excellent with a cure rate of > 95% following complete surgical resection[2,3,5]. Of the 2158 patients with solid pseudopapillary neoplasm reported in a systematic review, outcome data were available in 1952 patients with a mean follow-up of 36.1 mo. Eighty-six patients (4.4%) had recurrent disease and twenty-nine patients (1.5%) died of the disease[5]. Long-term survival has been reported for patients with locally advanced, recurrent, and metastatic disease[3,12]. It is worth emphasizing that malignant behaviour cannot be predicted by vascular invasion, perineural invasion, and invasion of adjacent structures in these tumours[2]. However, it has been suggested that tumours with an undifferentiated carcinoma component have a dismal outcome[19], and large tumour size, high proliferation index, and lymph node metastasis may be risk factors for a poor prognosis[38].

CONCLUSION

In summary, solid pseudopapillary neoplasms are rare low-grade malignant tumours occurring predominantly in adolescent girls and young women with an excellent prognosis. It is therefore important to distinguish solid pseudopapillary neoplasms from morphological mimics.

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MINIREVIEWS

Therapeutic plasma exchange in liver failure

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Abstract

The multi-organ failure syndrome associated with acute and acute-on-chronic liver failure (ACLF) is thought to be mediated by overwhelming systemic inflammation triggered by both microbial and non-microbial factors. Therapeutic plasma exchange (TPE) has been proven to be an efficacious therapy in autoimmune conditions and altered immunity, with more recent data supporting its use in the management of liver failure. Few therapies have been shown to improve survival in critically ill patients with liver failure who are not expected to survive until liver transplantation (LT), who are ineligible for LT or who have no access to LT. TPE has been shown to reduce the levels of inflammatory cytokines, modulate adaptive immunity with the potential to lessen the susceptibility to infections, and reduce the levels of albumin-bound and water-bound toxins in liver failure. In patients with acute liver failure, high volume TPE has been shown to reduce the vasopressor requirement and improve survival, particularly in patients not eligible for LT. Standard volume TPE has also been shown to reduce mortality in certain sub-populations of patients with ACLF. TPE may be most favorably employed as a bridge to LT in patients with ACLF. In this review, we discuss the efficacy and technical considerations of TPE in both acute and acute-on-chronic liver failure.

Key Words: Therapeutic plasma exchange; High volume plasma exchange; Acute liver failure; Acute-on-chronic liver failure; Cirrhosis; Liver transplantation; Cytokines

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Core Tip: Multi-organ failure accompanying liver failure is mediated by overwhelming systemic inflammation and altered host immunity. Therapeutic plasma exchange has been proven to be an efficacious therapy in autoimmune conditions and altered immunity. We review the efficacy and technical considerations of therapeutic plasma exchange in both acute and acute-on-chronic liver failure.

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INTRODUCTION

Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) are two distinct classifications of severe hepatic dysfunction associated with secondary multi-organ failures (MOFs), both of which effect significant morbidity and mortality[1-4]. The exact mechanisms by which MOFs are mediated have not been definitively established but are thought to be driven by excessive systemic inflammation and dysregulated immune activation triggered by both microbial and non-microbial factors, and less so by the primary insult to the liver[3,5-7].

The pathogenesis of MOFs in ALF has been attributed to the release of damage-associated molecular patterns (DAMPs) from injured hepatic cells and microbial pathogen-associated molecular patterns (PAMPs) in the presence of superimposed infection or bacterial translocation[7]. The innate immune cells activated by PAMPs and DAMPs produce proinflammatory cytokines [interleukin (IL)-6, IL-1ß, IL-8, tumor necrosis factor-alpha (TNF-α)] that mediate systemic inflammation and further hepatocyte injury[7,8]. In support of this hypothesis, levels of TNF-α and IL-6 have been shown to be significantly higher in patients with fulminant hepatitis when compared to patients with acute liver injury[9].

Similarly, the hallmark of the ACLF clinical syndrome is excessive systemic inflammation and bacterial translocation mediated by PAMPs and DAMPs[1,6,10]. ACLF patients have been shown to manifest elevated levels of pro- and anti-inflammatory cytokines, as well as white blood cell count and C reactive protein. Moreover, there is a proven correlation between cytokine levels and number of organ failures in ACLF[6,11].

Despite advances in the supportive medical management of patients with liver failure, significant morbidity and mortality persist[12,13]. Urgent liver transplantation (LT) remains the definitive treatment in patients with high likelihood of death; however, access to transplant remains limited. In addition, eligibility for transplant can be hampered by psychosocial factors, active substance use, and progressive MOFs that may preclude safe LT or contribute to mortality while awaiting LT[14,15]. Expanded treatment options are needed to bridge critically ill patients to LT or to preserve liver function when LT is either contra-indicated or unavailable. Therapeutic plasma exchange (TPE) has been proposed as a beneficial treatment modality in these patients. The practice of exchange transfusion in patients with cirrhosis dates back to the 1960s when exchange blood transfusion was employed for the treatment of hepatic coma [16]. Therapies were later modified to TPE as apheresis equipment became more widely available and as a means to reduce the risks associated with whole blood transfusion[17,18]. Historically, TPE in liver failure has been primarily described in case series and cohort studies. The first randomized control trial (RCT) describing the utility of TPE in ALF patients was reported in 2016 by Larsen *et al*[19].

TPE in liver failure requires the extracorporeal removal of large compounds from the blood, including albumin-bound and water-soluble toxins and replacement with plasma and/or albumin. As shown in Figure 1, these toxins include cytokines, endotoxins, bilirubin, bile acids, ammonia, and aromatic amino acids[20,21]. These substances have been proposed as important mediators of both hepatic encephalopathy (HE) and MOFs in ALF and ACLF[8,22-24]. By comparison, extracorporeal albumin dialysis (ECAD) systems remove albumin-bound and water-soluble toxins *via* hemodialysis augmented by an albumin-infused dialysate with or without the addition of adsorption columns (charcoal filter and anion exchange resins). These

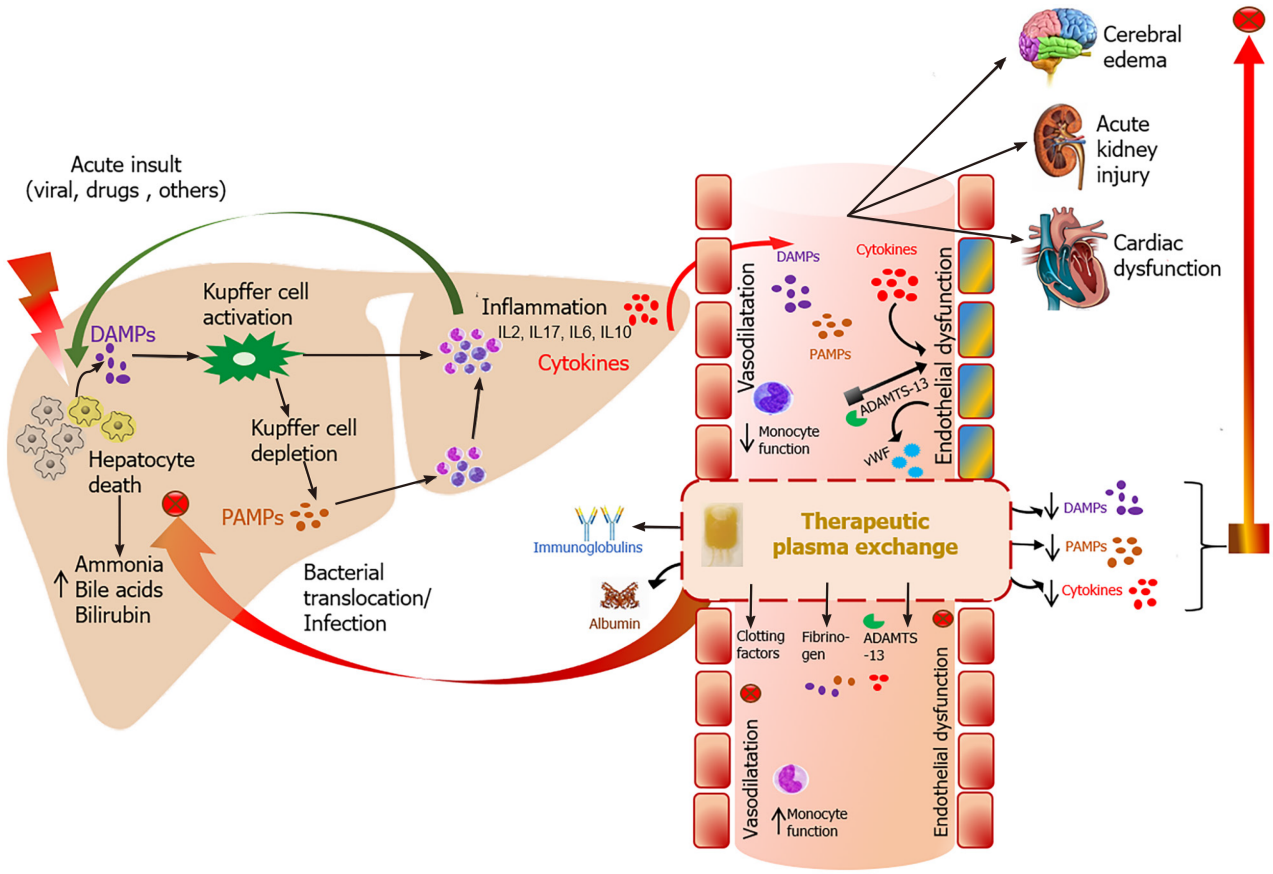

Figure 1 Theoretical model depicting the therapeutic effects of therapeutic plasma exchange in liver failure.

ECAD systems include the molecular adsorbent recirculation system (MARS), single pass albumin dialysis, and fractionated plasma separation and adsorption[25-27].

When considering the therapeutic differences between TPE and ECAD, MARS in particular has been recognized to be more costly than TPE and can entail a more logistically complex initiation. Furthermore, the MARS filter-membrane dictates a size selection threshold of approximately 50 KDa[28], whereas TPE is capable of removing larger molecular proteins, including antibodies, immune complexes, and lipoproteins [29]. To date, no head-to-head adult clinical trial has directly compared TPE with MARS or any of the ECAD systems. However, in a retrospective single center pediatric study comparing MARS with the combination of TPE and hemodialysis, TPE and hemodialysis effected a greater reduction in bilirubin, ammonia, and international normalized ratio[30]. Another theoretical advantage of TPE over ECAD hinges on the exchange of plasma, which replaces plasma proteins, including clotting factors, that may be decreased as a result of impaired hepatic synthetic function in both ALF and ACLF.

EFFECT ON BIOCHEMICAL PARAMETERS AND CLINICAL OUTCOMES

Acute liver failure

TPE has been shown to reduce levels of circulating inflammatory cytokines, improve hemodynamics, and improve transplant-free survival in ALF[9,19,31-33]. While encouraging, head-to-head comparisons between the studies supporting these findings have been challenging due to the broad variation in treatment protocols. Often the volume of exchange, treatment frequency and duration of therapy vary between studies.

Specifically, TPE has been shown to moderate TNF-α, histone-associated DNA (member of the DAMP family), IL-6, IL-8, endotoxins, bilirubin, ammonia, and to improve coagulopathy[9,19,34]. In addition, TPE modulates adaptive immunity in ALF through the reduction of soluble B7 molecules, particularly sCD86[35]. Soluble B7 molecules are produced by injured hepatocytes and increase the expression of

cytotoxic T-lymphocyte-associated protein 4 on CD4+ T cells, resulting in impaired antimicrobial responses and increased susceptibility to infections[35].

In the only RCT designed to study outcomes associated with high volume TPE (HV-TPE) in ALF, patients who received HV-TPE manifested significantly improved mean arterial blood pressure (MAP) with associated reduction in vasopressor requirement when compared to patients who received standard medical therapy (SMT) only[19]. In the same study, plasma creatinine remained stable in the HV-TPE group but increased significantly in the SMT group. Accordingly, fewer HV-TPE patients required renal replacement therapy when compared to those who received SMT. In contrast, Wiersema *et al*[31] reported no significant reduction in vasopressor requirement in ALF patients receiving TPE, despite reporting significantly improved MAP on therapy. Notably, this single arm, single centered study employed standard volume TPE as opposed to HV-TPE.

In addition to hemodynamic benefits, TPE has been shown to reduce ammonia level, improve HE grades and cerebral hemodynamics independent of simultaneous filtration or dialysis[33,36]. However, TPE has not been shown to effect significant differences in intracranial pressure (ICP) in ALF, though few patients in Larsen's study underwent invasive ICP assessment (32 of the randomized 182 patients)[19]. On the contrary, a retrospective review of 43 patients with Wilsonian-ALF who received HV-TPE manifested no improvement in ammonia or creatinine levels, but did demonstrate improved transplant-free survival at 90 d[37].

Finally, Larsen's RCT in ALF demonstrated a significant improvement in transplant-free survival in patients who received HV-TPE when compared to SMT [hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.36-0.86, P = 0.0083], with no difference in outcomes between paracetamol and non-paracetamol etiology of liver failure[19]. In subgroup analysis of the same study, HV-TPE was shown to specifically improve survival among patients not listed for LT due to contraindications. By contrast, no survival benefit was identified in patients who received HV-TPE as a bridge to LT. Other non-randomized studies in ALF have reported improvement in survival days with TPE in non-transplanted patients[38,39]. There have been no studies to date that have examined the combination of TPE with any of the ECAD systems in ALF patients.

Acute on chronic liver failure

Patients with ACLF have been shown to manifest significantly higher levels of cytokines (TNF- alpha, IL-10, IL-2, IL-4, and IFN-Y) compared to healthy controls. These same cytokines are also effectively reduced after TPE[40]. In the same study by Mao *et al*[40], higher cytokine levels predicted poor prognosis irrespective of the treatment received. Moreover, bilirubin levels, coagulopathy, and ammonia levels have been shown to improve after TPE-based therapy[41-43]. The effect of TPE on blood pressure and vasopressor requirement in ACLF patients has not been reported. In their single center and small sample size study, Stahl et. al. reported no difference in vasopressor requirement between patients who underwent TPE *vs* SMT[44].

TPE has been shown in limited series to improve survival in ACLF; however, this data is limited by protocol variation. Many of these studies have been performed in Asia among patients with hepatitis B virus- (HBV) related ACLF, used different definitions for ACLF, combined TPE with other liver support systems, and were single center retrospective studies[42,45-47]. Tan *et al*[48] reported improved survival with TPE-based therapies (combined with other extracorporeal therapy) compared to SMT in non-transplanted patients at 30 d and 90 d with a pooled odds ratio (OR) of 0.60 [95%CI: 0.46-0.77]. In the only RCT of TPE in ACLF, patients with HBV ineligible for LT who received TPE-based therapies manifested significantly improved survival rates when compared to patients who received SMT (60% *vs* 47%, P < 0.05) at 90 d[47]. In addition, Mao *et al*[45] demonstrated improved survival with TPE among patients with HBV-ACLF and model for end-stage liver disease (MELD) scores between 20-30 (50%) when compared to patients with MELD scores above 30 (31.7%)[45]. Whether the results of these studies can be extrapolated and generalized to the ACLF patient population at large remains uncertain. Stahl *et al*[44] retrospectively studied the differences in outcomes between ACLF patients bridged to LT *vs* patients bridged to spontaneous recovery. In this study, the risk of 30-d mortality was significantly lower in LT candidates (bridge to transplant group) than in non-transplant candidates (recovery strategy group) treated with TPE (HR 0.35, 95%CI 0.14-0.87, P = 0.024).

As described above, TPE is commonly combined with another dialysis modality depending on the individual patient profile (coagulopathy, renal function, HE, or water and/or electrolyte imbalance). Although continuous renal replacement therapy (CRRT), without TPE, is commonly employed in liver failure-induced severe hyperam-

monemia to reduce the risk of cerebral edema and intracranial hypertension (ICH)[49,50], no head-to-head comparison study has yet been done to compare ammonia clearance in TPE *vs* CRRT. Among patients with HBV-ACLF, Yao *et al*[43] compared TPE with double plasma molecular adsorption (DPMAS) therapy, a special broad-spectrum adsorption column that binds inflammatory mediators and bilirubin. Their group found a significantly higher rate of 28-d survival in the TPE with DPMAS group compared with TPE alone (57.4% *vs* 41.7%, $P = 0.043$) only among patients with intermediate and advanced stage ACLF (defined as prothrombin activity less than 30%)[43]. Separate studies have shown that DPMAS alone or in combination with TPE in ACLF does not confer survival benefits despite increasing the clearance of bilirubin [42,43].

Severe acute alcohol-associated hepatitis (SAH) is recognized to be a common precipitant of ACLF[5]; however, TPE has not been specifically studied in this important patient population. Moreover, sub-group analysis of the limited number of patients with alcohol-associated liver disease included in the available trials has not been described. Case reports suggest that TPE with standard medical therapy may lead to clinical improvement in patients with SAH[51,52]. Randomized, controlled trials in patients with SAH are needed to better define the therapeutic effect of TPE for this indication.

TECHNICAL ASPECTS

TPE can be performed by either centrifugation or filtration-based mechanisms. Centrifugation separates the blood into its components using density, whereas filtration uses a hollow fiber design to separate the plasma from the cellular components. Both centrifugation and filtration-based systems are similar in safety, efficiency, therapeutic effects[53,54], and are approved by the Food and Drug Administration for use in the United States. TPE is usually provided in collaboration with nephrologists or hematologists depending on the center's preference.

REPLACEMENT FLUID, VOLUME, AND DURATION

Acute liver failure

Typical TPE treatments exchange 1 to 1.5 times the patient's estimated plasma volume, approximately 3 L in an average sized adult. For reference, a plasma volume is an estimate of the total volume of plasma in an individual and is a common unit of measurement in therapeutic apheresis procedures. Plasma volume can be calculated from estimated total blood volume using common physiological variables, including an individual's sex, height, weight, body muscle composition, and hematocrit[55]. The removal of substances using TPE follows the formula: $y/y_o = e^{-x}$, where y and y_o are the concentration of the removed substance after and before plasma exchange and x is the number of plasma volumes processed[56]. A 1 to 1.5 plasma volume exchange will remove approximately 70% of the substances in the intravascular space[56].

The only RCT comparing TPE and SMT in ALF patients studied HV-TPE, defined as plasma replacement at 15% of ideal body weight or 8 to 12 L per session[19]. HV-TPE should remove approximately 90%-98% of the toxins in the intravascular space. The majority of studies on TPE in ALF patients before this RCT treated one plasma volume (2 L to 4 L) during each exchange[38,57-59]. Recently, Stahl *et al*[60] in their single center study compared 20 patients with ALF who received low volume TPE and SMT with 20 matched historical controls who received SMT only. TPE volume exchange was employed using 3 L to 4L per session daily until clinical improvement or LT. No head-to-head comparison of standard volume and HV-TPE in ALF has been performed, but the current evidence favors HV-TPE for ALF[61,62].

There is also no consensus or evidence-based strategy for the frequency and duration of treatment. A small single center study showed that one treatment session of TPE is associated with improvement in biochemical parameters and survival in patients with Wilsonian ALF[37]. The RCT by Larsen et. al performed HV-TPE for 3 consecutive days[19]. Other studies employed either the same regimen or every other day treatments, and continued until the patient improved clinically, died, or underwent LT[63-65]. The most commonly used replacement fluid is plasma, although albumin or plasma substitute is sometimes used in conjunction with plasma[66-69]. However, no studies have used albumin alone as a replacement fluid. Plasma is typically chosen as a replacement fluid as it contains coagulation factors and is

thought to replenish those missing as a consequence of the underlying liver dysfunction.

Acute on chronic liver failure

All studies in the ACLF population have used standard volume replacement ranging from 2 L to 4.5L exchange per session. Most studies utilized plasma as replacement fluid and performed TPE sessions 2 to 3 times per week and continued until clinical improvement, transplant, or death[41,70-72]. Only one study reported daily plasma exchange, but the proportion of the study population that received daily exchanges was not described[41].

ANTICOAGULATION

Sodium citrate and heparin are the two common anticoagulants employed to prevent clotting of the extracorporeal circuits. The patient's clinical condition and physician's preferences guide selection; both agents can be used if a single agent is inadequate for anticoagulation. Citrate is preferred because of its shorter half-life of 30-60 min, favorable safety profile, rapid reversibility with intravenous calcium, and its minimal systemic anticoagulation effect[73]. Sodium citrate undergoes hepatic and renal metabolism. Patients with liver failure are particularly susceptible to citrate toxicity as a consequence of impaired hepatic metabolism, often exacerbated by concomitant renal impairment. Citrated plasma replacement fluid can further worsen the risk of procedural hypocalcemia. Citrate is partly cleared by the kidney and can be safely utilized in acute kidney injury as long as the acid-base balance is closely monitored[74,75]. In a single study, tandem procedure with dialysis reduced the risk of citrate toxicity in ACLF patients undergoing TPE[76].

Common adverse effects of citrate include hypocalcemia (with or without symptoms) and metabolic alkalosis. Symptomatic hypocalcemia is not uncommon and occurs in 1.5% to 9% of all patients undergoing TPE[74]. Notably patients receiving TPE for liver failure are at increased risk of hypocalcemia due to the associated metabolic impairment. Prophylactic calcium replacement based on citrate load and continuous ionized calcium monitoring is recommended[29]. Supplementation with Calcium gluconate or Calcium chloride can reduce the risk of symptomatic hypocalcemia[77].

Some physicians favor heparin because of the associated risks with citrate as described above. The application of both unfractionated and low molecular weight heparin have been reported[78,79]. Nevertheless, most patients can undergo filtration-based TPE without the need for anticoagulation similar to anticoagulation-free hemodialysis and hemofiltration[80-82].

COMBINATION WITH OTHER EXTRACORPOREAL THERAPY

Acute kidney injury requiring CRRT is a common manifestation of MOF in both ALF and ACLF[83-85]. In addition, CRRT is commonly utilized in patients with severe hyperammonemia to reduce the risk of ICH and cerebral edema[49,50,86]. CRRT is usually delivered over 24 h and the interruption of CRRT for TPE may compromise the duration of CRRT. Moreover, additional vascular access for TPE exposes the patient to the otherwise avoidable risk of catheter related complications. Simultaneous dialysis and TPE was first introduced in 1999; descriptions of the safety and feasibility of the combined therapies are limited to case reports and case series[21,87-90]. There are no defined standards for connection; tandem procedures connected in series or parallel have been reported in the literature[21,80,87,75,91]. These tandem connections have the advantage of minimizing vascular access procedures.

The combination of TPE with other extracorporeal therapies aside from CRRT in adults is not well described. In a randomized controlled study from Huang *et al*[92], MARS in combination with TPE was shown to reduce serum total bilirubin more effectively when compared with MARS monotherapy. There was no significant difference in survival between the two groups. However, the theoretical benefit of MARS therapy combined with TPE is unclear, as both therapies rely on the removal of albumin-bound toxins. TPE employed simultaneously with extracorporeal membrane oxygenation (ECMO) in adults with liver failure has not been reported. However, tandem ECMO, TPE, and CRRT combination therapy has been described in the

pediatric population with sepsis-induced multiorgan failure[93].

COMPLICATIONS

The common complications associated with TPE are related to the choice of anticoagulation, replacement fluid, and vascular access. This includes citrate-induced hypocalcemia, hemodynamic instability, and transfusion reactions. In their RCT of HV-TPE in ALF patients, Larsen et. al found no significant differences in cardiac arrhythmias, pancreatitis, transfusion related acute lung injury, acute respiratory distress syndrome, hemorrhage, and infection between patients who received HV-TPE *vs* SMT[19]. A prospective study comparing HV-TPE with SMT in Wilsonian ALF similarly demonstrated no significant difference in the incidence of complications[37]. In addition, TPE has been shown to be safe and tolerable in ACLF patients; severe procedure-related adverse effects have not been reported[44,47]. An open label RCT in ACLF patients reported a higher rate of hypotension in patients who received TPE-based therapy compared to SMT (20.2% *vs* 9.2%, $P = 0.02$)[46]. Moreover, there were no significant differences in the rates of bleeding, infection, and respiratory failure between groups[47].

CURRENT GUIDELINES

The 2019 American Society for Apheresis (ASFA) has recommended HV-TPE as a first line therapy for ALF and fulminant Wilson disease. In ALF, ASFA recommends performing at least 3 HV-TPE procedures daily and to consider performing daily treatments until LT or liver recovery. In fulminant Wilson disease, daily standard volume plasma exchange treatments until LT or liver recovery is recommended[61]. The 2016 European Association for the study of liver disease recommended HV-TPE as a level I, grade I evidence in ALF, but no recommendation has been made for ACLF [62]. The 2011 American Association for the Study of Liver Disease guidelines suggested plasma exchange as a means to acutely lower serum copper and limit copper-mediated kidney damage in Wilsonian ALF while waiting LT. However, no recommendation was made for the general use of TPE in ALF and ACLF patients[94].

CONCLUSION

Advanced therapies aimed at improving survival in liver failure rely on the removal of toxins and inflammatory mediators while simultaneously supporting the synthetic and metabolic function of the liver while awaiting either LT or spontaneous hepatic regeneration. Although no ideal extracorporeal liver replacement therapy yet exists, TPE remains a safe, reliable, and feasible treatment. Future studies should replicate the survival benefit demonstrated by Larsen *et al*[19], examine the role of combination therapies with ECADs, identify which etiologies of ALF and ACLF are best served by TPE, and confirm the optimal exchange volume, frequency, and duration of treatment.

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MINIREVIEWS

Association of non-alcoholic fatty liver disease and COVID-19: A literature review of current evidence

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has swept through nations, crippled economies and caused millions of deaths worldwide. Many people diagnosed with COVID-19 infections are often found to develop liver injury, which, in a small portion of patients, progresses to severe liver disease. Liver injury in the form of elevated transaminases, hyperbilirubinemia and alterations in serum albumin has been observed to be higher in patients with severe forms of the disease. Those who already have insult to the liver from chronic disease, such as nonalcoholic fatty liver disease (NAFLD) may be at the greatest disadvantage. The severity of COVID-19 also seems to be driven by the presence of NAFLD and other co-morbidities. About 25% of the global population has NAFLD. With such a widespread prevalence of NAFLD, understanding the disease progression of COVID-19 and the occurrence of liver injury in this vulnerable population assumes great significance. In this review, we present an overview of COVID-19 infection in patients with NAFLD.

Key Words: SARS-CoV-2; Fatty liver; Mitochondria; Nitrosative stress; Oxidative stress; COVID-19; Metabolic associated fatty liver disease; Nonalcoholic fatty liver disease; Progressive liver disease; Nonalcoholic steatohepatitis

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Core Tip: Liver injury in the form of elevated transaminases and hyperbilirubinemia in coronavirus disease 2019 (COVID-19) may be attributed to multiple factors, including the presence of pre-existing liver disease. The presence of nonalcoholic fatty liver disease (NAFLD) in patients with COVID-19 is likely to make them susceptible to severe forms of liver injury. Given the high prevalence of NAFLD worldwide, it is important to understand the implications of COVID-19 in such patients including role of comorbidities, disease progression, and the severity of COVID-19.

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INTRODUCTION

The worldwide figures of coronavirus disease 2019 (COVID-19) presently stand at 154640649 confirmed cases with 3232285 deaths[1]. Although primarily a respiratory syndrome, COVID-19 has been reported to cause liver injury in multiple studies, including metanalyses[2-4]. The incidence of liver injury as assessed by several indicators like transaminases, bilirubin and albumin has been found to be higher in patients with severe COVID-19 infection[3,5]. Increasing severity of liver chemistry abnormalities on hospital admission predicts early in-hospital mortality in COVID-19 patients[4].

There is a high global burden of pre-existing liver disease[6], including chronic viral hepatitis, nonalcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease (ALD). For example, in China, where the pandemic originated, liver cirrhosis affects around 7 million people[7]. Similarly, in the United States which has the highest number of recorded COVID 19 cases, about 4.5 million of adults are diagnosed with chronic liver disease[8]. In a cross-sectional analysis based on data from National Health and Nutrition Examination Surveys (NHANES), it was observed that the prevalence of NAFLD (by US-Fatty Liver Index) spiked from 20.0% (1988-1994) to 28.3% (1999-2004) to 33.2% (2009-2012) and 31.9% (2013-2016)[9]. This increasing trend is in concurrence with increases in obesity, diabetes mellitus, hypertension and insulin resistance[9]. It is also to be noted that many patients with fatty liver disease remain undiagnosed and are incidentally detected. Therefore, the actual prevalence of NAFLD may be much higher. In such a background of widespread prevalence of chronic liver disease especially NAFLD, the incidence of liver injury in COVID-19 and its impact on disease progression assumes greater significance. In a recent study, we found that mortality associated with the known risk factors of COVID19 (hypertension, diabetes, male sex, and old age) was accentuated in the presence of liver chemistry abnormalities in those diagnosed with COVID-19[4].

PATHOGENESIS AND PATTERN OF LIVER INJURY IN COVID-19

The pathogenesis of liver injury in COVID-19 is multifactorial. A number of factors have been identified for perpetuating and potentiating liver injury in COVID-19. Direct viral-mediated hepatocyte injury, liver injury ensuing from cytokine release syndrome, drug-induced liver injury and ischemic hepatitis are just some of the mechanisms responsible for hepatic dysfunction in COVID-19[10]. The pattern of liver injury in COVID-19, as evidence from multiple studies, is a rise in liver enzymes [primarily aspartate aminotransferase and alanine aminotransferase (ALT)] with mild increases in bilirubin[10]. In a study by Cai *et al*[11] from China, among 417 patients, 20.75% had hepatocellular pattern of liver injury, 29.25% had a cholestatic pattern, while 43.4% had a mixed type of liver injury. Liver injury is transient in most cases and liver enzymes usually return to normal with recovery from COVID-19[2]. The rampant use of multiple medications-antibiotics, antivirals, nonsteroidal anti-inflammatory drugs, herbal medications, interferon and other immunomodulators has been as-

sociated with increased liver test abnormalities[11]. To add to this is the presence of pre-existing liver disease in patients with COVID-19 which makes the pathogenesis of hepatic dysfunction even more complex. In the largest reported cohort of 745 chronic liver disease and cirrhotic patients with COVID-19, it was observed that baseline liver disease stage and ALD were independent risk factors for death from COVID-19[12]. The APASL COVID19 Liver Injury Spectrum (APCOLIS) Study has shown that pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection. Additionally, if these patients also have chronic liver disease, diabetes and/or obesity, they are more vulnerable and should be closely monitored[13]. In a study on 12 COVID-19 patients with pulmonary embolism on autopsy, hepatic steatosis involving 50-60 percent of hepatocytes was found in all patients. This data supports the fact that pre-existing liver diseases like ALD and NAFLD could play significant roles in COVID-19 progression[14].

COVID-19 IN THE SETTING OF NAFLD

Whether NAFLD is an independent or dependent determinant for worse outcomes in COVID-19 has been a hot topic of debate in recent times. A look at the figures and the results of several studies done in the midst of this pandemic opens up conflicting and debatable viewpoints in this regard. Interestingly, in this above-mentioned cohort of 745 patients, 43% of patients had NAFLD, while hypertension, diabetes and obesity — established risk factors for developing severe COVID-19 — constituted the major comorbidities[12]. While one can argue that it is ALD and not NAFLD which has been observed to be a significant predictor of mortality in COVID-19, it would be worthwhile to take note of the fact that patients with ALD had more severe underlying liver disease compared to those with NAFLD. In a retrospective study on 202 patients with confirmed COVID-19, it was observed that patients with NAFLD had a higher risk of disease progression, greater likelihood of abnormal liver function from admission to discharge and longer viral shedding time[15]. An association between the presence of metabolic associated fatty liver disease (MAFLD) and COVID-19 severity was observed in younger patients[16]. In another study on 589 patients from the eastern Mediterranean region, NAFLD has been found to be a predictor of liver injury in COVID-19. However, quite contrary to the results of other studies, NAFLD did not seem to be an independent predictor of mortality, disease severity, or markers of disease progression[17]. Similarly, in another study by Huang *et al*[18], although more patients with NAFLD developed abnormal liver function tests, concurrent NAFLD was not found to be associated with adverse clinical outcomes in patients with COVID-19. Table 1 shows a summary of the various studies describing the association between NAFLD and COVID-19.

MECHANISM OF COVID-19 PROGRESSION IN PATIENTS WITH NAFLD

The role of inflammation in the pathophysiology of NAFLD has been well recognized [19]. It has been hypothesized that hepatic inflammation resulting from pro-inflammatory cytokines released by adipose tissue is even furthered by COVID-19[15]. The liver is a major site of lipid metabolism and the generation of lipid species plays an important role in regulating metabolic inflammation. The complex pathways in lipid metabolism drive innate immunity and have been found to affect the progression to steatohepatitis and fibrosis in NAFLD[20]. Additionally, NAFLD patients are found to have elevated plasma levels of von Willebrand factor and circulating plasminogen activator inhibitor type 1[21]. This has been hypothesized to predispose such patients to higher risks of adverse cardiovascular events. It has also been postulated that hepatic and systemic immune responses due to underlying NAFLD could contribute to the cytokine storm in younger patients with COVID-19[16,22]. While severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to angiotensin-converting enzyme 2 (ACE2) receptors and attaches to the cell, cellular entry is made possible by cleavage of the SARS-CoV-2 spike protein by transmembrane serine protease 2 (TMPRSS2)[23]. Interestingly, it has been seen that while there were no differences in liver mRNA expression of both ACE2 and TMPRSS2 between subjects without liver injury and patients with only steatosis, upregulation of these genes occurred in obese patients with nonalcoholic steatohepatitis (NASH). Additionally, there was positive correlation of ACE2 and TMPRSS2 with NAFLD activity score and TMPRSS2 positively correlated with weight, body mass index (BMI) and cholesterol[24]. However,

Table 1 Summary of various studies describing the association between nonalcoholic fatty liver disease and coronavirus disease 2019

Ref.	Type of study	Study origin	Number of COVID patients/number of NAFLD/NASH patients	Overall impact of occurrence of concomitant NAFLD and COVID-19	Impact of NAFLD on COVID-19 liver injury
Marjot *et al*[12]	Retrospective	Multinational Cohort	No. of COVID patients with CLD: 745; No. of NAFLD patients: 322	Baseline liver disease stage and ALD are independent risk factor for death from COVID-19	NA
Sarin *et al*[13]	Retrospective	Multinational Cohort	No. of COVID patients with CLD: 228; No. of fatty liver disease patients: 113	CLD patients with diabetes and obesity are more vulnerable and should be closely monitored	Comorbidities like MAFLD, obesity and diabetes were present in 80% of the patients. MAFLD was the commonest cause for CLD without cirrhosis. Obese cirrhotics had more acute liver injury than normal weight patients [OR 8.9 (95%CI: 1.9-38.8) P = 0.02]. Patients of CLD with diabetes had higher risk [57.7% *vs* 39.7%, P = 0.01, OR = 2.061.14-3.73)] of liver injury
Ji *et al*[15]	Retrospective	China	No. of COVID patients: 202; No. of NAFLD patients: 76	Patients with NAFLD also had a higher risk of progression to severe COVID-19 and longer viral shedding time	Patients with NAFLD had a higher likelihood of abnormal liver function from admission to discharge [70% (53/76) *vs* 11.1% (14/126); P < 0.0001] compared to patients without NAFLD
Zhou *et al*[16]	Retrospective	Wenzhou, China	No. of COVID patients: 327; No. of patients with fatty liver disease: 93	In patients younger than 60 yr, a more than 2-fold higher prevalence of severe COVID-19 was observed in those with MAFLD compared to those without. MAFLD was not associated with disease severity in multivariable analysis in elderly patients	NA
Mushtaq *et al*[17]	Retrospective	Qatar	No. of COVID patients: 589; No. of NAFLD patients: 320	NAFLD was not an independent predictor of mortality, disease severity on presentation, or disease progression in patients with COVID-19	Presence of NAFLD was a predictor of the development of mild liver injury (OR 2.99; 95%CI: 1.62-4.37; P = 0.000) and moderate liver injury (OR 5.104; 95%CI: 3.21-6.99; P = 0.000)
Huang *et al*[18]	Retrospective	Jiangsu, China	No. of COVID patients: 280; No. of NAFLD patients: 86	No patient developed severe liver-related complications during hospitalization	Concurrent NAFLD was identified as a risk factor of elevated ALT (OR, 2.962; 95%CI: 1.745-5.028; P < 0.001) on univariate analysis. Concurrent NAFLD (OR, 2.956; 95%CI: 1.526-5.726; P = 0.001) was an independent risk factor of ALT elevation on multivariate analysis
Fondevila *et al*[24]	Retrospective	Spain	No. of patients without NAFLD: 17; No. of patients with NAFLD: 77	Obese patients with NASH show markedly higher expression of *ACE2* and *TMPRSS2*, suggesting that advanced stages of NAFLD might predispose individuals to COVID-19	NA
Biquard *et al*[25]	Retrospective	France	No. of patients without fatty liver disease: 28; No. of patients with fatty liver disease: 26	MAFLD is not associated with changes in liver expression of genes implicated in SARS-CoV-2 infection	NA
Zheng *et al*[28]	Retrospective	Wenzhou, China	No. of COVID patients: 214; No. of NAFLD patients: 66	Risk of obesity to COVID-19 severity is greater in those with compared to those without MAFLD	NA
Ghoneim *et al*[29]	Retrospective	Multination electronic health records	No. of COVID patients: 8885; No. of NAFLD patients: 102	The adjusted odds ratio of having COVID-19 were higher in patients if they were diagnosed with NASH	NA
Targher *et al*[33]	Retrospective	Zhejiang Province, China	No. of COVID patients: 310; No. of NAFLD patients: 94	Patients with MAFLD with increased FIB-4 or NFS are at higher likelihood of having severe COVID-19 illness, irrespective of metabolic	COVID-19 patients with MAFLD with intermediate or high FIB-4 scores were more likely to have higher liver enzymes [AST > 40 IU/L (%) -27.8/57.1, ALT > 40 IU/L (%) -30.6/42.9],

				comorbidities	compared with their counterparts with low FIB-4 score or those without MAFLD [AST > 40 IU/L (%) 7.9/9.1, ALT > 40 IU/L (%) -13/29.6], $P < 0.001$
Forlano *et al*[34]	Retrospective	Imperial College Healthcare NHS Trust (London, United Kingdom)	No. of COVID patients: 193; No. of NAFLD patients: 61	Presence of NAFLD *per se* was not associated with worse outcomes in hospitalised patients. Mortality was associated with pronounced inflammatory response in NAFLD group	NA
Gao *et al* [35]	Retrospective	3 Chinese hospitals: (the First Affiliated Hospital of Wenzhou Medical University, the Ningbo No. 2 Hospital, and the Ruian People's Hospital)	No. of COVID-19 patients: 167; No. of MAFLD patients: 46	MAFLD patients with elevated serum IL-6 levels at admission are at higher risk for severe illness from COVID-19	NA
Sachdeva *et al*[37]	Pooled analysis	-	No. of COVID patients: 8142; No. of NAFLD patients: 833	NAFLD is a predictor of severe COVID-19, even after adjusting for the presence of obesity	NA

NAFLD: Nonalcoholic fatty liver disease; COVID-19: Coronavirus disease 2019; CLD: Chronic liver disease; ALD: Alcohol-associated liver disease; NA: Not available; MAFLD: Metabolic associated fatty liver disease; CI: Confidence interval; OR: Odds ratio; ALT: Alanine aminotransferase; NASH: Nonalcoholic steatohepatitis; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane serine protease 2; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; AST: Aspartate aminotransferase; IL-6: Interleukin-6.

to complicate matters, in another study by Biquard *et al*[25], none of the genes necessary for SARS-CoV-2 infection-TMPRSS2 and ACE2 included- were differentially expressed between lean or obese controls and patients with simple steatosis or with NASH. Hence the role of underlying NAFLD on the outcomes of COVID-19 infection is still up for debate.

ROLE OF COMORBIDITIES

In such a background of conflicting data, it is worthwhile to analyze the role of comorbidities that are present in patients with NAFLD which might lead to disease progression in COVID-19. It needs no reiteration that NAFLD is usually accompanied by a cluster of several other conditions such as obesity, insulin resistance, dyslipidemia and hypertension, collectively reflecting underlying metabolic syndrome (MS). According to the ATP III criteria, the prevalence of the MS in patients with NAFLD is 22.8%[26]. The strong association between MS and NAFLD has led investigators to term NAFLD the hepatic component of MS[27]. Thus, it is entirely understandable that the presence of these components would potentially cause increased severity of COVID-19. This has been validated by a multicentric study by Zheng *et al*[28] which showed that obesity conferred a nearly sixfold higher risk of severe COVID-19 in patients with NAFLD. A strong positive association between the different components of MS and COVID-19 has also been reported in a population-based study[29]. Obesity and a state of insulin resistance impairs the ability to mount an effective immune response and predisposes to viral infections and respiratory diseases[30,31]. The questions that naturally arise from these observations are: (1) Do the different components of MS drive outcomes in COVID-19 infection and is NAFLD merely a bystander? and (2) Does NAFLD independently drive inflammation and disease progression in COVID-19? The latter is supported by the finding that NAFLD is associated with 30-d all-cause mortality in patients with community-acquired pneumonia with a significant higher degree of association in patients with advanced hepatic fibrosis[32].

IS NAFLD INDEPENDENTLY ASSOCIATED WITH COVID-19 SEVERITY?

In the population-based study by Ghoneim *et al*[29], among different components of MS, NASH was found to be associated with the highest risk of COVID-19 after calculating the adjusted odds ratio. A study by Targher *et al*[33] sheds some light on

this conundrum. In this study on 310 COVID-19 patients, subjects with MAFLD with increased fibrosis-4 (FIB-4) or NAFLD fibrosis score were more likely to have severe COVID-19 illness, irrespective of metabolic comorbidities like obesity and diabetes. Forlano *et al*[34] showed that although NAFLD patients have higher levels of inflammatory markers like CRP compared to the non-NAFLD group, the presence of NAFLD *per se* was not associated with adverse outcomes in the whole study population. Additionally, the presence of intermediate/high-risk FIB-4 scores as well as the presence of liver cirrhosis did not demonstrate any association with adverse outcomes in the NAFLD cohort[34]. Furthermore, a study by Gao *et al*[35] showed that patients with MAFLD and elevated serum interleukin-6 levels at admission are at higher risk for severe illness from COVID-19. However, mortality in the NAFLD cohort was associated with a pronounced inflammatory response. Therefore, what could be inferred from these results is that rather than attributing the severity of COVID-19 to underlying liver disease, it might possibly be a result of the general state of host inflammation in NAFLD patients. Increased liver fat has been independently associated with a higher likelihood of testing positive for COVID-19 in a United Kingdom based study[36]. In a pooled analysis on the association of fatty liver and COVID-19, it was found that NAFLD was associated with an increased risk of severe COVID-19, even after adjusting for obesity as a possible confounding factor[37]. From these results, one is led to believe that NAFLD is indeed independently associated with increased severity in COVID-19. Whether it is the liver disease that is responsible for this increasing severity, the general state of inflammation that accompanies NAFLD or the associated comorbidities that drives the outcome is a matter of debate. Interestingly, a recent study showed that the presence of fibrosis rather than the presence of MAFLD is associated with increased risk for mechanical ventilation, development of acute kidney injury, and higher mortality in COVID-19 patients[38].

LEAN *VS* OBESE NAFLD IN COVID-19

While a BMI greater than 23 kg/sq. metres increases the risk of developing fatty liver disease[39], many people with normal BMI's are capable of developing NAFLD. Additionally, significant proportion of NAFLD patients do not have insulin resistance either[40,41]. Termed 'lean' NAFLD, this so-called 'entity' indicates that there is more to NAFLD than just the mere presence of MS. Zheng *et al*[28] showed that compared to MAFLD patients without obesity those with obesity were at a 6-fold increased risk of severe COVID-19 illness and this association was significant even after adjusting for various parameters like diabetes, hypertension and dyslipidemia. This raises an important question as to whether the worse outcome in NAFLD patients is related to underlying liver disease or related to associated obesity? However, the small sample size of this study makes it difficult to arrive at such sweeping conclusions. Also, the cut-off for obesity in this study has been taken as 25 kg/m^2.

INFLAMMATION IN NAFLD

The bidirectional relationship between hepatic steatosis and insulin resistance is well established[42]. Hepatic steatosis can itself be a driver of insulin resistance and MS has opened avenues for further investigation in the pathophysiology of inflammation in NAFLD. There has been increasing evidence of the presence of significant cross-talk between the liver and other extrahepatic tissues and organs mediated by cytokines, hepatokines. It also involves nuclear factor-κB and c-Jun N-terminal kinase pathways which implies that hepatic inflammation could be a potential driver of cellular dysfunction, cell death and deleterious remodelling in various body tissues and organs [43]. This state of chronic inflammation may directly impact disease severity by adding up to the dysregulated immune response in COVID-19. In a peripheral blood genome-wide gene expression analysis among 1650 participants, it was observed that after adjustment for known risk factors, fatty liver was associated with blood gene sets of extracellular matrix turnover, inflammatory response, immune system activation and a prothrombotic state[44]. This could lead to morbidities in multiple organs including the cardiovascular system, and may, in our opinion, exacerbate disease processes in COVID-19.

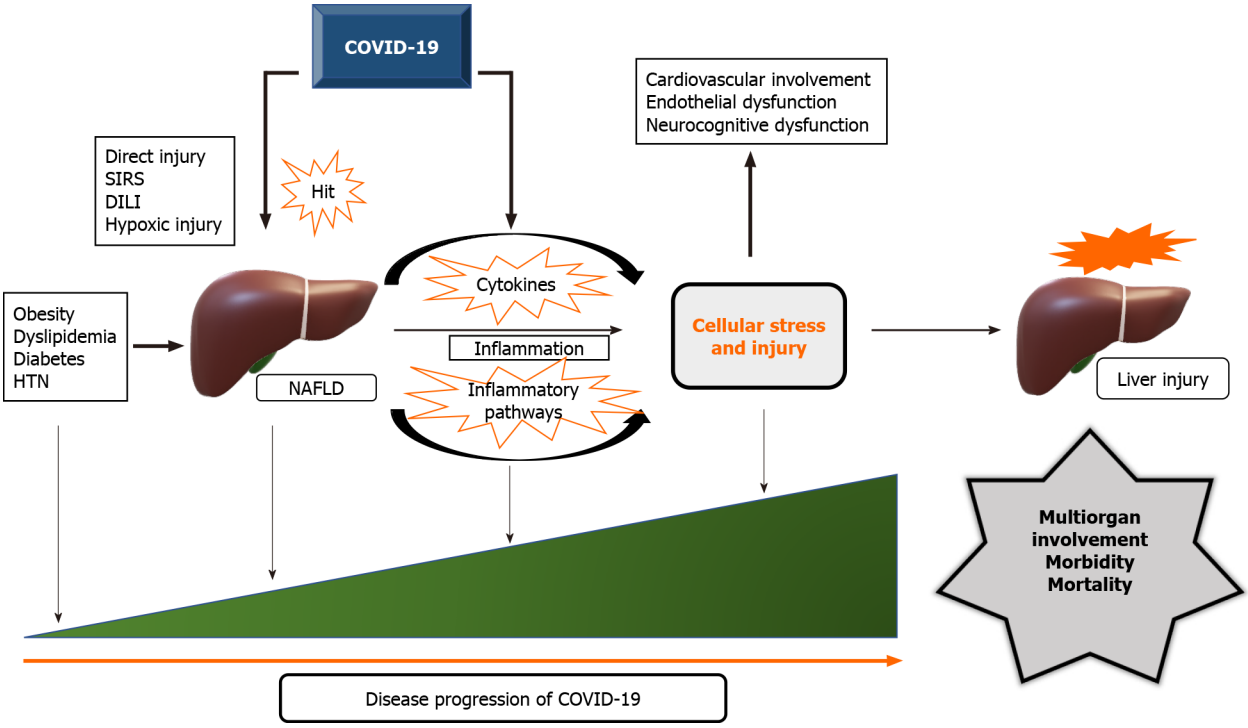

Figure 1 Pathophysiological processes driving disease progression in patients of nonalcoholic fatty liver disease with coronavirus disease 2019 and the impact on hepatic status. NAFLD: Nonalcoholic fatty liver disease; COVID-19: Coronavirus disease 2019.

LIVER INJURY IN NAFLD PATIENTS WITH COVID-19

NAFLD patients have been reported to be more likely to develop liver injury when infected by COVID-19[18]. Median ALT levels and the proportion of elevated ALT were found to be significantly greater in patients with NAFLD than in patients without NAFLD on admission. In addition, the proportion of elevated ALT in patients with NAFLD was significantly higher than patients without NAFLD during hospitalization. However, severe liver-related complications during hospitalization were not observed in any of the patients. Mushtaq *et al*[17] found that NAFLD is an independent predictor of the development of mild to moderate liver injury in hospitalized patients with COVID-19. Moreover, COVID-19 patients with persistent liver injury have been found to have NAFLD and high BMI in one particular study[15]. The APCOLIS study also found that the presence of MAFLD aggravates the risk of liver injury in COVID-19[13]. In the study by Targher *et al*[33], COVID-19 patients with MAFLD with intermediate or high FIB-4 scores were more likely to have higher liver enzymes, compared with their counterparts with low FIB-4 score or those without MAFLD. The reasons for this increased likelihood of liver injury in NAFLD patients affected by COVID-19 could be multifactorial- pre-existing steatohepatitis, systemic inflammation, the severity of COVID-19 itself and a combination of any of these. The 'cocktail' of medications used in this pandemic deserves special attention while evaluating the relationship between NAFLD and COVID-19. Antivirals, antibiotics and glucocorticoids have been the most rampantly used medications in the quest to control COVID-19 and may contribute to liver injury, especially in those with NAFLD.

A summary of the pathophysiological processes that could presumably drive disease progression in patients of NAFLD with COVID-19 and the resulting impact on hepatic status is illustrated in Figure 1.

CONCLUSION

The bulk of the evidence-based on pooled analysis so far shows NAFLD patients are at increased risk of severe COVID-19 infection. However, judging by the results based on few studies that have been carried out to date, it seems the disease severity is determined more by the presence of co-morbidities like obesity, insulin resistance and dyslipidemia which are frequent accompaniments of NAFLD. The studies showing the

association of NAFLD/MAFLD with severity of COVID-19 independent of associated comorbidities have shown conflicting results. The presence of fibrosis rather than the presence of MAFLD/NAFLD is associated with worse clinical outcomes and higher mortality in COVID-19 patients. Additionally, there seems to be an increased likelihood of liver injury in NAFLD patients with COVID-19. Further studies are required to delineate these pathophysiological details.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clostridioides difficile infection in liver cirrhosis patients: A population-based study in United States

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Abstract

BACKGROUND

Clostridioides (formerly *Clostridium*) *difficile* infection (CDI) is an increasingly frequent cause of morbidity and mortality in hospitalized patients. Multiple risk factors are documented in the literature that includes, but are not limited to, antibiotics use, advanced age, and gastric acid suppression. Several epidemiological studies have reported an increased incidence of CDI in advanced liver disease patients. Some have also demonstrated a higher prevalence of nosocomial infections in cirrhotic patients.

AIM

To use a large nationwide database, we sought to determine CDI's risk among liver cirrhosis patients in the United States.

METHODS

We queried a commercial database (Explorys Inc™, Cleveland, OH, United States), and obtained an aggregate of electronic health record data from 26 major integrated United States healthcare systems comprising 360 hospitals in the United States from 2018 to 2021. Diagnoses were organized into the Systematized Nomenclature of Medicine Clinical Terms (SNOMED–CT) hierarchy. Statistical analysis for the multivariable model was performed using Statistical Package for Social Sciences (SPSS version 25, IBM Corp™). For all analyses, a two-sided *P* value of < 0.05 was considered statistically significant.

interests (personal or financial).

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RESULTS

There were a total of 19387760 patients in the database who were above 20 years of age between the years 2018-2021. Of those, 133400 were diagnosed with liver cirrhosis. The prevalence of CDI amongst the liver cirrhosis population was 134.93 per 100.000 *vs* 19.06 per 100.000 in non-cirrhotic patients ($P < 0.0001$). The multivariate analysis model uncovered that cirrhotic patients were more likely to develop CDI (OR: 1.857; 95%CI: 1.665-2.113, $P < 0.0001$) compared to those without any prior history of liver cirrhosis.

CONCLUSION

In this large database study, we uncovered that cirrhotic patients have a significantly higher CDI prevalence than those without cirrhosis. Liver cirrhosis may be an independent risk factor for CDI. Further prospective studies are needed to clarify this possible risk association that may lead to the implementation of screening methods in this high-risk population.

Key Words: *Clostridioides difficile*; Chronic liver disease; Liver cirrhosis; Liver transplant

Core Tip: *Clostridium difficile* infections (CDI) are a leading cause of hospital morbidity and mortality. The risk factors for CDI in liver cirrhosis patients are studied in the national data base. CDIs in liver transplantation is a life-threatening situation as these patients are malnourished and immunocompromised. Therefore, special emphasis was given to the cohort with history of liver transplantation and relevant literature was reviewed.

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INTRODUCTION

Clostridiodes difficile is a gram-positive anaerobic bacillus. It is widespread in the surrounding environment and a significant contributor to inpatient mortality in vulnerable subgroups[1]. Risk factors for being predisposed to CDI include advanced age, enteral feeding, smoking, alcohol abuse, and use of antibiotics and acid-suppressive therapy. It is particularly predominant in elderly patients who reside in nursing homes and long-term acute care facilities and have a history of recurrent hospitalizations. CDI carries a significant economic burden on the USA health care system. A recent study by Desai *et al*[2] uncovered that CDI's economic cost was roughly $5.4 billion, with $4.7 billion in the healthcare settings and $725 million in the community.

CDI has a spectrum of clinical symptoms, including nausea, vomiting, abdominal pain, watery diarrhea with the formation of pseudomembranous, progression to fulminant colitis, and even toxic mega colon[3-8]. CDI can culminate in the possible rupture of the large colon, septic shock, and death. Reactive arthritis is also seen as one of the complications of CDI[9].

Broad-spectrum antibiotic use (penicillin, cephalosporins, clindamycin, fluoroquinolones) predispose individuals to selective elimination of healthy gut microbiota and overgrowth of *Clostridium difficile* (*C. difficile)* in the gastrointestinal flora[10,11] with the highest risk of CDI within the first three months of antibiotic exposure[12]. As the environment and normal human gastrointestinal tract are heavily colonized with C. *difficile*[5,13-15], it is just a matter of loss of balance where C. *difficile* invades the protective gastrointestinal barriers through the production of toxins (enterotoxin A, cytotoxin B, binary toxin/CDT) and enzymes (collagenase, chondroitin sulfatase, hyaluronidase) which promote inflammation[16-18]. The virulence and

pathogenicity are compounded by new hypervirulent strains and the potential ability of C. *difficile* to create biofilms *in vivo* (after an *in vitro* demonstration)[19,20]. For instance, *C. difficile*, especially the new hypervirulent strain, NAP1/BI/027 that was uncovered in the year 2000, was responsible for a significant CDI-related mortality increase 5.7 deaths per million in 1999 to 23.7 deaths per million in 2004[21]. CDI is currently considered the most common cause of nosocomial diarrhea in the western world.

CDI's have been classified based on the severity of infection, utilizing the markers of inflammation and organ function, including white blood cell count (WBC), creatinine and albumin levels. Prognostic markers in patients with *C. difficile* colitis included low serum albumin (< 2.5 mg/dL) or a 1.1 mg/dL reduction in serum albumin from baseline, use of multiple antibiotics, and a positive CD cytotoxin in stool after completion of treatment (after seven or more days of treatment)[22].

The poor outcomes with CDI are not uncommon. They are particularly pronounced in patients with underlying chronic comorbidities (congestive heart failure, chronic obstructive pulmonary disease, and chronic kidney disease), history of solid organ transplants and immunosuppressive therapy, and chronic inflammatory diseases, including Crohn's disease and Ulcerative colitis[23-29]. The morbidity and mortality from liver cirrhosis is on the rise[30]. A prospective study by Bouza *et al*[31] that focused on the recent outbreak of *C. difficile* PCR ribotype 027 in Spain uncovered that this strain was most evident in patients with age > 75 years, the male gender, and comorbidities such hypertension, chronic cardiovascular disease, type 2 diabetes, and liver cirrhosis. Interestingly, liver cirrhosis was associated with an increased CDI recurrence risk of 44.4% *vs* 14.8%[31]. The increased prevalence of CDI in patients with advanced liver disease is being investigated as they are already immunocompromised [32,33].

Poor outcomes in cirrhotic patients who acquired CDI are reported in a recent study by Abdalla *et al*[34]. Liver cirrhosis itself can predispose the individuals to nosocomial infections, the deadliest of them being CDI. For instance, several studies have reported that CLD patients with CDI have a higher mortality rate, prolonged length of stay, and higher hospital cost[35-37]. We performed this large database study to re-evaluate the risk and severity of CDI in patients with cirrhosis. Prevalence of *C. difficile* associated disease (CDAD) was determined in the subgroups with established risk factors and comorbidities and prior history of liver disease and liver transplant.

MATERIALS AND METHODS

Database

Our study is a retrospective cohort analysis of a large, multicenter database (Explorys, Cleveland, OH, United States). Explorys aggregates healthcare data of more than 50 million unique patient records. Diagnoses, findings, and procedures are arranged into the Systematized Nomenclature of Medicine–Clinical Terms (SNOMED-CT) hierarchy, whereas prescription drug orders are mapped into RxNorm. Explorys provides an interactive search engine to generate multiple cohorts based on medical diagnoses. Medical data are de-identified, and therefore, it is a Health Insurance Portability and Accountability Act-compliant platform.

Patient selection

Using the Explorys platform, we identified cohorts of patients diagnosed with Liver cirrhosis between the period of March 2018 and March 2021. The study cohorts (liver cirrhosis) were identified by searching the database for a SNOMED-CT diagnosis of "Cirrhosis of Liver" after excluding patients younger than 20 years old. The control group was then identified for those who have no liver cirrhosis. Subsequently, a cohort of patients with "clostridioides difficile infection" diagnosis was identified between the period of March 2018 to March 2021 to calculate the prevalence of CDI in both study groups. Risk factors and predisposing medical conditions associated with CDI, in addition to demographic information, were collected. Possible risk factors included comorbid medical conditions, antibiotics, acid-suppressive therapy, liver transplant, and inpatient/skilled nursing facility settings were investigated using SNOMED-CT diagnostic codes.

Statistical analysis

The prevalence was calculated by dividing the total number of individuals with CDI in each cohort (liver cirrhosis and non-cirrhotics) by the total number of individuals in

each cohort as identified by Explorys [2018-2021], thus making sure that all patients in the denominator had an equal opportunity of being diagnosed with CDI. We calculated the prevalence in subgroups based on sex, race, and age by dividing the number of individuals with CDI in each subgroup by a total number of patients in the same subgroup. A multivariate regression model was constructed using binary logistic regression, with CDI being the outcome to adjust for possible confounding from the covariates listed previously. We used SPSS version 25 (IBM Corp) to perform the multivariate regression analysis. A 2-sided *P* value of < 0.05 was considered statistically significant.

RESULTS

Descriptive epidemiology

There were a total of 19387760 patients in the database who were above 20 years of age. Of those, 133400 were diagnosed with liver cirrhosis. The baseline characteristics of the study population are presented in Table 1. The prevalence of CDI amongst the liver cirrhosis population was 134.93 per 100.000 *vs* 19.06 per 100.000 in non-cirrhotic patients ($P < 0.0001$). Figure 1 represents the prevalence of CDI in different age groups among cirrhotics. Females and Caucasian patients had a higher CDI prevalence than males and non-caucasian among both study groups (Table 2). Patients with nonalcoholic liver disease (NAFLD) as well as an alcoholic liver disease were found to have a higher prevalence of CDI when compared to cirrhotic patients with viral hepatitis (184.9/100.000 in NAFLD *vs* 174.0/100.000 in alcoholic liver disease *vs* 117.9/100.000 in hepatitis C *vs* 81.7/100.000 in hepatitis B) (Figure 2).

Multivariate analysis

The multivariate analysis model uncovered that cirrhotic patients were more likely to develop CDI (OR 1.857; 95%CI: 1.665-2.113, $P < 0.0001$) compared to those without any prior history of liver cirrhosis. The characteristics of the liver cirrhosis patients who developed CDI revealed that they were more likely to be of advanced age (age > 65) as opposed to being young (age < 65) with an OR 2.307, 95%CI: 2.179-2.442 ($P < 0.0001$); had prior use of antibiotics (OR 19.749, 95%CI: 17.3-22.545, $P < 0.0001$); had used acid-suppressive therapy (OR 2.243, 95%CI: 2.122-2.371, $P < 0.0001$); and were mostly inpatients/skilled nursing facility occupants *vs* the community (OR 2.02, 95%CI: 1.911-2.134, $P < 0.0001$). Among cirrhotic patients, those with a history of liver transplant (OR 2.737, 95%CI: 2.087-3.589) were highly likely to develop CDI. The multivariate analysis model with CDI being the outcome is presented in Table 3.

DISCUSSION

The multivariate analysis of this database study holds true for the high prevalence of CDI in cirrhotic patients with all the established risk factors (advanced age, use of antibiotics and acid suppression therapy, enteral feeding, residence at long term care facilities, and frequent hospitalizations) and comorbidities (obesity, hypertension, Diabetes Mellitus, chronic obstructive pulmonary disease, congestive heart failure)[38-45]. The highest prevalence of CDI was reported in patients with a history of antibiotic use. CDI's were also encountered in traditionally low-risk population groups in hospitalized patients with recent antibiotic exposure[46].

The colonization of *C. difficile* has been higher in cirrhotic patients with simultaneous hepatic encephalopathy and advanced stage (Child-Pugh C)[47]. Risk factors of CDI in cirrhotic patients have been determined by Yan *et al*[48] in their latest study (advanced age, antibiotics, and proton pump inhibitors, prolonged and recurrent hospitalizations, hyponatremia, *C. difficile* colonization, hepatic encephalopathy).

The bacterial infections, which generally would have been countered with immunoregulatory mechanisms (chemotaxis, phagocytosis, oxidation, interferon cascade, complement system, inflammatory response) in an immunocompetent individual, go rampant[49-52]. High ammonia levels alter these neutrophilic responses [53]. The inflammation response is also dampened from poor nutrition status and alcoholism, which come with cirrhosis. The mechanisms responsible include reticuloendothelial system dysfunction, portosystemic shunting, hyperdynamic circulation, increased permeability of gut, and bacterial translocation. The systemic inflammatory response syndrome (SIRS) is amplified by the increased nitric oxide (NO) and the

Table 1 Baseline characteristics of study population, *n* (%)

	Patients with history of liver cirrhosis (*n* = 133400)	Patients with no history of liver cirrhosis (*n* = 19254360)
Age groups (yr)		
20-64	73620 (55)	14934590 (78)
> 65	59780 (45)	4319770 (22)
Gender		
Male	71230 (53)	8702330 (45)
Female	62170 (47)	10552030 (55)
Race		
Caucasian	101680 (76)	11165060 (58)
Non-Caucasian	31720 (24)	8089300 (42)
Comorbidities		
Smoking	54400 (41)	2985460 (16)
Alcohol abuse	30040 (23)	359900 (2)
HTN	100830 (76)	5307920 (28)
DM	63770 (48)	2211420 (11)
Obesity	24400 (18)	1148460 (6)
Chronic kidney disease	33640 (25)	853630 (4)
Coronary artery disease	6280 (5)	229410 (1)
Heart failure	39960 (30)	761710 (4)
Chronic obstructive pulmonary disease	42740 (32)	986400 (5)

DM: Diabetes mellitus.

Table 2 Prevalence of *Clostridioides difficile* infection in different age and race groups in patients with liver cirrhosis *vs* no cirrhosis (per 100000)

	Liver cirrhosis	No cirrhosis
Female	176.93	23.31
Male	112.31	14.34
Caucasian	147.52	26.87
African American	54.59	7.34
Hispanic/Latino	257.73	10.96

cytokine storm.

The rate of CDI was significantly high in patients who underwent hepatic transplantation. CDI risk is increased in immunocompromising health conditions involving any solid organ transplant[54,55], including liver transplant recipients[56]. The timeline of CDI in post-transplant patients has been established based on the underlying severity of cirrhosis dictated by model for end-stage liver disease (MELD) scoring, concurrent intra-abdominal hemorrhage, repeat grafting and transplant, vascular complications, infections, and the need for endoscopy with sicker patients developing CDI earlier with higher mortality[57,58]. Musa *et al*[59] researched CDI and chronic liver disease with an additional focus on liver transplant patients. Male sex and high pre-op creatinine levels (> 1 g/L) are considered predisposing risk factors for CDI in the subgroup who received a living donor hepatic transplant[60]. Advanced cirrhosis (High MELD score), impaired renal function in the donor, and postoperative complications (infection, bleeding, wound) leading to prolonged hospital stay were

Table 3 Multivariable model with *Clostridioides difficile* infection being the outcome

Multivariable model	Odds ratio	95%CI	*P* value
Age (> 65 yr *vs* < 65 yr)	2.307	2.179-2.442	< 0.0001
Gender (female *vs* male)	1.29	1.221-1.363	< 0.0001
Race (non-Caucasian *vs* Caucasian)	1.16	1.088-1.237	< 0.0001
Antibiotics	19.749	17.3-22.545	< 0.0001
Skilled nursing facility or inpatients	2.02	1.911-2.134	< 0.0001
Acid suppressive therapy (Proton pump inhibitors or H2 blockers)	2.243	2.122-2.371	< 0.0001
Comorbidities[1]	1.258	1.192-1.328	< 0.0001
Liver transplant	2.737	2.087-3.589	< 0.0001
Liver cirrhosis	1.875	1.665-2.113	< 0.0001

[1]Comorbidities: One or more of the following (heart failure, coronary artery disease, chronic kidney disease, inflammatory bowel disease, chronic obstructive pulmonary disease, diabetes mellitus, obesity, hypertension or metabolic syndrome).

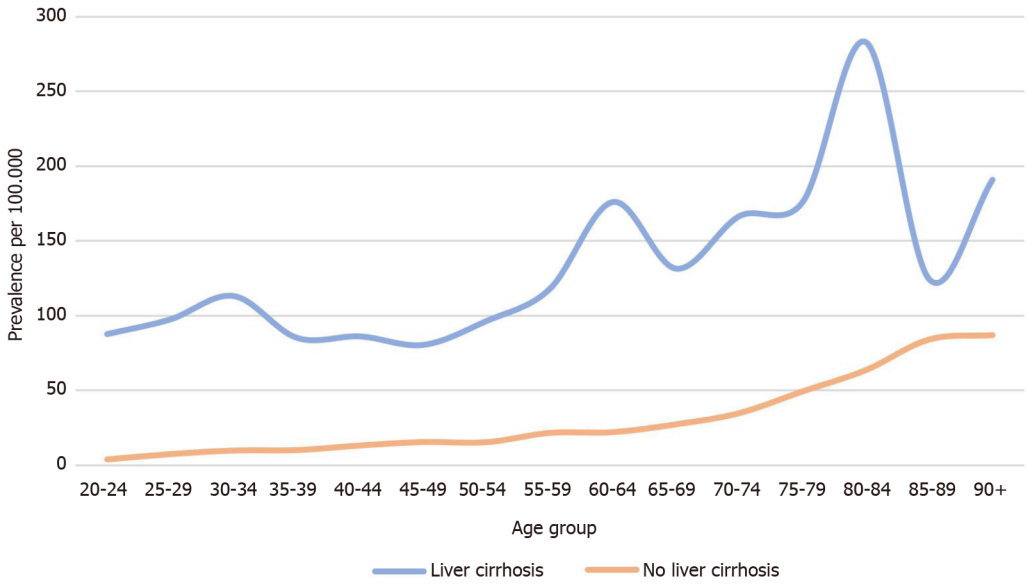

Figure 1 Prevalence of *Clostridioides difficile* infection in patients with liver cirrhosis *vs* no cirrhosis.

concluded predisposing factors for CDI after a deceased liver transplant[57]. Recurrence of pseudomembranous colitis up to five times after living donor liver transplantation has been reported in the literature[61].

The CDI rate was higher in patients with autoimmune hepatitis, prolonged hospital stay, and antibiotic exposure in a study performed by Vanjak *et al*[62]. Hepatitis C is increasingly identified as an underlying viral infection responsible for cirrhosis in patients who developed CDI later in life[63]. Comparing CDI incidence in cirrhosis due to hepatitis B and hepatitis C has not been explored yet. Our study explores this comparison and demonstrates that the prevalence of CDI is higher in inpatient subgroups with hepatitis C than hepatitis B. Sundaram *et al*[36] reported higher inpatient mortality secondary to CDI in patient subgroups with alcohol abuse-related hepatic cirrhosis. Additionally, NAFLD has been identified as a risk factor for CDI by Papić *et al*[64]; after adjusting for other comorbidities, hospitalization rates, and antibiotic exposure (Sundaram *et al*[36]).

Acid suppressive therapy has been implicated with CDI in the general population. A study reported increased 30-d mortality in cirrhotic patients with proton pump inhibitor (PPI) use[35]. The association is being attributed to their excessive unindicated use. The majority of people presenting with variceal bleed get discharged with PPIs renewed on each visit[33,65]. Chronic use of PPIs causes altered gut flora

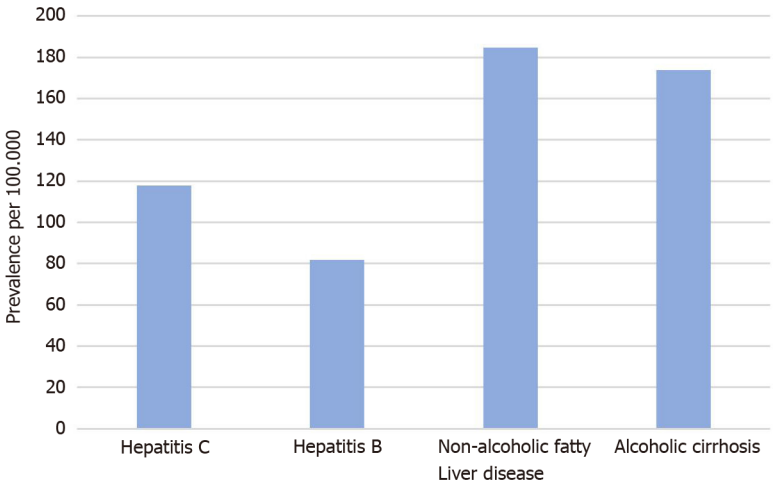

Figure 2 Prevalence of *Clostridioides difficile* infection in cirrhotic patients based on the etiology of cirrhosis.

and motility and decreased neutrophilic function[66]. Long-term PPIs use has been attributed to CDI's by suppressing gastric acid, although the evidence[67-71]. PPIs are said to have worse outcomes in cirrhotic patients than H2 blockers in one study[8]. Hence, the proper need for PPIs should be assessed at each visit and discharge.

Generally, women are more likely to get CDI regardless of their liver function, which was also reflected in our study[72]. The incidence rate of CDI is higher in Caucasians with cirrhosis. A higher incidence and mortality rate from CDI in the caucasian population has been reported in the literature[73-75]. An even higher prevalence of CDI was seen in the African American and Hispanic/Latin subgroups, which could be due to regional data differences[76]. The hospitalization patterns have been fluctuating, and long-term mortality from CDI has been counterintuitively low, as concluded by recent studies[59,76,77].

Vancomycin and metronidazole have been used historically in the treatment of initial and recurrent CDI. Several meta-analyses have been performed, emphasizing the non-inferiority of metronidazole, and thereby, guidelines have been revised. Vancomycin and fidaxomicin are considered the mainstay of antibiotic treatment now, along with fecal microbiota transplantation (FMT). Surgery is pursued when there is a suspicion of toxic megacolon or colon perforation[5,17,78-82]. Lactulose was also evaluated in liver cirrhosis patients carrying *C. difficile* in a study done by Ito *et al*[83] with promising results. Lactulose may increase fecal acidity by decreasing short-chain fatty acids and increasing lactate and acetate, leading to possible suppression of *C. difficile* growth. FMT has been used in patient subgroups with cirrhosis to help with recurrent CDI colonization[78,84]. Additionally, lactulose as a prebiotic may play a prominent role in restoring the hosts' indigenous microbiota and conferring resistance against CDI[85]. Recently, the benefit of preventing CDI by using maintenance rifaximin[86].

The benefit of screening hospitalized cirrhotic patients for *C. difficile* might be purely theoretical, as screening in the absence of symptoms would lead to over-reporting[87, 88]. Meltzer *et al*[89] did a 10-wk surveillance study after screening asymptomatic patients on admission. They demonstrated a higher incidence of CDI during hospitalization in patients who tested positive for *C. difficile* on admission rectal swabs. Whether clinicians should treat a prior CDI carrier state still remains unclear, as most of the positive patients in that particular study had the classical risk factors for CDI (prolonged hospital and rehabilitation stays, exposure to infections, and antibiotics). Third-generation cephalosporins are the treatment of choice for subacute bacterial peritonitis (SBP), which are counterintuitively associated with increased risk of CDI. Both SBP and CDI translate into poor outcomes for the patient[21]. Bactrim and fluoroquinolones (ciprofloxacin, norfloxacin) are recommended as SBP prophylaxis in high-risk patients, but their long-term benefit is questionable for now[90].

C. difficile toxins in stool sample or visualization of pseudomembrane formation on endoscopic or histological examination are diagnostic for CDI. Due to its ability to spread by spore formation[91,92], poor hygiene contributes to its rapid spread *via* the fecal-oral route and can result in outbreaks in health care facilities. Hand hygiene, therefore, has been the cornerstone in the control of CDI spread along with isolation of symptomatic patients and implementation of environmental sanitation protocols[93-

97].

The results obtained from this database are significant due to the large sample size, appropriate gender and racial representation, and inclusion of patients above the age of twenty years. Recent studies have confirmed poor outcomes with concurrent CDI and CLD[37]. All data prior to 2018 has been excluded to determine the persistence of historically established risk factors for CDI based on point prevalence. Relevant comorbidities have been included along with a subgroup of patients with liver transplants. The underlying cause of cirrhosis has also been delineated (Table 2).

The study is at a disadvantage as it is retrospective. The sample size is subjected to selection bias which was attempted to be minimized by relevant inclusion and exclusion criterion. The prevalence of liver cirrhosis in the population database is lower than the general population (0.69 %)[98]. While this may reduce the effective sample size, it has no bearing on the conclusions drawn regarding the risk factors associated with CDI in cirrhotic patients. The inclusion of patient classification based on their MELD score would have indicated the severity of CDI at different cirrhosis stages. The multivariate analysis by Hong *et al*[99] had suggested that the patients with higher MELD scoring are at increased risk of mortality from CDI (1.06 ± 0.02, *P*-value < 0.022 with an increase of 21.5% mortality rate with every five-unit increase of MELD score), and MELD scoring should be used to triage them and monitor their outcomes. However, the application of MELD score in SNOMED-CT would be scrupulous as the routine discharge diagnoses are not updated based on the patient's current MELD scores. Results from future perspective studies with patient cohorts stratified into liver, solid organ transplants and MELD classes can vindicate the yield of *C. difficile* screening in asymptomatic patients.

CONCLUSION

The prevalence of CDI is seven times higher in cirrhotic patients than those without liver cirrhosis. In the multivariate analysis, cirrhotic patients with advanced age, frequent hospitalizations, residence in a nursing home and long-term facilities, along with the use of antibiotics, acid-suppressive therapy, chronic comorbidities, and history of hepatic transplantation, were more likely to develop CDI. Further studies are needed to explore this risk, and precautionary measures are needed to be implemented to prevent CDI in this group of patients.

ARTICLE HIGHLIGHTS

Research background

Clostridium difficile (*C. difficile*) is one of the major causes of nosocomial diarrhea and associated morbidity and mortality. The risk factors of *C. difficile* are historically established. Cirrhosis is a major disease burden in the United States health care system. The risk of morbidity and mortality is higher in cirrhotic patients who acquire *C. difficile* infection.

Research motivation

This research was motivated by the lack of recent large population study describing the risk factors of *C. difficile* in liver cirrhotic patients. We also wanted to study the association in patient cohorts who underwent liver transplant as it was not done previously with such higher sample size.

Research objectives

To determine the prevalence of *C. difficile* infection in patients with liver cirrhosis and to establish the risk factors of *C. difficile* infection in patients with liver cirrhosis with special emphasis on liver transplantation cohort.

Research methods

The authors used the Explorys database to obtain data that was classified using SNOMED diagnostic codes. Prevalence and association were calculated using multivariate regression and SPS Software. Details are in the main manuscript.

Research results

The prevalence of *C. difficile* infection (CDI) amongst the liver cirrhosis population was 134.93 per 100.000 *vs* 19.06 per 100.000 in non-cirrhotic patients. The multivariate analysis model showed that cirrhotic patients were more likely to develop CDI.

Research conclusions

This research study concluded that cirrhotic patients have a significantly higher CDI prevalence, and liver cirrhosis may be an independent risk factor for CDI.

Research perspectives

There is a possibility of reducing the CDI mortality in cirrhotic patients by screening them for CDI. Future prospective studies are needed in this regard.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Hepatocellular injury and the mortality risk among patients with COVID-19: A retrospective cohort study

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Abstract

BACKGROUND

Clearly, infection with severe acute respiratory syndrome coronavirus 2 is not limited to the lung but also affects other organs. We need predictive models to determine patients' prognoses and to improve health care resource allocation during the coronavirus disease 2019 (COVID-19) pandemic. While treating COVID-19, we observed differential outcome prediction weights for markers of hepatocellular injury among hospitalized patients.

AIM

To investigate the association between hepatocellular injury and all-cause in-hospital mortality among patients with COVID-19.

METHODS

This multicentre study employed a retrospective cohort design. All adult patients admitted to Al-Azhar University Hospital, Assiut, Egypt and Abo Teeg General Hospital, Assiut, Egypt with confirmed COVID-19 from June 1, 2020, to July 30, 2020 were eligible. We categorized our cohort into three groups of (1) patients with COVID-19 presenting normal aminotransferase levels; (2) patients with COVID-19 presenting one-fold higher aminotransferase levels; and (3) patients with COVID-19 presenting two-fold higher aminotransferase levels. We analysed the association between elevated aminotransferase levels and all-cause in-hospital

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mortality. The survival analysis was performed using the Kaplan–Meier method and tested by log-rank analysis.

RESULTS

In total, 376 of 419 patients met the inclusion criteria, while 29 (8%) patients in our cohort died during the hospital stay. The median age was 40 years (range: 28-56 years), and 51% were males (n = 194). At admission, 54% of the study cohort had liver injury. The pattern of liver injury was hepatocellular injury with an aspartate aminotransferase (AST) predominance. Admission AST levels were independently associated with all-cause in-hospital mortality in the logistic regression analysis. A one-fold increase in serum AST levels among patients with COVID-19 led to an eleven-fold increase in in-hospital mortality (P < 0.001). Admission AST levels correlated with C-reactive protein (r = 0.2; P < 0.003) and serum ferritin (r = 0.2; P < 0.0002) levels. Admission alanine aminotransferase levels correlated with serum ferritin levels (r = 0.1; P < 0.04). Serum total bilirubin levels were independently associated with in-hospital mortality in the binary logistic regression analysis after adjusting for age and sex but lost its statistical significance in the fully adjusted model. Serum ferritin levels were significantly associated with in-hospital mortality (P < 0.01). The probability of survival was significantly different between the AST groups and showed the following order: a two-fold increase in AST levels > a one-fold increase in in AST levels > normal AST levels (P < 0.0001).

CONCLUSION

Liver injury with an AST-dominant pattern predicts the severity of COVID-19. Elevated serum ferritin levels are associated with fatal outcomes.

Key Words: COVID-19; Liver injury; Aspartate amino transferase; All-cause in-hospital mortality; Serum ferritin; SARS-CoV-2

Core Tip: Liver injury with an aspartate aminotransferase (AST)-dominant pattern can predict the severity of coronavirus disease 2019 (COVID-19). A one-fold and two-fold increase in serum AST levels increased the odds of in-hospital mortality by eleven-fold and thirteen-fold, respectively, compared with individuals with normal AST levels. Our study confirmed an elevated level of ferritin in patients with COVID-19 that was associated with fatal outcomes. Meticulous monitoring is highly recommended for patients with COVID-19 presenting AST-dominant hepatocellular injury, especially those older than 60 years, those with elevated ferritin levels or those with diabetes mellitus.

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INTRODUCTION

Globally, coronavirus disease 2019 (COVID-19) has a substantial impact on the healthcare system. Over time, clinicians have clearly determined that the infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not limited to the lung but also affects the nervous system, gastrointestinal tract and hepatobiliary system[1].

The entry of SARS-CoV-2 into target cells is facilitated by angiotensin-converting enzyme 2 (ACE2) receptors. ACE2 receptors are expressed at high levels in lung alveolar epithelial cells, vascular endothelium and epithelium of the small intestine[2]. This pattern might explain the pathophysiology of gastrointestinal manifestations

associated with COVID-19, such as vomiting and diarrhoea. Moreover, ACE2 receptors are expressed at high levels on cholangiocytes (60% of cells) and to a lesser extent on hepatocytes (3% of cells)[3]. Therefore, the hepatobiliary system may be at increased risk of SARS-CoV-2 infection. The liver appears to be the second most affected organ after the lung[4].

In fact, many case series identified abnormal elevations in the levels of aminotransferases and hypoalbuminemia early and during the progression of COVID-19[5,6]. However, substantial variability in the reported prevalence of liver injury among patients with COVID-19 was noted (14% to 50%)[3]. Moreover, the clinical effect of de novo liver injury on the prognosis of patients with COVID-19 has not been investigated in detail. In addition, multiple clinical comorbidities that might confound liver injury-associated mortality should be studied[7].

Ideally, clinicians should be able to identify patient outcomes to improve health care resource allocation.

The aim of the present study was to investigate whether biomarkers of hepatocellular injury have prognostic value in predicting all-cause in-hospital mortality among patients with COVID-19.

MATERIALS AND METHODS

This multicentre study employed a retrospective cohort design. The medical records of all consecutive adult patients admitted to Al-Azhar University Hospital, Assiut, Egypt and Abo Teeg General Hospital, Assiut, Egypt with confirmed COVID-19 from June 1, 2020, to July 30, 2020 were retrieved and analysed. Both hospitals were designated to treat patients with confirmed COVID-19 by the Egyptian Ministry of Health. The inclusion criteria were hospitalization and adult patients > 18-years-old with confirmed COVID-19 based on a positive nasopharyngeal swab for SARS-CoV-2. Exclusion criteria were non-hospitalized patients, pregnant females, patients with chronic liver disease (in accordance with institutional clinical guidelines, patients with elevated aminotransferase levels were screened for markers of viral hepatitis and markers of autoimmune hepatitis), patients who refused to participate in the study and patients with incomplete data. The institutional review board granted approval for the study protocol.

Exposure measurement

The exposure of interest was the serum levels of aminotransferases at the time of hospital admission. We measured the levels of aminotransferases within 24 h of hospital admission. Elevated aminotransferase levels were defined as either an increase in the levels of aspartate aminotransferase (AST) (> 40 U/L), alanine aminotransferase (ALT) (> 40 U/L) or both proteins compared with the upper limit of normal. We classified our cohort into three groups based on serum levels of aminotransferases: (1) Patients with COVID-19 presenting normal aminotransferase levels; (2) Patients with COVID-19 presenting a one-fold increase in aminotransferase levels; and (3) Patients with COVID-19 presenting a two-fold increase in aminotransferase levels.

Covariates

In every enrolled participant, covariates analysed included baseline patient characteristics, such as age, sex and smoking status, comorbidities, such as diabetes mellitus, hypertension, ischaemic heart disease, chronic kidney disease and chronic obstructive pulmonary disease, Deyo–Charlson index, obesity and initial laboratory investigations and AST/ALT, serum total bilirubin, serum albumin, blood urea, serum creatinine, C-reactive protein (CRP), creatine kinase (CK), serum ferritin and D-dimer levels.

Outcome measurement

The predefined primary outcome of the study was all-cause in-hospital mortality. The secondary outcome was the length of the hospital stay. The vital status of the study participants was obtained from hospital records. The censoring date for follow-up of the outcome was August 15, 2020.

Statistical analysis

Continuous variables were presented as medians and interquartile ranges, and categorical variables were presented as absolute numbers and percentages. For the statistical analysis of group differences, we performed unadjusted binary logistic

regression analyses. We utilized a stepwise analysis adjusted for sex and age as well as for clinically relevant confounders listed above to investigate confounding factors. Spearman's correlation coefficients were calculated to analyse the relationships between variables. All *P* values presented were two-tailed; values less than 0.05 were considered statistically significant. We used Stata Software (Stata Statistical Software: Release 16. College Station, TX: Stata Corp LP) for data visualization and analysis.

RESULTS

In total, 376 of 419 patients met the inclusion criteria, and 8% of these patients died during the hospital stay (n = 29) (Figure 1). The median age was 40 years (range: 28-56 years), and 51% were males (n = 194) (Table 1). Patients in our study cohort were stratified according to all-cause in-hospital mortality into alive and dead groups, and their characteristics are presented in Table 1.

Predictors of the outcome

Regression analysis: (1) Unadjusted analysis. The unadjusted binary logistic regression analysis revealed that age, diabetes, hypertension, ischaemic heart disease, chronic kidney disease, obesity and Deyo-Charlson index were significant clinical factors associated with all-cause in-hospital mortality. In addition, AST, serum total bilirubin, serum albumin, serum creatinine and serum ferritin levels were the laboratory biomarkers significantly associated with all-cause in-hospital mortality. However, sex, chronic obstructive pulmonary disease and ALT, CRP, CK and D-dimer levels were not associated with all-cause in-hospital mortality; and (2) Adjusted analysis. The AST level at admission was the only biomarker of liver injury that was independently associated with all-cause in-hospital mortality in the unadjusted binary logistic regression analysis and model 1 adjusted for age and sex (Table 2). In addition, in model 2, after stepwise adjustment for several clinically relevant confounders, AST levels were still significantly associated with all-cause in-hospital mortality. Serum total bilirubin levels were independently associated with in-hospital mortality in the binary logistic regression after adjusting for age and sex but lost its statistical significance in the fully adjusted model.

Association of aminotransferase levels with CK levels

CK was studied as a marker of muscle injury. At admission, AST levels did not correlate with CK levels (r = -0.006; P = 0.9). In addition, admission ALT levels did not correlate with CK levels (r = -0.02; P = 0.6).

Association of aminotransferase levels with inflammatory markers

Serum ferritin and CRP levels were examined as markers of inflammation. At admission, AST levels correlated with CRP (r = 0.2; P < 0.003) and serum ferritin (r = 0.2; P < 0.0002) levels. Admission ALT levels correlated with serum ferritin levels (r = 0.1; P < 0.04) but not with CRP (r = 0.09; P = 0.08).

Association of serum ferritin levels with inflammatory markers

Admission serum ferritin levels correlated with CRP levels (r = 0.4; P < 0.0001).

Among our cohort, we identified 6 patients with biphasic hyperbilirubinemia. ALT levels correlated with serum total bilirubin levels (r = 0.2; P < 0.003). Therefore, hyperbilirubinemia was due to liver injury and not haemolysis.

Probability of survival

The probability of survival was significantly different between AST groups. As shown in the Kaplan-Meier curves (Figure 2), the probability of mortality progressively increased as the serum level of AST increased in the following order: two-fold increase in AST levels > a one-fold increase in AST levels > normal AST levels.

DISCUSSION

Numerous studies have reported the effect of liver injury on the outcomes of hospitalized patients with COVID-19[8]. However, a growing concern is that many demographic, clinical and laboratory markers might confound this association. These potential confounders should be recognized, and their effects on the association

Table 1 Baseline demographic, clinical and laboratory characteristics of alive and dead groups

Characteristics	Alive, *n* = 347	Dead, *n* = 29	Unadjusted odds ratio	*P* value
Age years median (IQR)			1.08 (1.05 to 1.11)	0.0001
< 40	186 (98.4)	3 (1.6)	Ref	
40-60	118 (93.6)	8 (6.3)	4.8 (1.7 to 13.4)	0.003
> 60	43 (70.5)	18 (29.5)	17.6 (6.5 to 48.0)	0.0001
Male sex, *n* (%)	179 (92.2)	15 (7.7)	1.1 (0.6 to 2.1)	0.98
Comorbidities				
Diabetes mellitus, *n* (%)	60 (77.0)	18 (23.0)	5.4 (2.9 to 10.2)	0.0001
Hypertension, *n* (%)	88 (83.8)	17 (16.2)	2.8 (1.5 to 5.2)	0.001
Ischaemic heart disease, *n* (%)	7 (50.0)	7 (50.0)	16.1 (5.2 to 50.2)	0.0001
Chronic kidney disease, *n* (%)	5 (45.5)	6 (54.5)	18.5 (5.2 to 65.5)	0.0001
Chronic respiratory disease, *n* (%)	57 (89.1)	7 (10.9)	1.7 (0.7 to 4.1)	0.25
Deyo–Charlson index, *n* (%)				
0-1	281 (96.6)	10 (3.4)	Ref	
2-3	64 (80.0)	16 (20.0)	7.8 (3.2 to 18.3)	0.0001
> 3	2 (40.0)	3 (60.0)	46.5 (6.9 to 313.5)	0.0001
Biochemical results on admission				
Serum ALT, *n* (%)				
< 40 U/L	225 (93.4)	16 (6.6)	Ref	
40-80 U/L	98 (89.9)	11 (10.1)	1.5 (0.6 to 3.3)	0.36
> 80 U/L	24 (92.3)	2 (7.7)	1.1 (0.3 to 5.4)	0.83
Serum AST, *n* (%)				
< 40 U/L	246 (96.8)	8 (3.2)	Ref	
40-80 U/L	87 (82.3)	18 (17.1)	6.1 (2.5 to 14.7)	0.0001
> 80 U/L	14 (82.3)	3 (17.6)	6.1 (1.5 to 25.5)	0.01
AST/ALT				
1.2-1.5	41 (87.2)	6 (12.7)	2.6 (1.0 to 7.2)	0.05
> 1.5	35 (81.4)	8 (18.6)	4.1 (1.6 to 10.4)	0.003
Serum albumin < 3.5 g/dL, *n* (%)	125 (85.6)	21 (14.4)	4.5 (1.9 to 10.5)	0.001
Serum total bilirubin > 1.5 mg/dL, *n* (%)	2 (33.3)	4 (66.7)	8.0 (2.2 to 29.4)	0.002
Serum creatinine > 1.1 mg/dL for males; > 0.95 mg/dL for females, *n* (%)	66 (77.7)	19 (22.3)	8.9 (3.9 to 20.6)	0.0001
C-reactive protein ≥ 1 mg/L, *n* (%)	338 (92.1)	29 (7.9)	1.0	
Serum ferritin > 400 μg/L for males; > 150 μg/L for females	183 (86.7)	28 (13.3)	24.7 (3.3 to 184.1)	0.002
D-dimer > 0.5 μg/mL	335 (92.0)	29 (8.0)	1.0	
Obesity (body mass index > 30)	106 (86.2)	17 (13.8)	3.2 (1.5 to 7.0)	0.003
Creatin kinase > 117 IU/L	11 (91.7)	1 (8.3)	1.1 (0.1 to 8.7)	0.9

Odds ratios were calculated by univariate logistic regression. Univariate logistic regression was used to calculate *P* value for the characteristics' differences between alive and dead patients. AST: Aspartate transferase; ALT: Alanine transferase; IQR: Interquartile range; Ref: Reference.

between biomarkers of hepatocellular injury and patient outcomes should be investigated. In fact, while treating COVID-19, we observed differential outcome prediction weights for markers of hepatocellular injury among hospitalized patients.

Table 2 Odds ratios of liver injury associated mortality and 95% confidence intervals by aspartate aminotransferase categories

	Unadjusted			Model 1 (adjusted for age and sex)			Model 2		
AST	**OR**	**CI**	***P* value**	**OR**	**CI**	***P* value**	**OR**	**CI**	***P* value**
< 40	Ref			Ref			Ref		
40-80	6.1	2.5-14.7	0.0001	4.8	1.9-12.1	0.001	10.8	2.5-40.9	0.001
> 80	6.1	1.5-25.5	0.01	2.9	0.6-13.7	0.18	12.8	1.5-93.4	0.02
						Covariates			
						Age			
						< 40	Ref		
						40-60	1.1	0.2-6.2	0.9
						> 60	6.3	1.2-33.1	0.03
						Sex	1.1	0.4-3.7	0.7
						DM	5.7	1.0-31.7	0.04
						HTN	0.3	0.1-2.0	0.2
						IHD	5.0	0.7-37.3	0.1
						COPD	0.7	0.1-3.6	0.6
						DCI			
						0-1			
						2-3	0.90	0.090-9.600	0.07
						> 3	0.200	0.001-25.600	0.5
						ALT			
						< 40	Ref		
						40-80	0.30	0.09-1.20	0.1
						> 80	0.10	0.02-1.20	0.07
						Albumin	0.8	0.2-2.5	0.7
						Bilirubin	17.2	0.9-312.8	0.05
						Ferritin	20.7	1.7-247.0	0.01
						Creatinine	1.8	0.6-5.8	0.3
						Obesity	3.3	0.9-11.4	0.06

Adjusted odds ratios for in-hospital mortality. Model adjusted for sex and age. Model 2 adjusted for age, sex. OR: Odds ratio; CI: Confidence interval; DCI: Deyo–Charlson index; DM: Diabetes mellites; HTN: Hypertension; IHD: Ischaemic heart disease; COPD: Chronic obstructive pulmonary disease; ALT: Alanine transferase; AST: Aspartate transferase, albumin, bilirubin, ferritin, creatinine and obesity.

At admission, 54.0% of patients in our cohort had liver injury. AST levels were elevated in 32.5% (n = 122), ALT levels were elevated in 36.0% (n = 135), and both ALT and AST levels were increased in 23.0% (n = 87). Among nonsurvivors, the pattern of liver injury was hepatocellular injury with an AST predominance. Both ALT and AST levels were elevated in 45.0% of nonsurvivors. An isolated elevation of AST levels was detected in 31.0% of nonsurvivors, while an isolated elevation of ALT levels was detected in 3.0%. Notably, 48.0% of nonsurvivors presented an AST/ALT ratio > 1.2, and serum total bilirubin levels were increased in 1.6% of patients in our study cohort.

We observed an obvious increase in mortality among patients with COVID-19 presenting elevated serum AST levels at the time of admission. A one-fold increase in the serum level of AST increased the odds of in-hospital mortality eleven-fold compared to those with normal AST levels at admission. Moreover, a two-fold increase in serum AST levels predicated a thirteen-fold increase in mortality. We can thus postulate from the findings of the present study that elevated AST levels at admission are a harbinger of a worse prognosis for patients with COVID-19. On the other hand, serum ALT, bilirubin and albumin levels did not alter mortality after

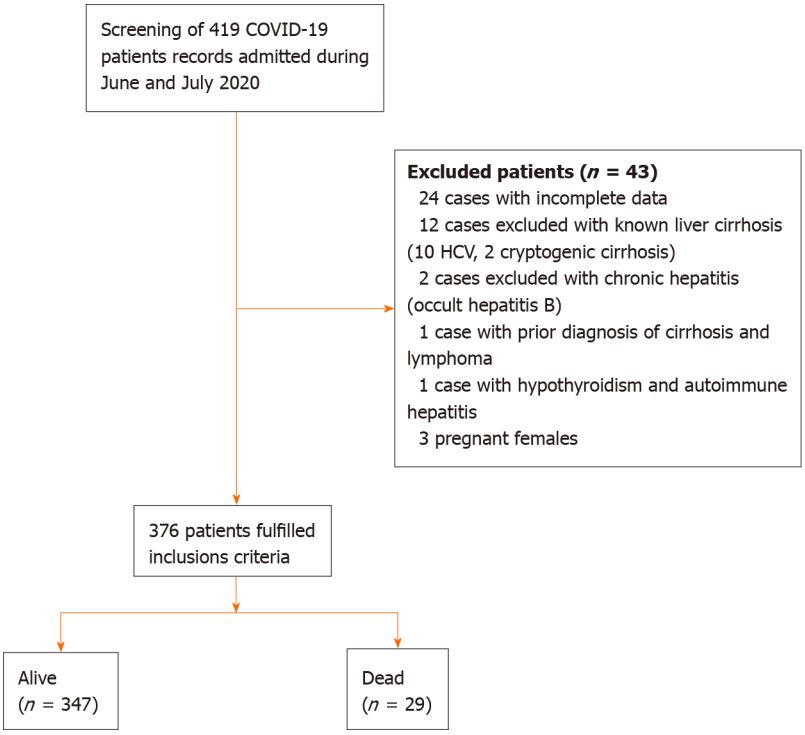

Figure 1 Flowchart of studied cohort. COVID-19: Coronavirus disease 2019; HCV: Hepatitis C virus.

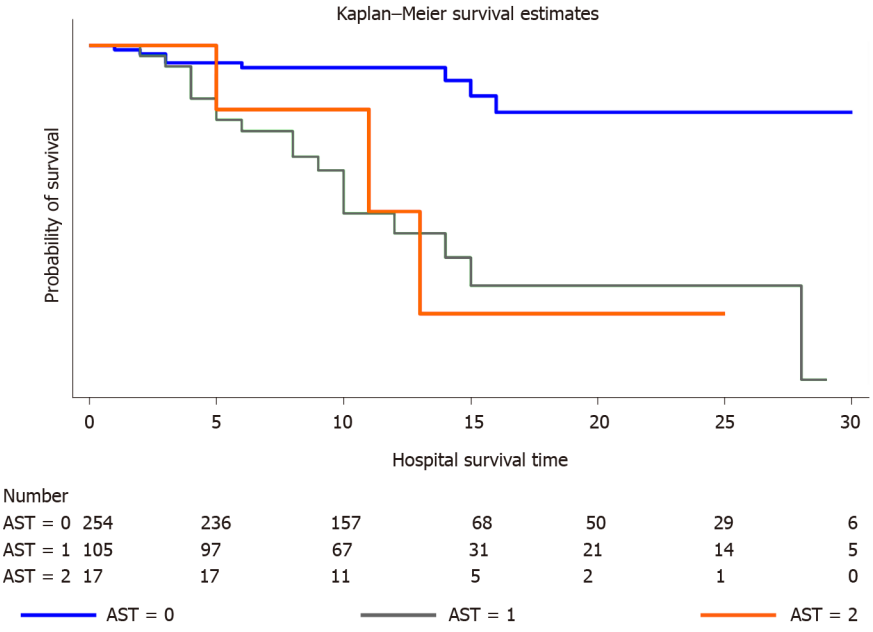

Figure 2 Kaplan–Meier curves. Survival curves show probability of survival (days) for aspartate aminotransferase (AST) groups, tested by log-rank test. AST = 0: Group with normal AST; AST = 1: Group with one-fold elevated AST; AST = 2: Group with two-fold elevated AST.

correction for age, sex and other relevant clinical factors. Our findings are consistent with recent reports investigating progressive liver injury and the risk of mortality among patients with COVID-19 where AST levels but not ALT levels at admission were a strong predictor of mortality[9-11].

In our cohort, AST levels did not correlate with the levels of CK, a marker of muscle injury, at admission. Moreover, AST levels correlated moderately with inflammatory markers at admission. Based on these findings, liver injury in patients with COVID-19 may be related to the proinflammatory state associated with cytokine release.

In healthy individuals, plasma levels of ALT and AST represent the balance between normal turnover of hepatocytes by apoptosis and the clearance rates of these

enzymes from hepatic sinusoids. Normally, ALT is present in the cytoplasm of hepatocytes, whereas AST is present in the cytoplasm and mitochondria of hepatocytes. Although the ratio of hepatic AST/ALT is 2.5:1, the serum levels of AST and ALT are similar after hepatocyte turnover because the clearance rate of AST is two times faster than the clearance rate of ALT[12,13].

In individuals with hepatocellular injury, serum levels of AST and ALT reflect the time course of hepatic injury and prognosis of hepatic insult. Early hepatocyte injury results in the release of cytosolic AST and ALT. If hepatocyte injury is severe, mitochondrial damage will result in increased release of mitochondrial AST in serum. Therefore, the predominant increase in the admission AST levels in our cohort might reflect early and severe hepatocyte injury. Furthermore, SARS-CoV-2 may induce endothelial cell injury in the hepatic microcirculation and promote portal or sinusoidal microthrombosis. In individuals with ischaemic liver injury (due to microthrombosis), serum AST levels peak before ALT levels, a pattern that was observed in our cohort[9,11,13].

In practice, an isolated and predominant elevation of AST levels indicates a nonhepatic source of AST, *e.g.*, muscle, and haemolysis.

Myositis results in increased levels of AST and, to a lesser extent, ALT; however, the increased serum levels of muscular aminotransferases should be associated with increased serum levels of CK. In our cohort, no significant correlation between AST and CK levels at admission was observed. This finding suggests true hepatic injury as the main source of elevated AST levels.

Haemolysis results in increased levels of AST and unconjugated bilirubin. In our cohort, we identified 6 patients with biphasic hyperbilirubinemia. ALT levels correlated with serum total bilirubin levels. Therefore, hyperbilirubinemia was due to liver injury and not haemolysis.

Among our cohort, 33.0% of patients were obese, perhaps with underdiagnosed nonalcoholic fatty liver disease. In addition, 20.0% of patients in our cohort were diagnosed with diabetes. Both diabetes mellitus and obesity increase serum levels of AST and ALT, but this change is more prominent for ALT than for AST[14].

The mechanism of liver injury among patients with COVID-19 is unclear and possibly multifactorial. The entry of SARS-CoV-2 into hepatocytes and cholangiocytes is mediated by ACE2 receptors. Liver biopsies obtained from deceased patients diagnosed with COVID-19 revealed focal degeneration and necrosis. In addition, SARS-CoV-2 particles were detected in hepatocytes[4]. Focal hepatic degeneration and necrosis may be due to the direct cytopathic effect of viral entry or could be an immune-mediated process. Entry of SARS-CoV-2 into hepatocytes triggers an innate and adaptive immune response that results in clearing of virus-infected cells. However, if the mounted immune response is exaggerated and uncontrolled, this aberrant immune response may contribute to the development of a cytokine storm and multisystem dysfunction[4,15]. Moreover, hyperinflammatory syndrome can induce disseminated intravascular coagulation with ischaemic hepatocellular injury by microvascular thrombosis in the hepatic microcirculation. In addition, direct endothelial cell damage in the hepatic microcirculation induced by SARS-CoV-2 may promote microvascular thrombosis and ischaemic liver injury[11].

In addition, our findings indicated that an age > 60 years, diabetes mellitus and increased serum ferritin levels were independent strong predictors of mortality among patients with COVID-19 presenting liver injury. These observations are consistent with recent studies[10].

Our study provides evidence that serum ferritin levels were associated with all-cause in-hospital mortality. Of our cohort, 56.0% of patients presented elevated serum ferritin levels. Moreover, 97.0% of nonsurvivors had elevated serum ferritin levels. In addition, logistic regression analysis showed that the serum ferritin level was an independent risk biomarker for in-hospital mortality among patients with COVID-19. Furthermore, admission serum ferritin levels correlated with CRP levels. These results suggest that elevated serum ferritin levels at admission may reflect disease severity. Our findings are consistent with a recent report confirming that increased ferritin levels are associated with in-hospital mortality in patients with COVID-19[16].

Inflammatory cytokines stimulate hepatocytes and macrophages to release ferritin, which plays a vital role in many autoimmune diseases and inflammatory disorders. A vicious loop exists between ferritin and inflammatory cytokines, *i.e.* activated hepatocytes and macrophages release ferritin, which in turn stimulates the production of various inflammatory cytokines. Serum ferritin is an inflammatory cytokine that indirectly stimulates proinflammatory pathways through the activation of the transcription factor nuclear factor kappa-B. Moreover, the heavy subunit of ferritin directly increases the mRNA expression of many inflammatory cytokines, such as

interleukin-1, interleukin-6, tumour necrosis factor and NOD-like receptor 3, indicating the proinflammatory properties of ferritin[16,17].

Patients with diabetes have elevated serum ferritin levels, and these patients are at increased risk of serious complications from COVID-19. Therefore, ferritin may be a key mediator of immune dysregulation that contributes to the cytokine storm in patients with diabetes mellitus and COVID-19[16,17].

Limitations

This retrospective study revealed an association between AST levels and mortality in patients with COVID-19 but did not reveal causality. Numerous medications and clinical and biological conditions injure hepatocytes but were only partially considered in the regression analysis. We used liver enzyme level at the time of admission for group categorization without knowing whether they were episodic or progressive changes. We did not consider concurrent medication use, such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers, in our analysis. Underdiagnosed nonalcoholic fatty liver disease and occult consumption of alcohol were not considered.

CONCLUSION

Our study revealed that liver injury is highly prevalent among patients with COVID-19 at admission. Liver injury with an AST-dominant pattern can be used to predict the severity of COVID-19. This study confirmed an elevated level of ferritin in patients with COVID-19. Admission serum ferritin levels are associated with fatal outcomes. Meticulous monitoring is highly recommended for patients with COVID-19 presenting AST-dominant hepatocellular injury, especially those older than 60 years, those with elevated levels of ferritin and those with diabetes mellitus.

ARTICLE HIGHLIGHTS

Research background

Clearly, infection with severe acute respiratory syndrome coronavirus 2 is not limited to the lung but also affects other organs.

Research motivation

Predictive models are needed to determine patients' prognoses and to improve health care resource allocation during the coronavirus disease 2019 (COVID-19) pandemic.

Research objectives

To investigate whether biomarkers of hepatocellular injury at admission have prognostic value in predicting all-cause in-hospital mortality in patients with COVID-19.

Research methods

A retrospective cohort study was conducted on 376 consecutive adult patients admitted to Al-Azhar University Hospital, Assiut, Egypt and Abo Teeg General Hospital, Assiut, Egypt with confirmed COVID-19 from June 1, 2020 to July 30, 2020.

Research results

High-risk populations, especially patients aged ≥ 60 years, patients with aspartate aminotransferase (AST)-dominant liver injury or those with diabetes, should be intensively monitored. Admission serum AST and serum ferritin levels have the strongest association with the prognosis of patients with COVID-19 and can be used to monitor patients with COVID-19 at risk of liver injury.

Research conclusions

Liver injury with an AST-dominant pattern can predict the severity of COVID-19. This study confirmed an elevated level of ferritin in patients with COVID-19. Elevated serum ferritin levels are associated with in-hospital mortality.

Research perspectives

Meticulous monitoring is highly recommended for patients with COVID-19 presenting AST-dominant hepatocellular injury, especially those older than 60 years, patients with elevated serum ferritin levels or those with diabetes mellitus.

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META-ANALYSIS

Non-invasive tests for predicting liver outcomes in chronic hepatitis C patients: A systematic review and meta-analysis

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Abstract

BACKGROUND

Liver fibrosis leads to liver-related events in patients with chronic hepatitis C (CHC) infection. Although non-invasive tests (NITs) are critical to early detection of the development of liver fibrosis, the prognostic role of NITs remains unclear due to the limited types of NITs and liver outcomes explored in previous studies.

AIM

To determine the prognostic value of NITs for risk stratification in CHC patients.

METHODS

The protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42019128176). The systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Search was performed using MEDLINE and EMBASE

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databases under a timeframe from the inception of the databases through February 25, 2020. We restricted our search to CHC cohort studies reporting an association between liver fibrosis assessed by NITs and the development of hepatocellular carcinoma, decompensation, or mortality. Pooled hazard ratios (HR) and area under the receiver operating characteristic (AUROC) for each NIT were estimated using a random effects model. Subgroup analyses were performed for NITs assessed at pre-treatment or post-treatment with sustained virologic response (SVR), treatment with either pegylated interferon and ribavirin or direct acting antiviral, Eastern or Western countries, and different cutoff points.

RESULTS
The present meta-analysis included 29 cohort studies, enrolling 69339 CHC patients. Fibrosis-4 (FIB-4) index, aspartate aminotransferase to platelet ratio (APRI) score, and liver stiffness measurement (LSM) were found to have hepatocellular carcinoma predictive potential with pooled adjusted HRs of 2.48 [95% confidence interval (CI): 1.91-3.23, I^2 = 96%], 4.24 (95%CI: 2.15-8.38, I^2 = 20%) and 7.90 (95%CI: 3.98-15.68, I^2 = 52%) and AUROCs of 0.81 (95%CI: 0.73-0.89, I^2 = 77%), 0.81 (95%CI: 0.75-0.87, I^2 = 68%), and 0.79 (95%CI: 0.63-0.96, I^2 = 90%), respectively. Pooled adjusted HR with a pre-treatment FIB-4 cutoff of 3.25 was 3.22 (95%CI: 2.32-4.47, I^2 = 80%). Pooled adjusted HRs for post-treatment with SVR FIB-4, APRI, and LSM were 3.01 (95%CI: 0.32-28.61, I^2 = 89%), 9.88 (95%CI: 2.21-44.17, I^2 = 24%), and 6.33 (95%CI: 2.57-15.59, I^2 = 17%), respectively. Pooled adjusted HRs for LSM in patients with SVR following direct acting antiviral therapy was 5.55 (95%CI: 1.47-21.02, I^2 = 36%). Pooled AUROCs for post-treatment with SVR FIB-4 and LSM were 0.75 (95%CI: 0.55-0.95, I^2 = 88%) and 0.84 (95%CI: 0.66-1.03, I^2 = 88%), respectively. Additionally, FIB-4 and LSM were associated with overall mortality, with pooled adjusted HRs of 2.07 (95%CI: 1.49-2.88, I^2 = 27%) and 4.04 (95%CI: 2.40-6.80, I^2 = 63%), respectively.

CONCLUSION
FIB-4, APRI, and LSM showed potential for risk stratification in CHC patients. Cutoff levels need further validation.

Key Words: Non-invasive tests; Prognosis; Hepatitis C virus; Hepatocellular carcinoma; Mortality; Liver-related outcomes

Core Tip: Previous meta-analyses have evidenced the potential of non-invasive tests (NITs) in determining prognosis. However, these syntheses included studies on chronic liver diseases from various etiologies and did not comprehensively explore all liver-related outcomes. We aimed to assess the importance of validated NITs in risk stratification, specifically in chronic hepatitis C (CHC) patients. Fibrosis-4 (FIB-4) index, aspartate aminotransferase to platelet ratio (APRI) score and liver stiffness measurement (LSM) were found to have prognostic value and can be leveraged to stratify risk for CHC patients, regardless of treatment status or regimen. Further validation of FIB-4, APRI and LSM cutoff levels are needed.

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INTRODUCTION

Chronic hepatitis C (CHC) infection can lead to the development of liver fibrosis and cirrhosis that are commonly associated with hepatocellular carcinoma (HCC), other

liver-related events (LREs), and mortality. Liver biopsy is considered the gold standard for evaluating liver fibrosis in patients with chronic liver disease. Since the introduction of non-invasive tests (NITs), biopsy use has substantially declined. Currently available NITs for liver fibrosis assessment include direct and indirect serum markers and radiologic examination such as liver stiffness measurement (LSM). According to the 2018 European Association for the Study of the Liver guidelines, the degree of liver fibrosis should be assessed by NITs in CHC patients prior to any treatment[1]. The degree of liver fibrosis determines optimal treatment regimen and whether the patient requires post-treatment monitoring of HCC development. NITs are also recommended for monitoring untreated CHC patients every 1 to 2 years[2].

Although serum markers and LSM have been shown to identify accurately patients with cirrhosis (F4) and patients without fibrosis (F0), their ability to stage intermediate degrees of fibrosis and post-treatment residual fibrosis is suboptimal[2,3]. The difficulties in the prediction of significant or advanced fibrosis without histologic confirmation has made risk stratification problematic for some CHC patients. For instance, the decision to pursue HCC surveillance following successful treatment of hepatitis C virus (HCV) infection [*i.e.* sustained virologic response (SVR)] is controversial for patients with advanced fibrosis (F3)[2,4].

Previous meta-analyses have evidenced the potential of NITs in determining prognosis. However, these syntheses included studies on chronic liver diseases from various etiologies and did not comprehensively explore all liver-related outcomes[5,6]. Types of NITs investigated in these meta-analyses were also limited. In this present review, we provided an updated systematic review and meta-analysis to assess the importance of validated NITs in risk stratification specific to CHC patients.

MATERIALS AND METHODS

Literature search

The protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42019128176). The systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[7]. Search was performed using MEDLINE and EMBASE databases from the inception of databases to February 25, 2020. The NITs for hepatic fibrosis included in our review were retrieved from the European Association for the Study of the Liver, Asociación Latinoamericana para el Estudio del Hígado Clinical Practice Guidelines [1]. The list of serum biomarkers and respective formulae are provided in Supplemental Table 1. In addition to the list of NITs, the terms prognosis, decompensation, hepatocellular cancer, chronic hepatitis C, and their related terms were selected as keywords. The details of the search strategy are provided in Supplemental Table 2. We restricted our search to cohort studies. Publications in the reference list of our included studies, publications that cited the included studies, and publications that were included in recent meta-analyses[8,9] of NITs and chronic liver diseases were also reviewed.

Study selection

Two reviewers (TY and CT) independently searched for studies on the prognosis of CHC patients based on non-invasive staging of liver fibrosis. Title and abstract of the studies were initially screened. The full-text of these studies were then independently assessed for eligibility by the two reviewers. Cohort studies that met the following criteria were included: (1) NITs documented and used to identify CHC patients who had a risk of developing LREs including hepatic decompensation, HCC, and/or mortality. Hepatic decompensation (HD) was defined as the development of variceal bleeding, hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, jaundice, and/or hepatorenal syndrome; (2) Patients were free of HCC and HD at enrollment; (3) Development of HD, HCC and mortality were assessed; and (4) Outcomes of interest were reported by hazard ratio (HR), relative risk, or area under the receiver operating characteristic (AUROC). Whereas studies of any size or language were included, the following studies were excluded: (1) Case-control studies, cross-sectional studies, case series, and conference abstracts; and (2) Trials enrolling patients with no evidence of HCV infection or when more than 10% of the patients were co-infected with HBV. Publications detailing the same patient cohorts but reporting different outcomes of interest were selected for separate analysis. When publications from the same cohort described the same outcomes, the study with the most comprehensive data or with the longest follow-up was selected for each outcome[10]. Any disa-

greement over study eligibility between reviewers was resolved through discussion with a third reviewer (PL).

Data extraction

A standardized form was used to extract data from the selected papers. Data included study characteristics (primary author, country, publication year, patient enrollment period, duration of follow-up), patient characteristics (age, sex, co-infection, baseline levels of NITs, fibrosis stages, HCV treatment regimen, response), method of NITs, endpoint (HD, HCC, overall and liver-related mortality), HR and AUROCs with 95% confidence intervals (95%CI), and control variables used for the adjusted analysis. Two reviewers (TY and CT) extracted the data independently, discrepancies were identified and discussed with a third reviewer (PL). Any missing data from the publications were requested from the study authors.

Risk of bias

A quality assessment of prognostic studies was performed independently by TY and CT using the Quality In Prognosis Studies tool[10]. Any disagreements between the reviewers over the risk of bias in particular studies were resolved *via* discussion with a third reviewer (PL).

Statistical analysis

Primary analysis assessed the performance of NITs in the prediction of LRE development in CHC patients. The analysis of each outcome was computed using a random-effects model. Since relative risk was provided by only one study[11], it was not included in our meta-analysis. Inverse variance method was used to pool the results. Unadjusted and adjusted HRs were pooled separately. Additionally, the significance of each NIT's prognostic value was assessed *vs* the random value (mean AUROC of each NIT was compared with 0.50 or the "random" value representing the absence of prognostic value). We then pooled the results, and 0.50 was added back to illustrate the overall prognostic value of each NIT. The AUROCs of different NITs were then compared using *t*-tests to identify any statistical difference in terms of prognostic ability. Subgroup analyses based on timing of liver fibrosis assessment (before or after HCV treatment) were performed when possible. Heterogeneity between studies was considered when I^2 value was greater than 50%. Publication bias was first evaluated by constructing funnel plots. Egger's linear regression test was also performed due to possible bias ascertained from funnel plots. All analyses were conducted using Review Manager (RevMan) [Computer program], Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, and ProMeta (Version 3) [Computer software] (Internovi, Cesena, Italy).

RESULTS

Study selection

After removing duplicate publications, 17248 papers were identified and screened by title and abstract. Of these, 104 full articles met our predefined selection criteria and were further examined. We further excluded 65 publications due to the following reasons: Non-relevant outcomes (n = 32), outcomes not reported as risk ratio (n = 13), patients meeting our exclusion criteria, *e.g.*, prior history of HCC (n = 10), studies of the same patient cohorts (n = 5), and NITs being used as diagnostic tests for HCC or HD (n = 5) (Figure 1).

Among the 39 cohort studies matching our selection criteria, 29 studies (69339 HCV-infected patients) were selected for quantitative analysis, with the 10 remaining studies slated only for qualitative analysis.

These 39 included studies enrolled a total of 77920 participants between 1990 and 2015. Seventeen and 22 studies were conducted in Western[12-28] and Asian countries [11,29-49], respectively (Table 1, Supplemental Table 3).

The performance of the Fibrosis-4 (FIB-4) index, aspartate aminotransferase to platelet ratio (APRI) score, and LSM tests for the prediction of LREs and mortality were characterized in 20, 11, and 19 studies, respectively. LSM was mainly performed by ultrasound-based transient elastography (TE), except in two studies that used either magnetic resonance elastography (MRE)[30], or 2D-shear wave elastography (2D-SWE)[29].

Table 1 Characteristics of the cohort studies included in the systematic review

Ref.	Country	*n*	NITs	Outcomes
Chun *et al*[49], 2020	South Korea	669	FIB-4	HCC
Chalouni *et al*[18], 2019	France	998	APRI, FIB-4, TE	LRE
Chen *et al*[45], 2019	China	691	FIB-4	OM
Hansen *et al*[20], 2019	Denmark	591	TE	OM, LRD, HD
Ioannou *et al*[13], 2019	United States	48135	FIB-4	HCC
Na *et al*[33], 2019	South Korea	295	APRI, FIB-4	HCC
Nakagomi *et al*[34], 2019	Japan	1146	TE	HCC
Ogasawara *et al*[38], 2019	Japan	398	FIB-4, TE	HCC, HD
Ogasawara *et al*[47], 2019	Japan	457	FIB-4	OM
Peleg *et al*[23], 2019	Israel	515	TE	HCC, OM, HD
Pons *et al*[14], 2019	Spain	572	TE	HCC
Rinaldi *et al*[15], 2019	Italy	258	TE	HCC
Shili-Masmoudi *et al*[28], 2019	France	1062	TE	OM, LRM
Sou *et al*[41], 2019	China	1884	APRI, FIB-4	HCC
Tamaki *et al*[30], 2019	Japan	346	FIB-4, MRE	HCC
Watanabe *et al*[44], 2019	Japan	1174	APRI, FIB-4	HCC
Bloom *et al*[17], 2018	Australia	780	TE	LRE
Hamada *et al*[29], 2018	Japan	196	FIB-4, SWE	HCC
Munteanu *et al*[22], 2018	France	3449	Fibrotest	OM, LRM
Cepeda *et al*[25], 2017	United States	964	TE	OM
Gomez-Moreno *et al*[19], 2017	Spain	343	TE	HCC, HD, LRM
Merchante *et al*[26], 2017	Spain	446	TE	HD
Thandassery *et al*[43], 2017	Qatar	1605	APRI, FIB-4	HCC, HD, LRE
Akuta *et al*[39], 2016	Japan	958	FIB-4	HCC
Lee *et al*[31], 2016	South Korea	598	APRI	HCC
Lee *et al*[46], 2016	South Korea	190	TE	LRE
Ng *et al*[36], 2016	China	105	APRI	HCC
Pérez-Latorre *et al*[24], 2016	Spain	957	TE	LRE, OM
Sato *et al*[40], 2016	Japan	355	APRI, FIB-4	HCC
Tada *et al*[48], 2016	Japan	1723	FIB-4	LRM, OM
Berenguer *et al*[12], 2015	Spain	903	FIB-4	LRE, OM
Macías *et al*[21], 2015	Spain	1046	TE	HD, OM
Narita *et al*[35], 2014	Japan	151	TE	HCC
Nojiri *et al*[37], 2014	Japan	142	APRI, FIB-4, Forns index	HCC
Tamaki *et al*[42], 2014	Japan	1046	FIB-4	HCC
Bambha *et al*[16], 2012	United States	450	APRI, FIB-4	OM
Nunes *et al*[27], 2010	United States	303	APRI, FIB-4	LRM
Masuzaki *et al*[32], 2009	Japan	984	TE	HCC
Yu *et al*[11], 2006	China	1338	APRI	HCC, OM

N/A: Not available; APRI: Aspartate aminotransferase to platelet ratio index; FIB-4: Fibrosis-4 index; HCC: Hepatocellular carcinoma; HD: Hepatic

decompensation; LSM: Liver stiffness measurement; LRM: Liver-related mortality; LRE: Liver-related event; NIT: Non-invasive test; OM: Overall mortality; TE: Transient elastography; MRE: Magnetic resonance elastography.

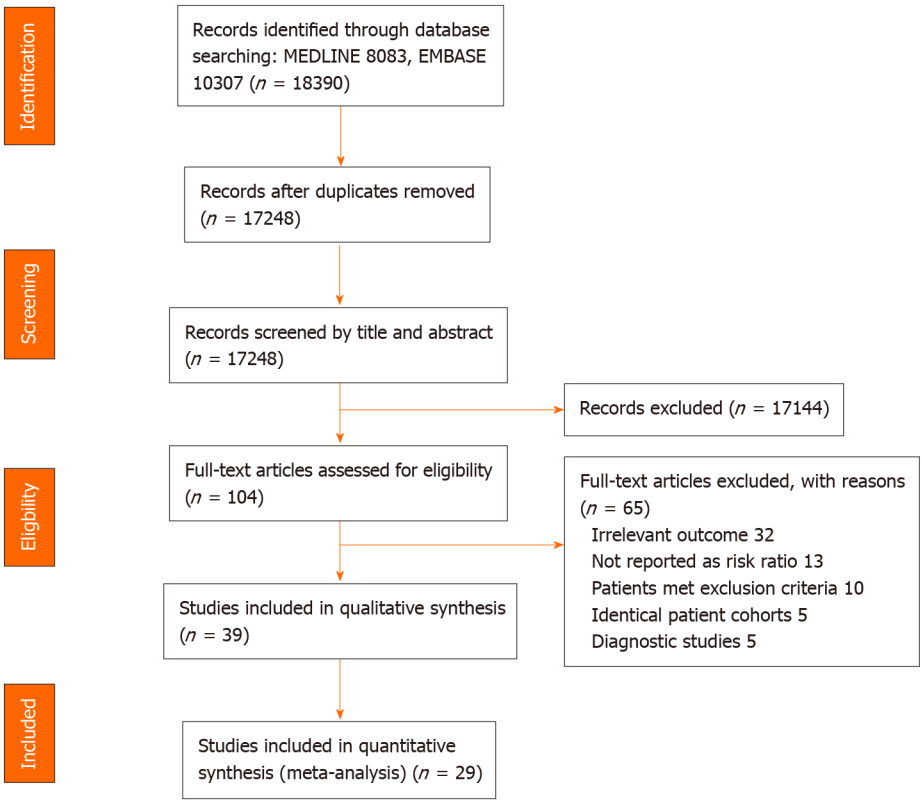


Figure 1 Flow diagram of search methodology and selection process.

The primary outcomes of interest were HCC, overall mortality, and liver-related mortality in 21[11,13-15,29-44,49], 12[3,12,17-24,38,46], and 10[16,18,20,21,25,27,28,45,47,48] studies, respectively. Twelve studies selected HD or a compound of LREs as relevant outcome(s)[12,17-21,23,24,26,38,43,46]. Characteristics of all the studies are summarized in Table 1 and Supplemental Table 3.

Eleven studies enrolled patient cohorts with HCV and human immunodeficiency virus co-infection[12,16,18,21,22,24-28,45]. Fifteen reports included only patients who were successfully treated, *i.e.* having SVR[13,14,23,29-31,33,36,38-40,44,46,47,49], while two studies enrolled only patients with cirrhosis[13,15]. All studies had a mean or median follow-up time of at least 1 year.

FIB-4, APRI, and LSM were among the most extensively explored NITs (Table 2). We did not conduct quantitative analysis using other NITs due to their very limited usage (n = 1 for Forns index[37] and Fibrotest[22], n = 0 for other NITs).

The included studies were mostly rated as low risk of bias (n = 27)[11-14,16,19-23,25,26,28-30,32,33,35-39,42-44,46,48] (Supplementary Table 4, Supplementary Figure 1). However, five studies were rated as high risk of bias because of concerns about selective reporting of multivariate analysis and other biases[34,40,41,45,49]. Only 13 studies provided the number of patients lost to follow-up[13,14,17,20-22,24,28,32,36,37,44,45]. The agreement between the two reviewers' assessment was excellent (93%).

Association between NITs and HCC risk

Among NITs included in the present analysis, FIB-4 score was the most studied NIT for its role in HCC prediction. Eleven studies including 1891 HCC cases examined the relationship between FIB-4 values and HCC development[13,29,30,33,38-42,44,49]. The FIB-4 cutoffs selected in these studies ranged from 2.5 to 4.5. All these studies reported a significant positive association between high FIB-4 values and risk of HCC development, with pooled unadjusted and adjusted HRs of 5.17 (95%CI: 4.03-6.63, I^2 = 76%) and 2.48 (95%CI: 1.91-3.23, I^2 = 96%), respectively (Figure 2A).

Table 2 Pooled unadjusted and adjusted hazard ratios of pre- and post-treatment fibrosis-4 index, aspartate aminotransferase to platelet ratio index, liver stiffness measurement for the prediction of hepatocellular carcinoma development

Analysis	HR				aHR			
	Pooled HR (95%CI)	I^2 (%)	Ref.	No. of cases	Pooled aHR (95%CI)	I^2 (%)	Ref.	No. of cases
FIB-4	5.17 (4.03-6.63)	76	[13,29,30,38,40-42]	1831	2.48 (1.91-3.23)	96	[13,33,39-42,44,49]	1842
pre-Rx	4.91 (3.71-6.49)	81	[13,38,40-42]	1781	3.20 (1.77-5.80)	97	[13,33,39-40,42,44]	1699
post-Rx with SVR	5.44 (2.25-13.15)	69	[29,30,38,41]	173	3.01 (0.32-28.61)	89	[33,49]	21
APRI	5.27 (2.34-11.83)	91	[31,40,41]	150	4.24 (2.15-8.38)	20	[33,36,41]	149
pre-Rx	4.23 (1.42-12.62)	83	[31,40,41]	142	-	-	[33]	12
post-Rx with SVR	9.33 (5.85-14.88)	0	[31,41]	130	9.88 (2.21-44.16)	24	[33,41]	134
LSM	9.45 (4.49-19.92)	70	[14,15,29,30,34,38]	301	7.90 (3.98-15.68)	52	[15,29,30,32,34,35,38]	362
pre-Rx	4.68 (2.00-10.96)	40	[15,38]	54	3.76 (1.77-8.02)	7	[15,35,38]	63
post-Rx with SVR	8.90 (4.10-19.33)	36	[14,29,30,38]	76	6.33 (2.57-15.59)	17	[29,30,38]	51

aHR: Adjusted hazard ratio; APRI: Aspartate aminotransferase to platelet ratio index; FIB-4: Fbrosis-4 index; HCC: Hepatocellular carcinoma; LSM: Liver stiffness measurement; pre-Rx: Pre-treatment; post-Rx with SVR: Post-treatment with sustained virologic response.

Five studies totaling 169 HCC cases evaluated the prognostic value of APRI and found a statistically significant positive association between high APRI values and HCC occurrence[31,33,36,40,41]. The APRI cutoffs used in these studies ranged from 0.5 to 2.0. The overall pooled unadjusted and adjusted HRs were 5.27 (95%CI: 2.34-11.83, I^2 = 91%) and 4.24 (95%CI: 2.15-8.38, I^2 = 20%), respectively (Figure 2B).

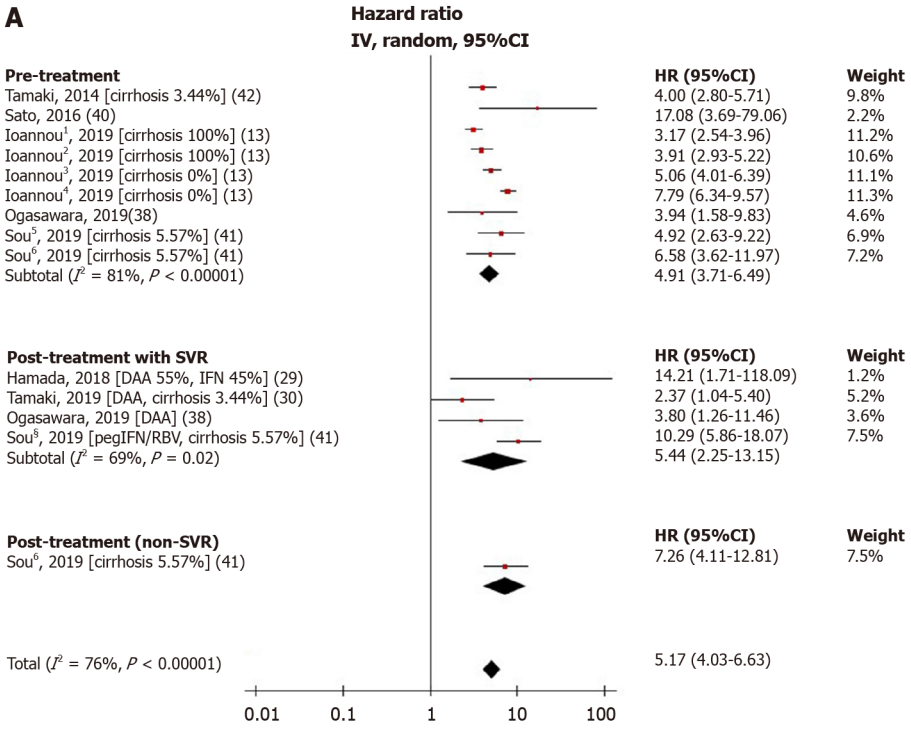
Eight studies with 387 HCC cases investigated the association between LSM and HCC risk[14,15,29,30,32,34,35,38]. The LSM cutoffs chosen for each study were all unique and ranged from 3.75 to 30. Consistent with FIB-4 score and APRI results, the overall pooled unadjusted and adjusted HRs were 9.45 (95%CI: 4.49-19.92, I^2 = 70%) and 7.90 (95%CI: 3.98-15.68, I^2 = 52%), respectively (Figure 2C).

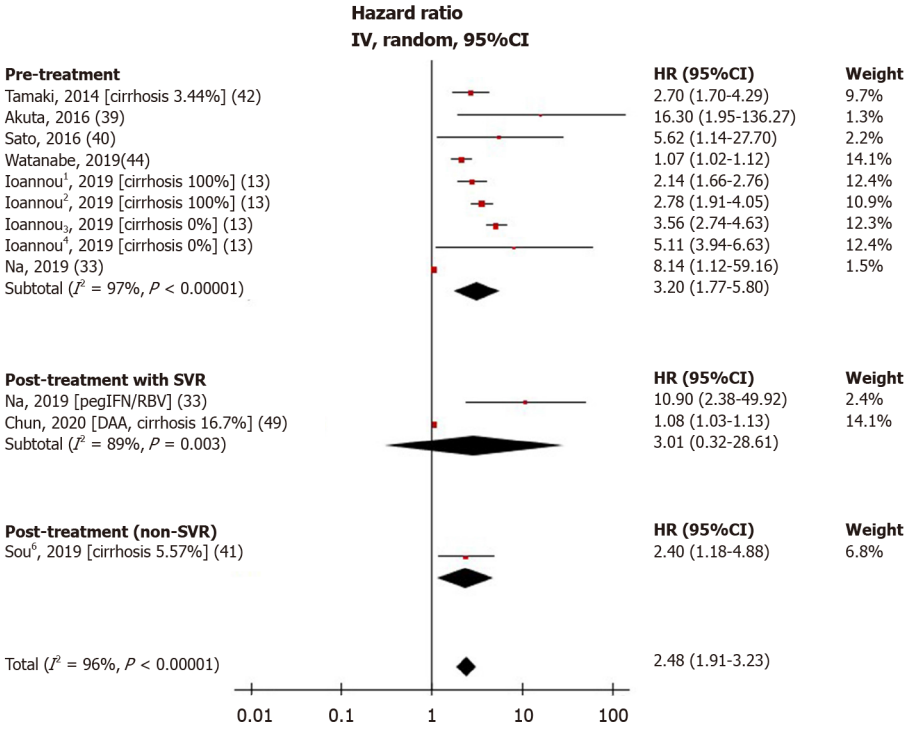
Subgroup analyses were performed for NITs assessed at pre-treatment and post-treatment with SVR. Pooled adjusted HRs for pre-treatment FIB-4 and LSM were 3.20 (95%CI: 1.77-5.80, I^2 = 97%) and 3.76 (95%CI: 1.77-8.02, I^2 = 7%), respectively. Pooled adjusted HRs for post-treatment with SVR FIB-4, APRI, and LSM were 3.01 (95%CI: 0.32-28.61, I^2 = 89%), 9.88 (95%CI: 2.21-44.16, I^2 = 24%), and 6.33 (95%CI: 2.57-15.59, I^2 = 17%), respectively (Figure 2). The prognostic ability of these NITs remains valid even after the introduction of direct-acting antiviral (DAA) therapy. Pooled unadjusted and adjusted HRs for LSM in patients with SVR following DAA therapy were 6.80 (95%CI: 3.54-13.05, I^2 = 0%) and 5.55 (95%CI: 1.47-21.02, I^2 = 36%), respectively (Supplementary Figure 2).

To determine the optimal cutoff for HCC prediction, we pooled the results using a pre-treatment FIB-4 cutoff of 3.25 as this cutoff was applied in four studies, accounting for over 51360 CHC patients (Supplementary Figure 3). We found that the pooled, unadjusted and adjusted HRs were 4.79 (95%CI: 3.58-6.42, I^2 = 85%) and 3.22 (95%CI: 2.32-4.47, I^2 = 80%), respectively, for predicting HCC development.

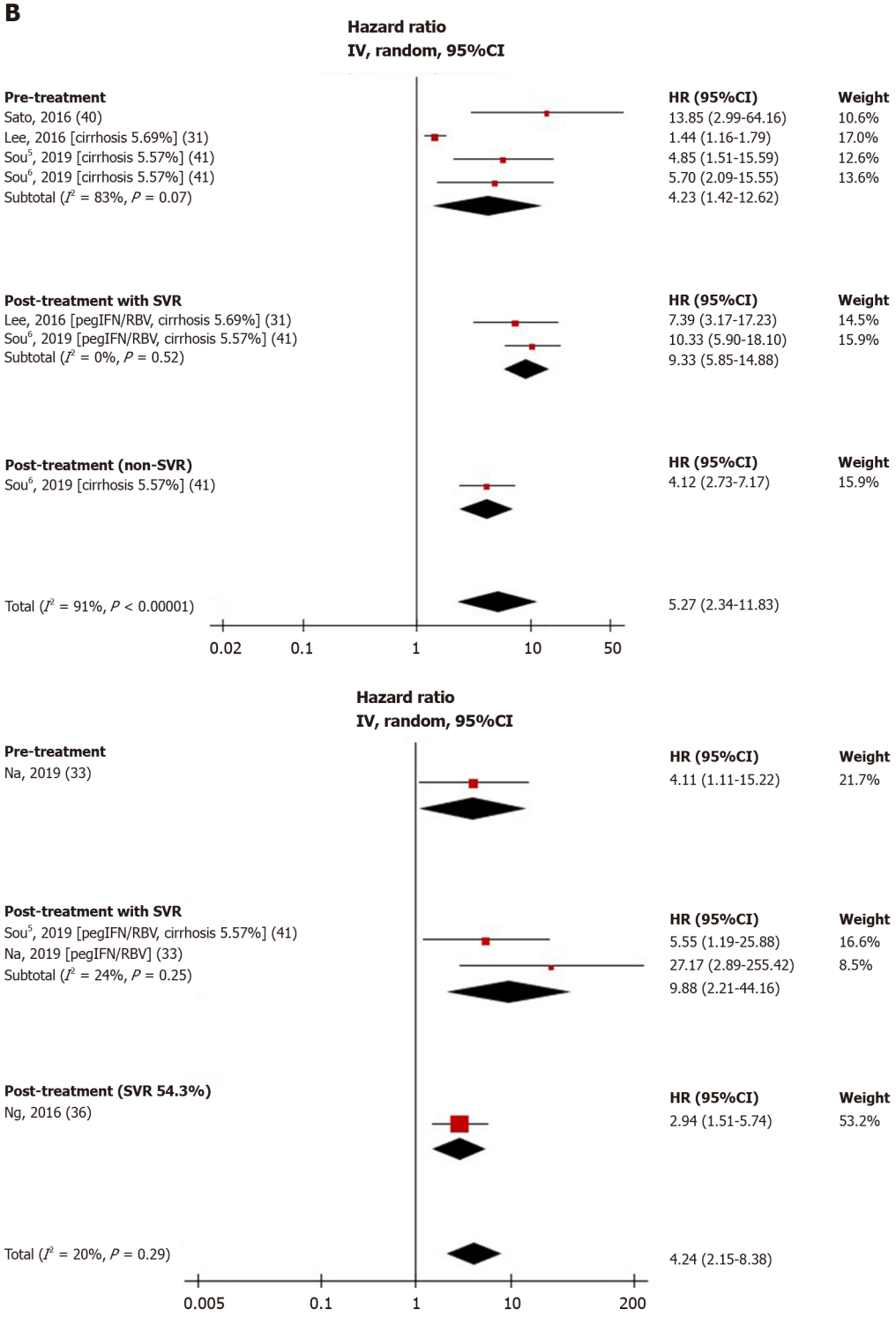
Given the high heterogeneity of the analysis of pre-treatment FIB-4, we performed subgroup analyses by location of study. We found that, in the subgroup of Asian countries, pooled unadjusted and adjusted HRs of 4.91 (95%CI: 3.60-6.70, I^2 = 18%) and 3.12 (95%CI: 1.31-7.42, I^2 = 87%) for the pre-treatment FIB-4 and HCC development (Supplementary Figure 4). The I^2 of pooled unadjusted HR decreased from 76% to 18%, while the I^2 of pooled adjusted HR slightly decreased from 97% to 87%. We hypothesized that the remaining high heterogeneity stemmed from the variety of FIB-4 cutoff used in the different studies.

Figure 3 shows the performance of NITs for HCC prediction. FIB-4 score, APRI, and LSM was significantly greater than random (AUROC = 0.5), with pooled AUROCs of 0.81 (95%CI: 0.73-0.89, I^2 = 77%), 0.81 (95%CI: 0.75-0.87, I^2 = 68%), and 0.79 (95%CI: 0.63-0.96, I^2 = 90%), respectively. The pooled AUROCs of FIB-4 and APRI were both statistically higher than that of the LSM, P < 0.0001 for both, respectively.


A
Hazard ratio
IV, random, 95%CI
Pre-treatment
HR (95%CI)
Weight
Tamaki, 2014 [cirrhosis 3.44%] (42) 4.00 (2.80-5.71) 9.8%
Sato, 2016 (40) 17.08 (3.69-79.06) 2.2%
Ioannou[1], 2019 [cirrhosis 100%] (13) 3.17 (2.54-3.96) 11.2%
Ioannou[2], 2019 [cirrhosis 100%] (13) 3.91 (2.93-5.22) 10.6%
Ioannou[3], 2019 [cirrhosis 0%] (13) 5.06 (4.01-6.39) 11.1%
Ioannou[4], 2019 [cirrhosis 0%] (13) 7.79 (6.34-9.57) 11.3%
Ogasawara, 2019(38) 3.94 (1.58-9.83) 4.6%
Sou[5], 2019 [cirrhosis 5.57%] (41) 4.92 (2.63-9.22) 6.9%
Sou[6], 2019 [cirrhosis 5.57%] (41) 6.58 (3.62-11.97) 7.2%
Subtotal (I^2 = 81%, P < 0.00001) 4.91 (3.71-6.49)
Post-treatment with SVR
HR (95%CI)
Weight
Hamada, 2018 [DAA 55%, IFN 45%] (29) 14.21 (1.71-118.09) 1.2%
Tamaki, 2019 [DAA, cirrhosis 3.44%] (30) 2.37 (1.04-5.40) 5.2%
Ogasawara, 2019 [DAA] (38) 3.80 (1.26-11.46) 3.6%
Sou[§], 2019 [pegIFN/RBV, cirrhosis 5.57%] (41) 10.29 (5.86-18.07) 7.5%
Subtotal (I^2 = 69%, P = 0.02) 5.44 (2.25-13.15)
Post-treatment (non-SVR)
HR (95%CI)
Weight
Sou[6], 2019 [cirrhosis 5.57%] (41) 7.26 (4.11-12.81) 7.5%
Total (I^2 = 76%, P < 0.00001) 5.17 (4.03-6.63)
0.01
0.1
1
10
100


Hazard ratio
IV, random, 95%CI
Pre-treatment
HR (95%CI)
Weight
Tamaki, 2014 [cirrhosis 3.44%] (42) 2.70 (1.70-4.29) 9.7%
Akuta, 2016 (39) 16.30 (1.95-136.27) 1.3%
Sato, 2016 (40) 5.62 (1.14-27.70) 2.2%
Watanabe, 2019(44) 1.07 (1.02-1.12) 14.1%
Ioannou[1], 2019 [cirrhosis 100%] (13) 2.14 (1.66-2.76) 12.4%
Ioannou[2], 2019 [cirrhosis 100%] (13) 2.78 (1.91-4.05) 10.9%
Ioannou[3], 2019 [cirrhosis 0%] (13) 3.56 (2.74-4.63) 12.3%
Ioannou[4], 2019 [cirrhosis 0%] (13) 5.11 (3.94-6.63) 12.4%
Na, 2019 (33) 8.14 (1.12-59.16) 1.5%
Subtotal (I^2 = 97%, P < 0.00001) 3.20 (1.77-5.80)
Post-treatment with SVR
HR (95%CI)
Weight
Na, 2019 [pegIFN/RBV] (33) 10.90 (2.38-49.92) 2.4%
Chun, 2020 [DAA, cirrhosis 16.7%] (49) 1.08 (1.03-1.13) 14.1%
Subtotal (I^2 = 89%, P = 0.003) 3.01 (0.32-28.61)
Post-treatment (non-SVR)
HR (95%CI)
Weight
Sou[6], 2019 [cirrhosis 5.57%] (41) 2.40 (1.18-4.88) 6.8%
Total (I^2 = 96%, P < 0.00001) 2.48 (1.91-3.23)
0.01
0.1
1
10
100

B


Hazard ratio
IV, random, 95%CI
Pre-treatment
Sato, 2016 (40)
Lee, 2016 [cirrhosis 5.69%] (31)
Sou[5], 2019 [cirrhosis 5.57%] (41)
Sou[6], 2019 [cirrhosis 5.57%] (41)
Subtotal (I² = 83%, P = 0.07)
HR (95%CI)
13.85 (2.99-64.16)
1.44 (1.16-1.79)
4.85 (1.51-15.59)
5.70 (2.09-15.55)
4.23 (1.42-12.62)
Weight
10.6%
17.0%
12.6%
13.6%
Post-treatment with SVR
Lee, 2016 [pegIFN/RBV, cirrhosis 5.69%] (31)
Sou[6], 2019 [pegIFN/RBV, cirrhosis 5.57%] (41)
Subtotal (I² = 0%, P = 0.52)
HR (95%CI)
7.39 (3.17-17.23)
10.33 (5.90-18.10)
9.33 (5.85-14.88)
Weight
14.5%
15.9%
Post-treatment (non-SVR)
Sou[6], 2019 [cirrhosis 5.57%] (41)
HR (95%CI)
4.12 (2.73-7.17)
Weight
15.9%
Total (I² = 91%, P < 0.00001)
5.27 (2.34-11.83)
0.02
0.1
1
10
50
Hazard ratio
IV, random, 95%CI
Pre-treatment
Na, 2019 (33)
HR (95%CI)
4.11 (1.11-15.22)
Weight
21.7%
Post-treatment with SVR
Sou[5], 2019 [pegIFN/RBV, cirrhosis 5.57%] (41)
Na, 2019 [pegIFN/RBV] (33)
Subtotal (I² = 24%, P = 0.25)
HR (95%CI)
5.55 (1.19-25.88)
27.17 (2.89-255.42)
9.88 (2.21-44.16)
Weight
16.6%
8.5%
Post-treatment (SVR 54.3%)
Ng, 2016 (36)
HR (95%CI)
2.94 (1.51-5.74)
Weight
53.2%
Total (I² = 20%, P = 0.29)
4.24 (2.15-8.38)
0.005
0.1
1
10
200

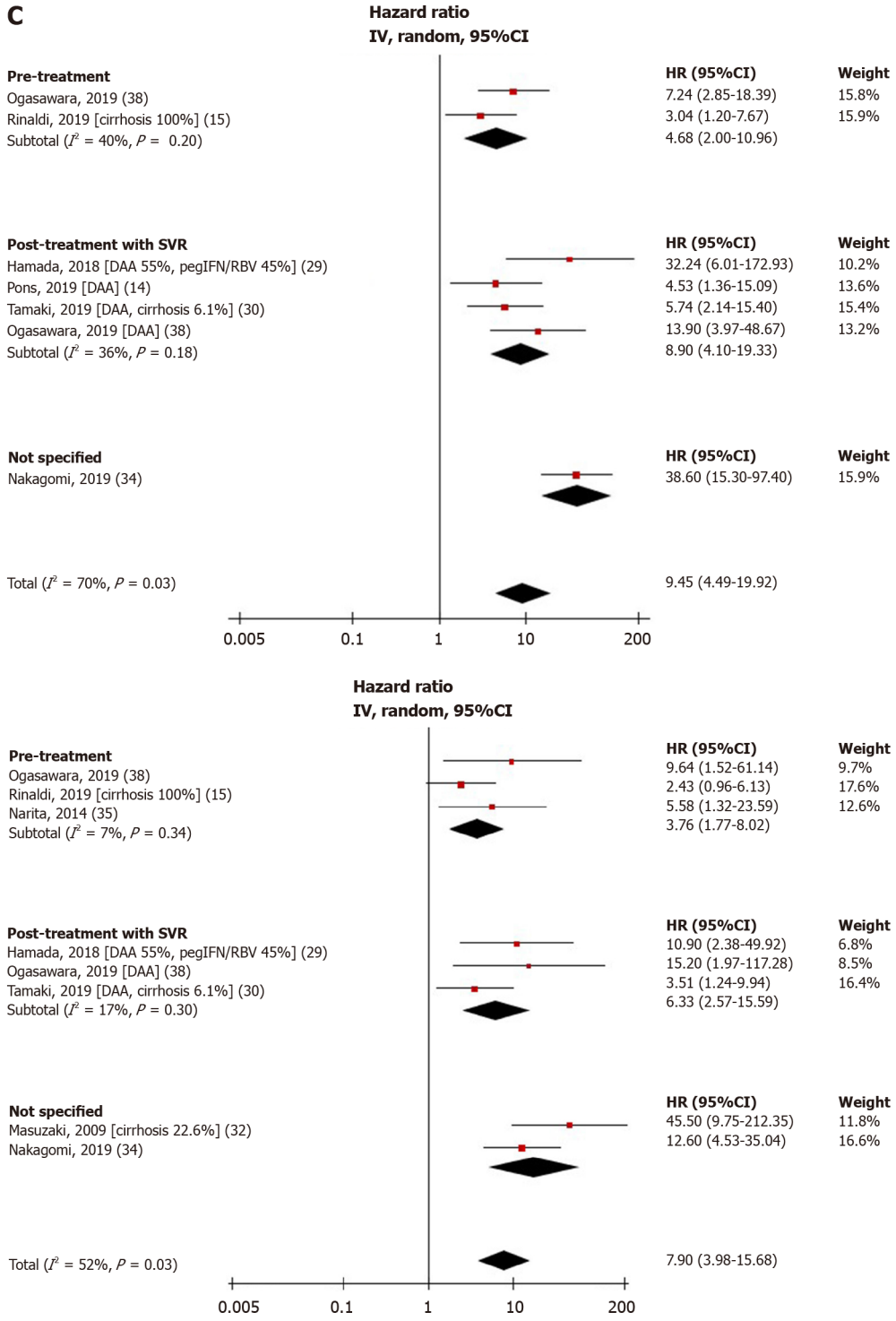


Figure 2 Unadjusted and adjusted hazard ratios of fibrosis-4 index (A), aspartate aminotransferase to platelet ratio score (B), liver stiffness measurement (C), and hepatocellular carcinoma risk. [1]Cirrhosis and direct acting antiviral-treated cohort. [2]Cirrhosis and interferon-treated cohort. [3]Non-cirrhotic and direct acting antiviral-treated cohort. [4]Non-cirrhotic and interferon-treated cohort. [5]Sustained virologic response cohort. [6]Non-sustained virologic response cohort. DAA: Direct-acting antiviral; FIB-4: Fibrosis-4 index; pegIFN/RBV: Pegylated interferon and ribavirin; SVR: Sustained virologic response.

We further analyzed the prognostic values of NITs before and after HCV treatment. For the pre-treatment period, the pooled AUROC of FIB-4 score was significantly greater compared to APRI (0.88, (95%CI: 0.83-0.92, I^2 = 0%) *vs* 0.77, (95%CI: 0.70-0.84, I^2 = 36%), P < 0.0001). For NITs assessed at post-treatment among patients with SVR, the pooled AUROC of LSM was 0.84 (95%CI: 0.66-1.03, I^2 = 88%), which was statistically higher than that of FIB-4 (pooled AUROC 0.75, 95%CI: 0.55-0.95, I^2 = 88%), P < 0.0001. The pooled AUROC of pre-treatment LSM and post-treatment APRI score was not estimated due to the limited number of studies (n = 1 each).

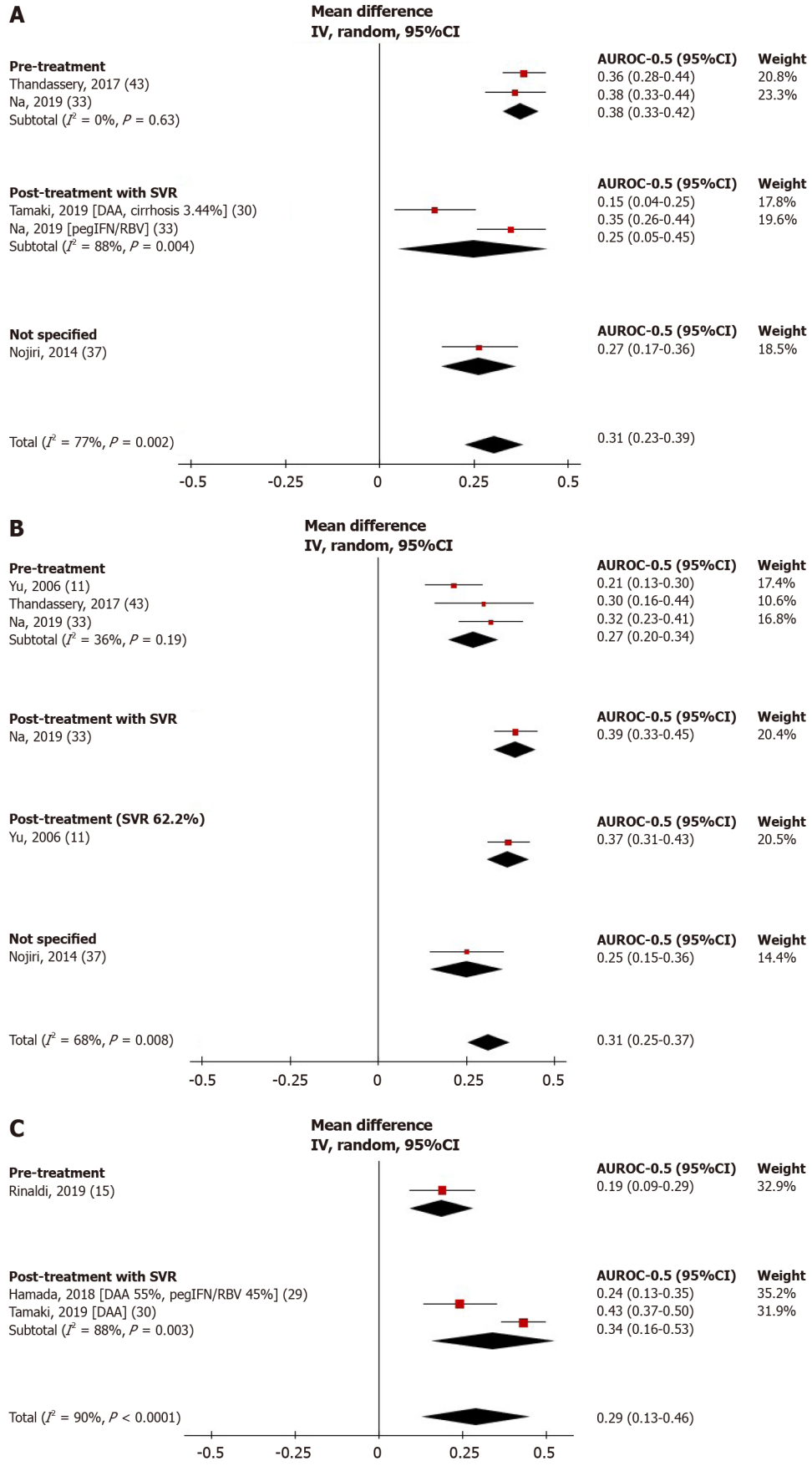


Figure 3 Forest plots showing hepatocellular carcinoma predictive performance *vs* random of fibrosis-4 (A), random of aspartate aminotransferase to platelet ratio (B), and random of liver stiffness measurement (C). DAA: Direct-acting antiviral; FIB-4: Fibrosis-4 index; pegIFN/RBV: Pegylated interferon and ribavirin; SVR: Sustained virologic response. APRI: Aspartate aminotransferase to platelet ratio index; LSM: Liver stiffness measurement.

Association between NITs and overall mortality

Four studies identifying 823 deaths among 3321 patients reported a significant positive association between FIB-4 score and overall mortality with pooled unadjusted and adjusted HRs of 3.06 (95%CI: 1.38-6.67, I^2 = 90%) and 2.07 (95%CI: 1.49-2.88, I^2 = 27%), respectively (Supplementary Figure 5)[16,45,47,48]. Likewise, a significant positive association between LSM and overall mortality was reported from four studies containing 3663 patients with 368 deaths[20,21,25,28], with pooled unadjusted and adjusted HRs of 5.52 (95%CI: 2.81-10.85, I^2 = 74%) and 4.04 (95%CI: 2.40-6.80, I^2 = 63%), respectively (Supplementary Figure 6).

The pooled HR and AUROC of APRI performance for the prediction of mortality was not estimated because only one study was included in this meta-analysis. The AUROCs for predicting overall mortality reported in individual studies are shown in Table 3.

Liver-related mortality, decompensation of cirrhosis, and composite outcomes

Due to the broad definitions of HD and LRE outcomes, we did not perform a meta-analysis on these outcomes. However, taken individually, any NIT showed statistically significant positive associations and predictive values for their respective outcomes. The HRs and AUROCs of NITs and liver-related outcomes are summarized in Tables 4 and 5[12,16-21,23-28,38,43,45-48].

Publication bias

Publication bias was assessed through Deeks funnel plots for unadjusted and adjusted HRs of NITs and LREs. The distribution of studies was symmetrical for all analyses, except for adjusted HRs of FIB-4, APRI, LSM, and HCC development, which showed asymmetry (Figure 4). Egger's regression asymmetry test detected publication bias in adjusted HRs of FIB-4 (P < 0.001) but not in HRs of APRI or LSM (P = 0.081 and 0.097, respectively). We found that five out of eight studies that reported an adjusted HR for FIB-4 score each had more than 1000 participants[33,39-41,49]. When only studies with > 1000 participants were selected for the subgroup analysis of adjusted HRs of FIB-4 and HCC development, publication bias was no longer detected (P = 0.12), suggesting that bias resulted from the inclusion of small studies.

DISCUSSION

NITs for liver fibrosis assessment play an important role in the management of HCV infection. Liver fibrosis staging is determinant for treatment prioritization and regimen in low- and middle-income countries as well as HCC surveillance. In addition to fibrosis staging, NITs are increasingly evaluated for their prognostic value. Our systematic review highlighted the potential use of FIB-4, APRI, and LSM to guide risk-stratified strategies in HCV-infected patients.

We found that LSM had a higher pooled HR for HCC development than APRI and FIB-4. TE is the most validated method for LSM as judged by its clinical implementation since 2003[3]. Other techniques such as MRE and 2D-SWE were also shown to have a better performance than TE in differentiating stages of fibrosis[50,51], but they are not as widely available. All of the studies included in our review performed LSM by TE, with the exception of those from Tamaki *et al*[30] and Hamada *et al*[29], which used MRE and real-time SWE, respectively. Although both studies[29,30] evidenced higher HRs for HCC development, the difference in prognostic ability compared to TE was not explored in our meta-analysis due to the limited number of studies using MRE and 2D-SWE.

Although LSM is the most commonly used and validated NIT for liver fibrosis staging, several drawbacks can limit its use in practice such as costly equipment and maintenance, need for frequent calibration and skilled operators, and limited performance in obese patients. Therefore, the use of serologic markers such as APRI or FIB-4 score were recommended by the World Health Organization (WHO)[52] to assess hepatic fibrosis in resource-limited settings. Indeed, these scores can be easily calculated using only patient age and common laboratory data (aspartate aminotransferase, alanine aminotransferase, platelets). Considering the current recommendation to measure the degree of liver fibrosis prior to HCV treatment[2], we found that in a pre-treatment setting APRI and FIB-4 score performed well in terms of HCC prediction, with AUROCs of 0.77 and 0.88, respectively. They could provide similar, if not higher, prognostic value in comparison to LSM.

WHO has committed to eradicate viral hepatitis by 2030. Since the introduction of direct acting antiviral (DAA) therapy, the number of treated CHC patients achieving

Table 3 Area under the receiver operating characteristic curves of non-invasive tests for overall mortality, liver-related mortality, and composite outcomes

Ref.	NIT[1]	Outcome	AUROC (95%CI)
Chalouni *et al*[18], 2019	APRI	OM	0.58 (N/A)
		LRM	0.80 (N/A)
		LRE	0.75 (N/A)
	FIB-4	OM	0.66 (N/A)
		LRM	0.88 (N/A)
		LRE	0.78 (N/A)
	TE	OM	0.69 (N/A)
		LRM	0.88 (N/A)
		LRE	0.88 (N/A)
Hansen *et al*[20], 2019	TE	OM	0.70 (0.62–0.78)
		LRM	0.93 (0.89–0.98)
		HD (HCC included)	0.89 (0.82–0.97)
Munteanu *et al*[22], 2018	Fibrotest	OM	0.74 (0.71-0.77)
		LRM	0.88 (0.85-0.90)
Thandassery *et al*[43], 2017	APRI (Pre-Rx)	HD	0.54 (0.06–0.78)
	FIB-4 (Pre-Rx)	HD	0.85 (0.74–0.96)
Pérez-Latorre *et al*[24], 2016	TE	OM	Estimation cohort 0.87 (0.84-0.90)
			Validation cohort 0.88 (0.84-0.91)
Lee *et al*[46], 2016	TE (Post-Rx)	A composite outcome of HD, HCC, and/or LRM	0.92 (0.84-1.00)
Berenguer *et al*[12], 2015	FIB-4 (Pre-Rx)	LRE (HD or HCC)	0.75 (0.72-0.78)
Yu *et al*[11], 2006	APRI (Pre-Rx)	OM	0.53 (0.35-0.72)
	APRI (Post-Rx)	OM	0.87 (0.81-0.93)

[1]NITs are not classified as either pre-treatment or post-treatment once the study did not specify when the NIT measurement regarding the initiation of hepatitis C virus therapy was done. N/A: Not available; APRI: Aspartate aminotransferase to platelet ratio index; FIB-4: Fibrosis-4 index; HCC: Hepatocellular carcinoma; HD: Hepatic decompensation; LSM: Liver stiffness measurement; LRM: Liver-related mortality; LRE: Liver-related event; NIT: Non-invasive test; OM: Overall mortality; pre-Rx: Pre-treatment; post-Rx: Post-treatment; AUROC: Area under the receiver operating characteristic curves; TE: Transient elastography.

SVR has greatly increased. SVR is independently associated with improved hepatic function and prognosis[35,36]. Despite achieving SVR, some patients can develop HCC or LREs suggesting that regular follow-up remains necessary[13,30,31,33,39,41,49]. Non-invasive assessment of residual fibrotic burden in post-therapy patients who achieved SVR is currently unreliable[2]. This issue could explain at least partly the decision of international guidelines not to recommend NITs for monitoring of post-treatment residual fibrosis[1,2]. Despite its questionable diagnostic potential, we found that among patients with SVR, APRI and LSM can predict HCC development with AUROC values of 0.75 and 0.84, respectively. This was shown to be helpful even in the DAA era, as shown in our study that the adjusted HR of LSM and HCC risk in patients achieving SVR after DAA era was 5.55.

Large variations in NIT cutoffs were observed in the studies included in our meta-analysis. For example, the cutoff of FIB-4 score recommended by WHO for predicting significant fibrosis (METAVIR ≥F2) is 1.45 for high sensitivity and 3.25 for high specificity[52]. We found that five out of 11 studies included in this meta-analysis chose the cutoff of 3.25[13,33,41,42,49], while no studies used the cutoff of 1.45. Accordingly, we pooled the results for unadjusted and adjusted HRs of pretreatment FIB-4 using the 3.25 cutoff and found that this cutoff had a statistically significant potential to be used clinically for HCC risk stratification, with a pooled adjusted HR of 3.22 (no subgroup analysis of post-treatment SVR population was done due to the lack

Table 4 Unadjusted and adjusted hazard ratios of non-invasive test for the prediction of liver-related mortality

Unadjusted hazard ratio (HR)				
Ref.	**NIT[1]**	**HR (95%CI)**	***P* value**	
Hansen *et al*[20], 2019	TE	97.00 (13.20–713.00)	< 0.005	
Shili-Masmoudi *et al*[28], 2019	TE	29.65 (8.88–99.01)	< 0.001	
Nunes *et al*[27], 2010	APRI	10.18 (4.86–21.32)	N/A	
	FIB-4	9.45 (4.51–19.79)	N/A	
Adjusted hazard ratio (aHR)				
Ref.	**NIT[1]**	**aHR (95%CI)**	***P* value**	**Adjustment variables**
Hansen *et al*[20], 2019	TE	11.00 (1.22–98.60)	0.018	SVR
Shili-Masmoudi *et al*[28], 2019	TE	20.60 (5.99–70.78)	< 0.001	Gender, alcohol consumption, drug consumption, CD4 count, HCV genotype, metabolic disorders, previous HCV treatment
Macías *et al*[21], 2015	TE	29.90 (4.30–217.00)	0.001	Age, gender, platelet counts, AIDS at baseline, alcohol use, treatment against HCV, time-varying CD4 cell counts, undetectable HIV RNA
Tada *et al*[48], 2016	FIB-4 (Pre-Rx)	13.02 (4.16–40.77)	< 0.001	Age, gender, AST concentration, ALT concentration, albumin, total bilirubin concentration, prothrombin time, platelet count, AFP concentration, FIB-4 index
Nunes *et al*[27], 2010	FIB-4	1.19 (1.12–1.27)	< 0.001	Gender, MELD
	FIB-4	1.13 (1.05–1.21)	0.001	Gender, CPT
	APRI	1.11 (1.01–1.22)	0.035	Gender, CPT
	APRI	1.25 (1.15–1.35)	< 0.001	Gender, MELD

[1]Non-invasive tests are not classified as either pre-treatment or post-treatment if the study did not specify when the non-invasive test measurement was done with regards to the initiation of hepatitis C virus therapy. NIT: Non-invasive test; HR: Hazard ratio; AFP: alpha-fetoprotein; APRI: Aspartate aminotransferase to platelet ratio index; CTP: Child-Turcotte-Pugh score; FIB-4: Fibrosis-4 index; N/A: Not available; LSM: Liver stiffness measurement; MELD: Model for end-stage liver disease score; pre-Rx: Pre-treatment; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; SVR: Sustained virologic response; TE: Transient elastography.

of studies). Notably, this does not justify excluding patients with FIB-4 below this cutoff from HCC screening, as it is still debatable whether this cutoff adequately identifies the at-risk population. Decisions regarding HCC screening in patients with low FIB-4 should be individualized based on patient risk profile.

The strength of this meta-analysis resides in the inclusion of all recently validated noninvasive fibrosis tests, including both radiological and serological tests, as we aimed to make this review as comprehensive as possible. There are some limitations. Although the present meta-analysis extensively assessed several clinically relevant outcomes including HCC, HD, and overall and liver-related mortality, our analysis was nevertheless narrowed by several unavailable data such as the timing in which NITs were assessed after receiving treatment or achieving SVR. Statistical heterogeneity was found in some of our analyses. However, this could be explained by subgroup-analyses of the following factors: NITs assessed at pre-treatment or post-treatment with SVR, treatment with either pegylated interferon and ribavirin or DAA, Eastern or Western countries, and different cutoff points. For instance, statistical heterogeneity found in the analyses of pre-treatment FIB-4 and HCC development is partially explained by country of study. In the subgroup analysis on Eastern countries, there was a reduction of I^2 from 76% to 18% for the unadjusted HR. Since the majority of studies are from Eastern countries with Asian participants, further studies conducted in other ethnicities are needed. Residual statistical heterogeneity seen in some of the analyses could also be explained by factors such as the presence of cirrhotic patients in the study and the type of HCV treatment regimen. Due to the limited number of studies and lack of information provided in some studies, we were unable to perform subgroup analysis on these factors. Instead, we provided this information in the figures, wherever subgroup analysis was not possible. More studies are needed to make it possible for us to explore the remaining statistical heterogeneity,

Table 5 Unadjusted and adjusted hazard ratios of non-invasive tests for the prediction of hepatic decompensation and other composite outcomes

Unadjusted hazard ratio (HR)

Ref.	Outcomes	NIT[1]	HR (95%CI)	*P* value
Hansen *et al*[20], 2019	HD (HCC included)	TE	59.00 (17.40–200.00)	< 0.005
Ogasawara *et al*[38], 2019	HD	TE (Pre-Rx)	7.77 (1.29–46.20)	0.025
		TE (Post-Rx)	17.80 (1.85–171.30)	0.013
Bloom *et al*[17], 2018	LRE (HD, HCC and OM)	TE	56.00 (7.00–415.00)	< 0.001
Gomez-Moreno *et al* [19], 2017	LRE (HD, HCC or LRM)	TE	33.27 (7.25–152.63)	< 0.001
Pérez-Latorre *et al* [24], 2016	HD or HCC, whichever occurred first	TE (Post-Rx)	37.76 (17.87–79.80)	< 0.001
Macías *et al*[21], 2015	HD (HCC included)	TE	39.90 (5.50–291.00)	< 0.0001

Adjusted hazard ratio (aHR)

Ref.	Outcomes	NIT[1]	aHR (95%CI)	*P* value	Adjustment variables
Hansen *et al*[20], 2019	HD (HCC included)	TE	9.00 (2.49-32.20)	0.001	Age, SVR, hyaluronic acid
Ogasawara *et al*[38], 2019	HD	TE (Pre-Rx)	4.85 (0.80–29.40)	0.086	Platelet count, albumin
		TE (Post-Rx)	14.90 (1.45-152.10)	0.023	Platelet count, albumin
Peleg *et al*[23], 2019	OM or HCC	TE (Post-Rx)	2.32 (0.97-6.59)	0.062	liver steatosis, baseline serum platelets
Gomez-Moreno *et al* [19], 2017	LRE (HD, HCC and OM)	TE	30.97 (6.73-142.51)	< 0.001	Age, gender, time since HCV diagnosis, HCV genotype, injection drug use, high alcohol intake, HCV antiviral therapy
Merchante *et al*[26], 2017	HD	TE	1.90 (1.04–3.64)	< 0.001	Age, gender, SVR during follow-up
Lee *et al*[46], 2016	HD, HCC, and/or LRM	TE (Post-Rx)	9.47 (1.02-88.13)	0.048	Age, AFP
Macías *et al*[21], 2015	HD (HCC included)	TE	59.50 (8.30-427.00)	< 0.001	Age, gender, platelet counts, AIDS at baseline, alcohol use, treatment against HCV, time-varying CD4 cell counts and undetectable HIV RNA.
Berenguer *et al*[12], 2015	OM/LRE (HD or HCC), whichever occurred first.	FIB-4 (Pre-Rx)	3.90 (2.46-6.16)	< 0.001	Age, gender, HIV transmission category, Centers for Disease Control and Prevention HIV clinical category, CD4 cell nadir, HCV genotype, HCV RNA, alcohol intake, methadone use, SVR

[1]Non-invasive tests are not classified as either pre-treatment or post-treatment if the study did not specify when the NIT measurement was done with regards to the initiation of hepatitis C virus therapy. APRI: Aspartate aminotransferase to platelet ratio index; FIB-4: Fibrosis-4 index; HCC: Hepatocellular carcinoma; HD: Hepatic decompensation; LSM: Liver stiffness measurement; LRM: Liver-related mortality; LRE: Liver-related event; NIT: Non-invasive test; OM: Overall mortality; pre-Rx: Pre-treatment; post-Rx: Post-treatment; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; SVR: Sustained virologic response; TE: Transient elastography.

by either subgroup analysis or meta-regression.

The publication bias in adjusted HR for FIB-4 index could be explained by biased selection of outcomes in four studies. Notably, only adjusted HRs for significant variables were reported, while non-significant variables were either omitted or considered as non-significant without providing a numerical adjusted HR[39-41,49]. However, through subgroup analysis, we have concluded that the publication bias detected was due to the inclusion of small studies.

CONCLUSION

FIB-4, APRI, and LSM showed predictive value in stratifying risk for CHC patients, particularly for pre-cirrhotic patients with significant fibrosis. Patients with a higher degree of fibrosis based on NITs were found to be at increased risk of complications, regardless of treatment regimen and response. Therefore, liver fibrosis measurement

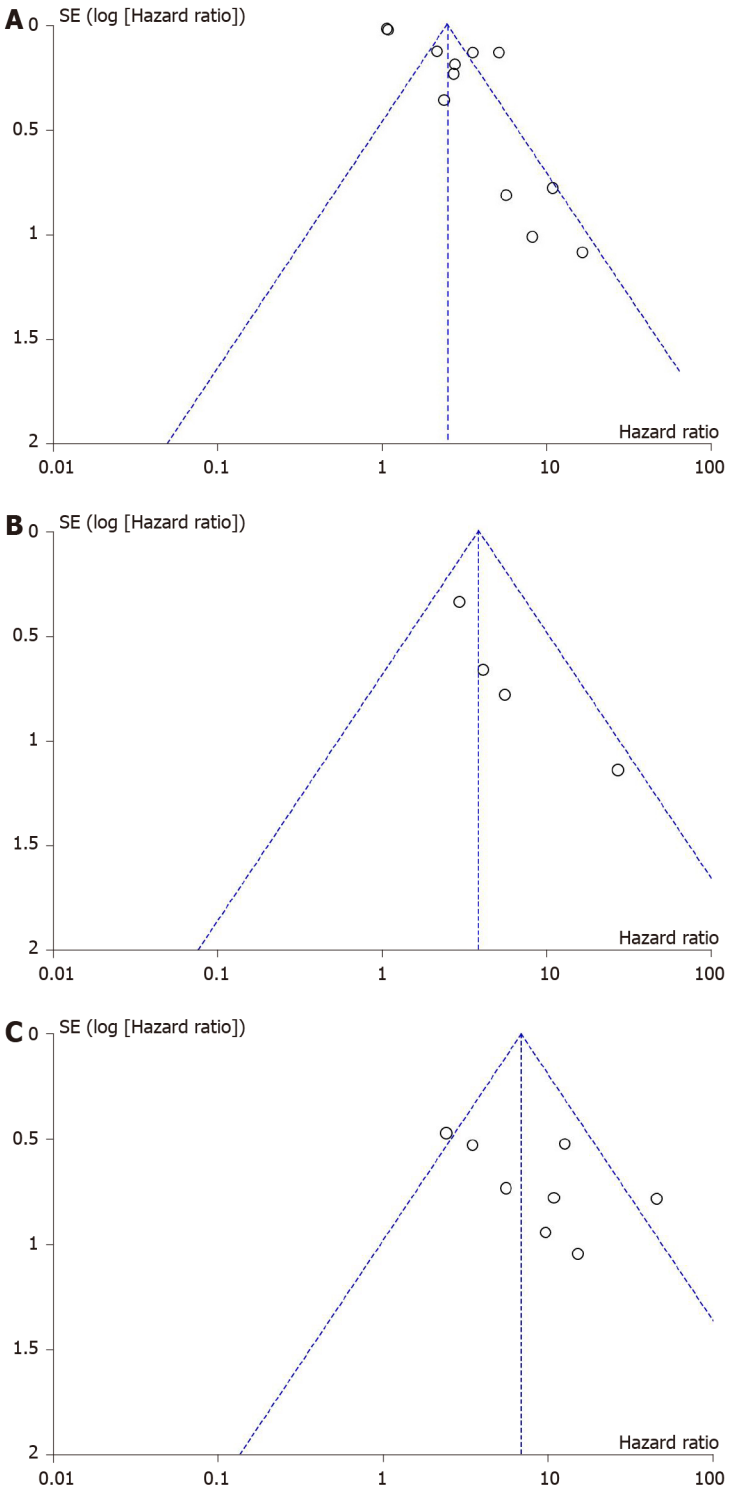


Figure 4 Funnel plots for adjusted hazard ratios of Fibrosis-4 (A), aspartate aminotransferase to platelet ratio (B), and liver stiffness measurement (C) for the evaluation of hepatocellular carcinoma development.

by NITs could benefit any HCV patient as it can determine the priority to monitor for the development of HCC and other LREs. The clinical implementation of these NITs does require future studies that can validate their respective cutoff levels.

ARTICLE HIGHLIGHTS

Research background

Non-invasive tests (NITs) have reduced the need for liver biopsy in chronic hepatitis C

(CHC) patients. Despite its limited diagnostic performance in patients with an intermediate degree of fibrosis or in post-treatment setting, previous meta-analyses have evidenced the potential of NITs in determining prognosis. However, these studies focused on chronic liver diseases from various etiologies and did not comprehensively explore all liver outcomes.

Research motivation

The authors aimed to explore all validated NITs for liver fibrosis, specifically their ability to predict liver-related outcomes in CHC patients.

Research objectives

The main goal was to determine the prognostic value of NITs for risk stratification in CHC patients.

Research methods

A literature search was performed to identify CHC cohort studies that reported an association between liver fibrosis assessment by NITs and outcomes such as hepatocellular carcinoma. Hazard ratios (HR) and area under the receiver operating characteristic from those studies were then pooled using the random effects model. Subgroup analyses were performed based on treatment status, treatment regimen, countries, and different cutoff points.

Research results

Fibrosis-4 (FIB-4) index, aspartate aminotransferase to platelet ratio (APRI) score, and liver stiffness measurement (LSM) were found to have hepatocellular carcinoma predictive potential with pooled adjusted HR of 2.48 (95%CI: 1.91-3.23, I^2 = 96%), 4.24 (95%CI: 2.15-8.38, I^2 = 20%) and 7.90 (95%CI: 3.98-15.68, I^2 = 52%) and area under the receiver operating characteristic of 0.81 (95%CI: 0.73-0.89, I^2 = 77%), 0.81 (95%CI: 0.75-0.87, I^2 = 68%) and 0.79 (95%CI: 0.63-0.96, I^2 = 90%), respectively.

Research conclusions

FIB-4, APRI, and LSM were found to have prognostic value, and can potentially be used to stratify risk for CHC patients, regardless of their treatment status or regimen.

Research perspectives

To facilitate clinical implementation, validation of FIB-4, APRI and LSM cutoff levels are needed.

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